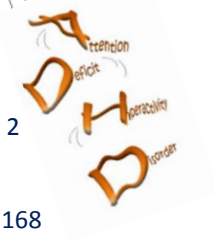
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD OTTOBRE 2021

Acta Orthop Belg. 2021 Mar;87:159-66.

CHILDREN WITH SUPRACONDYLAR HUMERUS FRACTURES HAVE AN INCREASED RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Genç E, Genç HA, Bulut GC.

Children with attention deficit hyperactivity disorder (ADHD) have an increased risk of sustaining fractures during their preschool years. Supracondylar humerus fractures (SHFs) comprise the majority of fracture surgeries in the pediatric age range. We hypothesized that ADHD symptoms would be present in children with SHFs, and this characteristic trauma may be associated with an ADHD diagnosis. Thus, we compared the ADHD symptoms of children with and without SHFs. Further, we compared the trauma characteristics, gender, proneness to injury, and presence of prior trauma history of children diagnosed with and without ADHD. We recruited 41 children who were admitted to emergency service with an SHF and 41 age- and gender-matched children without a fracture history. A semi-structured diagnostic inter- view and a Swanson Nolan Pelham questionnaire were used to obtain data about ADHD symptoms. A clinical intake form was utilized for further clinical data. ADHD symptoms were significantly higher in the fracture group ; male gender, parent- reported proneness to injury, and prior history of trauma were significantly associated with ADHD. Orthopedic surgeons may provide early detection of ADHD by using screening tools or asking questions to caregivers and making referrals when needed. This may lead to prevention of further injuries

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Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

Acta Paediatr. 2021 Nov;110:2944-50.

NEURODEVELOPMENTAL AND PSYCHIATRIC COMORBIDITIES NEGATIVELY AFFECT OUTCOME IN CHILDREN WITH UNPROVOKED SEIZURES-A NON-SYSTEMATIC REVIEW.

Åndell JE.

Children with epilepsy have at least one comorbidity in 80% of cases. This unstructured review provides insights into the most common comorbidities, their effects on seizure prognosis and treatment. We also review the epilepsy terminology and classifications. Neurodevelopmental and psychiatric comorbidities were common in children with seizures and had a negative effect on quality of life, and seizure freedom. Children with seizures were treated with drugs used for attention deficit hyperactivity disorder (ADHD), depression or psychosis, more often than the general population but less often than prevalence rates would suggested.
CONCLUSION: Multidisciplinary teams should assess comorbidities in children with epilepsy to improve their care and outcomes

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Acta Psychol (Amst). 2021 Oct;220:103420.

DEPRESSION AND LEARNING PROBLEMS IN CHILDREN: EXECUTIVE FUNCTION IMPAIRMENTS AND INATTENTION AS MEDIATORS.

Ciuhan GC, Iliescu D.

This study examines the relationship between depression and learning problems in children, focusing on the mediating role of executive function impairments and inattention. A sample of 115 children, aged 7 to 12 years, who had difficulties in school activities, were tested over the past three years, with different measures assessed by different raters. Regression analyses were employed in analyzing the data. The psychometric tests used were Child Depression Inventory (CDI) and Conners 3rdEdition. Children with a high level of depressive symptoms have also a very high level of learning problems, executive function impairments and inattention. Executive function impairments and inattention add significant explanatory variance for learning problems in school-aged children over and above depression. Executive function impairments and inattention have a partial mediating effect on the relationship between depression and learning problems. The assessment of the executive functions and attention is an important part in the assessment of children with depression; intervention and treatment programs for depression should include components focused on executive functions and attention

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Adv Child Dev Behav. 2021;60:229-60.

SLEEP'S ROLE IN MEMORY CONSOLIDATION: WHAT CAN WE LEARN FROM ATYPICAL DEVELOPMENT?

Luongo A, Lukowski A, Protho T, et al.

Research conducted over the last century has suggested a role for sleep in the processes guiding healthy cognition and development, including memory consolidation. Children with intellectual and developmental disabilities (IDDs) tend to have higher rates of sleep disturbances, which could relate to behavior issues, developmental delays, and learning difficulties. While several studies examine whether sleep exacerbates daytime difficulties and attention deficits in children with IDDs, this chapter focuses on the current state of knowledge regarding sleep and memory consolidation in typically developing (TD) groups and those at risk for learning difficulties. In particular, this chapter summarizes the current literature on sleep-dependent learning across developmental disabilities, including Down syndrome, Williams syndrome, Autism Spectrum Disorder, and Learning Disabilities (Attention-Deficit/Hyperactivity Disorder and Dyslexia). We also highlight the gaps in the current literature and identify challenges in studying sleep-dependent memory in children with different IDDs. This burgeoning new field highlights the importance of considering the role of sleep in memory retention across long delays when evaluating children's memory processes. Further, an understanding of typical and atypical development can mutually inform recent theories of sleep's role in memory

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Alcohol Clin Exp Res. 2021 Mar;45:596-607.

VALIDITY AND RELIABILITY OF EXECUTIVE FUNCTION MEASURES IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE: CORRESPONDENCE BETWEEN MULTIPLE RATERS AND LABORATORY MEASURES.

Bernes GA, Villodas M, Coles CD, et al.

BACKGROUND: Rating scales are designed to complement traditional performance-based measures, and both can provide useful information about the functioning of youth with histories of prenatal alcohol exposure. Few studies, however, have compared ratings from multiple informants or the relationship between these subjective rating scale scores and the objective results from laboratory performance-based scales.

METHODS: The current study addressed both of these questions in 3 study groups: children with histories of prenatal alcohol exposure (n = 47), attention-deficit/hyperactivity disorder (ADHD; n = 41), and typically developing controls (CON; n = 73). All subjects completed a standardized neuropsychological test battery, including laboratory measures of executive functioning and a self-report measure of executive function behaviors. Parents and teachers completed corresponding rating scales of executive function behaviors for each subject. This study assessed the relationship between these behavior rating scales and corresponding neuropsychological tests, and interrater agreement among the multiple informants.

RESULTS: Weak correlations were found between the rating scales and laboratory measures, indicating poor convergent validity for the behavior rating scale. Interrater reliability was found but it differed by group. Agreement was found between parent and teacher ratings for children with prenatal alcohol exposure, whereas teacher-child agreement was found for those with ADHD.

CONCLUSIONS: Findings from this study indicate that behavior ratings can be used to supplement laboratory measures but may not be measuring cognitive abilities regardless of whether a clinical diagnosis is present. A multimethod approach should be used when measuring skills in this domain. This was one of the first studies to examine cross-informant agreement in a sample of children with prenatal alcohol exposure. Further research is necessary to understand why interrater agreement differed for children with prenatal alcohol exposure and those with ADHD

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Alcohol Clin Exp Res. 2021.

PREVALENCE OF FETAL ALCOHOL SPECTRUM DISORDER IN GREATER MANCHESTER, UK: AN ACTIVE CASE ASCERTAINMENT STUDY.

McCarthy R, Mukherjee RAS, Fleming KM, et al.

Background: Despite high levels of prenatal alcohol exposure in the UK, evidence on the prevalence of fetal alcohol spectrum disorders (FASD) is lacking. This paper reports on FASD prevalence in a small sample of children in primary school.

Methods: A 2-phase active case ascertainment study was conducted in 3 mainstream primary schools in Greater Manchester, UK. Schools were located in areas that ranged from relatively deprived to relatively affluent. Initial screening of children aged 8-9 years used prespecified criteria for elevated FASD risk (small for age; special educational needs; currently/previously in care; significant social/emotional/mental health symptoms). Screen-positive children were invited for detailed ascertainment of FASD using gold standard measures that included medical history, facial dysmorphology, neurological impairment, executive function, and behavioral difficulties.

Results: Of 220 eligible children, 50 (23%) screened positive and 12% (26/220) proceeded to Phase 2 assessment. Twenty had a developmental disorder, of whom 4-áhad FASD and 4 were assessed as possible FASD. The crude prevalence rate of FASD in these schools was 1.8% (95% CI: 1.0%, 3.4%) and when including possible cases was 3.6% (2.1%, 6.3%). None of these children had previously been identified with a developmental diagnosis.

Conclusions: FASD was found to be common in these schools and most of these children's needs had not previously been identified. A larger, more definitive study that uses a random sampling technique stratified by deprivation level to select schools is needed to make inferences regarding the population prevalence of FASD

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Am J Reprod Immunol. 2021 Jan;85:e13335.

MATERNAL KNOWN DRUG ALLERGY AND LONG-TERM NEUROLOGICAL HOSPITALIZATIONS OF THE OFFSPRING.

Davidesko S, Pariente G, Wainstock T, et al.

Problem: Drug allergies are increasingly common. Immunological factors, implicated in many neurological diseases, also influence an individual's susceptibility. We sought to ascertain a possible association between maternal drug allergy and long-term neurological-related hospitalizations in the offspring.

Method of study: This is a population-based cohort analysis, comparing the long-term risk of neurological-related hospitalization, involving a predefined set of ICD9 codes as recorded in hospital records, of children born to mothers with and without drug allergies. Deliveries occurred between the years 1991 and 2014 in a tertiary medical center. Twin pregnancies, fetal malformations, and cases of perinatal mortality were excluded. A Kaplan-Meier survival curve was constructed to compare cumulative neurological hospitalizations. A Cox proportional hazards model was used to control for time to event.

Results: The study included 242 342 patients, 9714 with known drug allergy (4%). Offspring born to mothers with drug allergies had significantly more neurological hospitalizations compared to controls (4.2% vs 3.1%; P ≤ .001; Kaplan-Meier log-rank test P ≤ .001), specifically for psychiatric disorders including eating disorders (0.3% vs 0.2%;P = .002), attention-deficit/hyperactivity disorder (0.124% vs 0.056%; P = .008), emotional disorders (0.8% vs 0.5%; P ≤ .001), and movement disorders (2.3% vs 1.8%; P = .002). While controlling for birth year, gestational age, maternal age, maternal diabetes, hypertensive disorders, and cesarean delivery, using a Cox proportional hazards model, maternal drug allergy was found to be an independent risk factor for neurological hospitalization of the offspring (adjusted HR 1.3, 95% CI 1.19-1.45 P < .001).

Conclusion: Being born to a mother with known drug allergy is an independent risk factor for long-term neurological hospitalization of the offspring

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Ann Transplant. 2021 Oct;26:e932994.

OUTCOMES AFTER LIVING DONOR LIVER TRANSPLANTATION IN PEDIATRIC PATIENTS WITH INHERITED METABOLIC DISEASES.

Sanada Y, Sakuma Y, Onishi Y, et al.

BACKGROUND There is no consensus about the long-term prognosis of pediatric patients with a variety of rare liver diseases but with inherited metabolic diseases (IMDs). We retrospectively reviewed the developmental outcomes of patients with IMDs undergoing living donor liver transplantation (LDLT).

MATERIAL AND METHODS Between May 2001 and December 2020, of 314 pediatric patients who underwent LDLT, 44 (14%) had IMDs. The median age at LDLT was 3.0 years old (range 0-15.0 years). Associations between the post-transplant complications and graft survival rate in patients with IMDs and biliary atresia (BA) were calculated. We evaluated the safety of LDLT from heterozygous carrier donors, the prognosis of patients with IMDs who have metabolic defects expressed in other organs, and developmental outcomes of patients with IMDs.

RESULTS The 10-year graft survival rates in patients with IMDs and BA were 87% and 94%, respectively (P=0.041), and the causes of graft failure included pneumocystis pneumonia, acute lung failure, hemophagocytic syndrome, hepatic vein thrombosis, portal vein thrombosis, and sepsis. The rate of post-transplant cytomegalovirus viremia in patients with IMDs was higher than that of patients with BA (P=0.039). Of 39 patients with IMDs, 15 patients (38%) had severe motor and intellectual disabilities in 4 patients, intellectual developmental disorders including epilepsy in 2, and attention-deficit hyperactivity disorder in 2. Of 28 patients with IMDs, 13 (46%) needed special education.

CONCLUSIONS The long-term outcomes of LDLT in patients with IMDs are good. However, further long-term social and educational follow-up regarding intellectual developmental disorders is needed

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Appl Neuropsychol Adult. 2021 May;28:318-27.

CAN THE CANTAB IDENTIFY ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? A CONTROLLED STUDY.

Fried R, DiSalvo M, Kelberman C, et al.

We examined the diagnostic utility of the Cambridge Neuropsychological Test Automated Battery (CANTAB) for identifying adults with attention-deficit/hyperactivity disorder (ADHD). The sample consisted of clinically

referred adults aged 18 to 60â€‰years old, with (nâ€‰=â€‰474) and without (nâ€‰=â€‰163) DSM-IV diagnosis of ADHD. All subjects were administered seven subtests from the CANTAB that targeted domains of executive functioning and verbal memory. Data were analyzed to identify which CANTAB tasks would best predict ADHD status. Our results failed to show any diagnostic utility for the CANTAB in adults with ADHD, even when using the most robust tests (Affective Go/No-go [AGN] Total Commissions and [RTI] Simple Reaction Time) identified from stepwise logistic regression (forward selection; pâ€‰>â€‰0.05 for entry). However, the CANTAB was helpful in identifying executive functioning disorder (EFD) in adults with ADHD when compared with controls subjects. Even though the CANTAB lacked diagnostic utility for adults with ADHD, the findings provided further evidence that adult ADHD is strongly associated with EFD. This study represents the most comprehensive evaluation of the diagnostic utility of the CANTAB in a clinical sample of adults with ADHD

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Appl Neuropsychol Child. 2021 Jul;10:283-96.

A PEDIATRIC CASE OF NF1 AND MOYAMOYA SYNDROME: NEUROPSYCHOLOGICAL EVALUATION PRE- AND POST-EDAS.

DeDios-Stern S, Ventura LM.

Studies have shown that a subset of patients with neurofibromatosis type 1 (NF1) experience associated vascular conditions, with moyamoya syndrome one of the most common comorbidities. While NF1 and moyamoya syndrome are each associated with neurocognitive deficits, no neuropsychological data has been presented for an individual with comorbid NF1 and moyamoya syndrome, particularly pre- and post-re-vascularization surgery. The present case describes the neuropsychological profile of a bilingual Latina girl with NF1 and moyamoya syndrome, who was assessed pre- (age 5 years, 9 months) and post-EDAS (age 6 years, 1 month). Each evaluation included a clinical interview and comprehensive battery of neuropsychological tests. Results of pre-EDAS evaluation documented significant deficits in sustained attention, daily executive functioning, and academic abilities, and she met criteria for ADHD-combined type. Results of post-EDAS evaluation revealed generally stable abilities with relative improvements in social, emotional, and behavioral functioning, but relative decline in visuospatial skills, visual spatial learning/memory, and aspects of executive functioning. Math abilities also remained consistently poor and she was diagnosed with a specific learning disability (mathematics). This case study adds to the current literature by being among the first to present pre- and post-surgical neuropsychological data for a child with NF1 and moyamoya syndrome. Findings are discussed in the context of previous literature, the importance of individual socio-cultural considerations in the case (i.e., language, education, culture), and recommendations for future research

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Behav Genet. 2021 May;51:250-63.

GENETICALLY INFORMED REGRESSION ANALYSIS: APPLICATION TO AGGRESSION PREDICTION BY INATTENTION AND HYPERACTIVITY IN CHILDREN AND ADULTS.

Boomsma DI, Van Beijsterveldt TCEM, Odintsova VV, et al.

We present a procedure to simultaneously fit a genetic covariance structure model and a regression model to multivariate data from mono- and dizygotic twin pairs to test for the prediction of a dependent trait by multiple correlated predictors. We applied the model to aggressive behavior as an outcome trait and investigated the prediction of aggression from inattention (InA) and hyperactivity (HA) in two age groups. Predictions were examined in twins with an average age of 10Â years (11,345 pairs), and in adult twins with an average age of 30Â years (7433 pairs). All phenotypes were assessed by the same, but age-appropriate, instruments in children and adults. Because of the different genetic architecture of aggression, InA and HA, a model was fitted to these data that specified additive and non-additive genetic factors (A and D) plus common and unique environmental (C and E) influences. Given appropriate identifying constraints, this ADCE model is identified in trivariate data. We obtained different results for the prediction of aggression in children, where HA was the more important predictor, and in adults, where InA was the more important predictor. In children, about 36% of the total aggression variance was explained by the genetic and environmental components of HA and InA. Most of this was explained by the genetic components of HA and

InA, i.e., 29.7%, with 22.6% due to the genetic component of HA. In adults, about 21% of the aggression variance was explained. Most was this was again explained by the genetic components of InA and HA (16.2%), with 8.6% due to the genetic component of InA

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Behav Sleep Med. 2021 Nov;19:754-68.

AN EXPLORATION OF SLEEP AND FAMILY FACTORS IN YOUNG CHILDREN AT FAMILIAL RISK FOR ADHD.

Keating J, Bramham J, McNicholas F, et al.

Objective: The aim of the current study was to examine relations between sleep problems and family factors and early markers of ADHD in young children with and without a familial risk for ADHD.

Methods: Differences in sleep behavior and family functioning in children under 6 years with (n = 72) and without (n = 139) a familial risk for ADHD were investigated. The influence of family and sleep factors on the development of early temperament markers of ADHD (effortful control and negative affect) was explored. Parents/caregivers completed questionnaires on family functioning, child sleep behavior, and general regulatory behaviors.

Results: A significant difference was observed between high-risk and low-risk groups for family functioning in the infant/toddler (<3 years) and preschool (>3 years) cohorts. Parents of infants/toddlers in the high-risk group reported poorer infant sleep. However, there were no sleep differences reported for the preschool cohort. Family functioning was found to predict effortful control, while sleep quality predicted negative affect.

Conclusion: The results of this study highlight potential family and sleep issues for young children with a familial history of ADHD and the potential influence of these factors on early temperament markers of ADHD. Future research should explore these relations further in order to better establish whether early sleep and family interventions could mitigate later ADHD symptomatology

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Behav Ther. 2021.

MEASURING EMOTION DYSREGULATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: REVISITING THE FACTOR STRUCTURE OF THE EMOTION REGULATION CHECKLIST.

Silverman MR, Bennett R, Feuerstahler L, et al.

Emotion dysregulation (ED) is prevalent among youth with Attention-Deficit/Hyperactivity Disorder (ADHD) and significantly impacts functioning. Nuanced measurement of ED is central to understanding its role in this disorder and informing treatment approaches. The present study examined the factor structure of the Emotion Regulation Checklist (ERC) among children with ADHD with and without Oppositional Defiant Disorder (ODD). Exploratory factor analysis (EFA) conducted in a sample of 328 youth (mean age = 6.08) with ADHD indicated a four-factor solution, comprised of the following factors: Negative Emotion Lability, Positive Emotion Lability, Socially Appropriate Affect, and Socially Incongruent Affect. The Negative and Positive Emotion Lability subscales assess the reactivity of negatively and positively valenced emotions, respectively. The Socially Appropriate and Socially Incongruent Affect subscales provide an assessment of social-emotional functioning. All subscales discriminated between children with ADHD only and ADHD with co-morbid ODD, such that children with ODD had greater emotional lability and social-emotional difficulties. This revised factor structure of the ERC facilitates a uniquely brief, yet multifaceted and specific, assessment of emotional difficulties in children with ADHD that can inform treatment planning and operationalize emotional reactivity and social-emotional functioning in future research efforts

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Biol Psychiatry. 2021 Oct;90:529-39.

REWARD PROCESSING IN NOVELTY SEEKERS: A TRANSDIAGNOSTIC PSYCHIATRIC IMAGING BIOMARKER.

Qi S, Schumann G, Bustillo J, et al.

BACKGROUND: Dysfunctional reward processing is implicated in multiple mental disorders. Novelty seeking (NS) assesses preference for seeking novel experiences, which is linked to sensitivity to reward environmental cues.

METHODS: A subset of 14-year-old adolescents (IMAGEN) with the top 20% ranked high-NS scores was used to identify high-NS-associated multimodal components by supervised fusion. These features were then

used toÂ longitudinally predict five different risk scales for the same and unseen subjects (an independent dataset of subjects at 19 years of age that was not used in predictive modeling training at 14 years of age) (within IMAGEN, n 1100) and even for the corresponding symptom scores of five types of patient cohorts (non-IMAGEN), including drinking (n = 313), smoking (nÂ = 104), attention-deficit/hyperactivity disorder (n = 320), major depressive disorder (n = 81), and schizophrenia (n = 147), as well as to classify different patient groups with diagnostic labels.
RESULTS: Multimodal biomarkers, including the prefrontal cortex, striatum, amygdala, and hippocampus, associated with high NS in 14-year-old adolescents were identified. The prediction models built on these features are able to longitudinally predict five different risk scales, including alcohol drinking, smoking, hyperactivity, depression, and psychosis for the same and unseen 19-year-old adolescents and even predict the corresponding symptom scores of five types of patient cohorts. Furthermore, the identified reward-related multimodal features can classify among attention-deficit/hyperactivity disorder, major depressive disorder, and schizophrenia with an accuracy of 87.2%.
CONCLUSIONS: Adolescents with higher NS scores can be used to reveal brain alterations in the reward-related system, implicating potential higher risk for subsequent development of multiple disorders. The identified high-NS-associated multimodal reward-related signatures may serve as a transdiagnostic neuroimaging biomarker to predict disease risks or severity

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Biomedica. 2021 Mar;41:8-16.
VELAMENTOUS CORD INSERTION, ISCHEMIC-HYPOXIC ENCEPHALOPATHY, AND NEUROLOGICAL REHABILITATION: A CASE REPORT.
Ãšsuga MJ, Jaramillo GA, Palacio V, et al.
Hypoxic-ischemic encephalopathy is a frequent and important cause of neurological problems in term and preterm newborns. A sentinel event of this entity is the vasa previa, specifically when there is an abnormality of the placenta such as a velamentous cord insertion. Some reports have shown the association between these two entities, but those regarding the recovery process and the neurological prognosis of children with both conditions are scarce. We present the case of a patient with a history of velamentous cord insertion and hypoxicischemic encephalopathy who received therapeutic hypothermia (cool cap). We describe his neurological rehabilitation process and we calculated the percentage of probability of presenting this condition compared to the population without these factors. The patient was a five-year-old boy with an Apgar index at birth equal to zero at one minute and equal to two at fifteen minutes who developed severe hypoxic-ischemic encephalopathy secondary to a velamentous cord insertion without prenatal diagnosis and a marked initial neurological and multisystemic compromise. The recovery process included early multidisciplinary management in the neonatal intensive care unit and a focus on early neurological habilitation. The patient is currently in school and he undergoes comprehensive therapies; on physical examination, he presents no motor or sensory deficiencies. His neuropsychological test suggests the risk of attention deficit hyperactivity disorder. Children with severe hypoxicischemic encephalopathy usually have disabilities due to motor, cognitive, and/or behavioral deficiencies

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BJOG Int J Obstet Gynaecol. 2021;128:1917-27.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN FOLLOWING PRENATAL EXPOSURE TO ANTIDEPRESSANTS: RESULTS FROM THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY.
Lupattelli A, Mahic M, Handal M, et al.
Objective: To determine the association between child attention-deficit/hyperactivity disorder (ADHD) and prenatal exposure to selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitor antidepressants, by timing and duration, with quantification of bias due to exposure misclassification.
Design: Norwegian Mother, Father and Child Cohort Study and national health registries.
Setting: Nationwide, Norway.
Population: A total of 6395 children born to women who reported depression/anxiety in pregnancy and were either medicated with SSRI/SNRI in pregnancy (n=818) or non-medicated (n=5228), or did not report depression/anxiety but used antidepressants 6-ámonths before pregnancy (discontinuers, n=349).

Main outcome measure: Diagnosis of ADHD or filled prescription for ADHD medication in children, and mother-reported symptoms of ADHD by child age 5 years.
Results: When the hazard was averaged over the duration of the study follow up, there was no difference in ADHD risk between ever in utero SSRI/SNRI-exposed children and comparators (weighted hazard ratio [wHR] 1.07, 95% CI 0.76-1.51 versus non-medicated; wHR 1.53, 95% CI 0.77ΓÇô3.07 versus discontinuers). Underestimation of effects due to exposure misclassification was modest. In early childhood, the risk for ADHD was lower with prenatal SSRI/SNRI exposure compared with no exposure, and so were ADHD symptoms (weighted +¦ 0.23, 95% CI 0.39 to 0.08); this risk became elevated at child age 7-9 years (wHR 1.93, 95% CI 1.22-3.05). Maternal depression/anxiety before pregnancy was independently associated with child ADHD.
Conclusion: Prenatal SSRI/SNRI exposure is unlikely to considerably increase the risk of child ADHD beyond that posed by maternal depression/anxiety. The elevated risk at child age 7-9 years needs to be elucidated. Tweetable abstract: Women with depression who use antidepressants in pregnancy do not have greater risk of having children with ADHD. Findings in school-age children needs follow up

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BJPsych Open. 2019;5.

RETROSPECTIVE PARENTAL ASSESSMENT OF CHILDHOOD NEURODEVELOPMENTAL PROBLEMS: THE USE OF THE FIVE TO FIFTEEN QUESTIONNAIRE IN ADULTS.

Lugnegard T, Bejerot S.

BackgroundAttention-deficit hyperactivity disorder and autism are increasingly recognised in adults. For a diagnostic evaluation, parental information on childhood development is needed. However, no instruments that retrospectively describe neurodevelopmental problems in childhood are validated for evaluating adults. The 181-item parent-report questionnaire Five to Fifteen (FTF) is nevertheless frequently used for assessments in adulthood.
Aims To examine if FTF is reliable for obtaining retrospective neurodevelopmental history among young adults.
Method Details of parents who had assessed their children with the FTF for neuropsychiatric evaluation were retrieved and they were asked to complete the FTF again 10-19 years later. Agreements between original and retrospective scorings were analysed.
Results Long-term reliability for FTF varies considerably between individual items. Several difficulties are reported as more severe at the retrospective scoring than at the original scoring. A selection of 24 items (FTF-Brief) with good agreement over time, is presented for use in adult psychiatry settings.
Conclusion Neuropsychiatric symptoms may fluctuate over time and become more prominent when demands increase. Informants' recollections of their child's neurodevelopmental symptoms may be a selection of symptoms that are longstanding rather than present at a specific age in childhood.
Declaration of interest None

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BMC Health Serv Res. 2021 Oct;21:1063.

REFERRAL PATTERNS TO OUTPATIENT CHILD AND ADOLESCENT MENTAL HEALTH SERVICES AND FACTORS ASSOCIATED WITH REFERRALS BEING REJECTED. A CROSS-SECTIONAL OBSERVATIONAL STUDY.

Hansen AS, Christoffersen CH, TellÃ©us GK, et al.

BACKGROUND: Outpatient child and adolescent mental health services (CAMHS) are faced with the challenge of balancing increasing demands with limited resources. An additional challenge is high rejection rates of referrals which causes frustration for referring agents and families. In order to effectively plan and allocate available resources within CAMHS there is a need for up-to-date knowledge on referral patterns and factors associated with rejection of referrals.
METHODS: In this cross-sectional observational study we did a retrospective review of all referrals (nÂ =â€‰1825) for children (0-18) referred for assessment at the outpatient CAMHS of the North Denmark Region in 2018.
RESULTS: The most common referral reasons to CAMHS were attention deficit disorder (ADHD/ADD) (27.9%), autism spectrum disorder (22.4%), affective disorders (14.0%) and anxiety disorders (11.6%). The

majority of referrals came from general practitioners, but for neurodevelopmental disorders educational psychologists were the primary referral source. Re-referrals constituted more than a third of all referrals (35.9%). Children in care were overrepresented in this clinical sample and had an increased risk (Adj. OR 2.54) of having their referrals rejected by CAMHS. Referrals from general practitioners were also associated with an increased risk of rejection (Adj. OR 3.29).
CONCLUSIONS: A high proportion of children with mental disorders have a repeated need for assessment by CAMHS. There is a need for future research on predictors of re-referral to outpatient services to identify potential targets for reducing re-referral rates as well as research on how to optimize service provision for children with a repeated need for assessment. General practitioners are the main gatekeepers to CAMHS and research on interventions to improve the referral process should be aimed towards general practitioners

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BMC Pediatr. 2021 Sep;21:402.

A RANDOMIZED EPIREMED PROTOCOL STUDY ON THE LONG-TERM VISUO SPATIAL EFFECTS OF VERY PRETERM CHILDREN WITH A WORKING MEMORY DEFICIT.

Gire C, Beltran AA, Kaminski M, et al.

BACKGROUND: Very preterm children generally perform poorly in executive functions and particularly in working memory. Adaptive training tasks encouraging these children to work continuously on their personal working memory capacity can be very useful. Above all in preschool-age children, several cognitive training programs focused on improving working memory capacity. Cogmed is a computerized visuospatial cognitive training program that improves working memory in children and adolescents with attention-deficit/hyperactivity disorder. The main objective is to assess the long-term effects (18 months) of cognitive training (Cogmed) on visuospatial processing in preschool-age very preterm children with working memory impairment.
METHODS: The EPIREMED study is a prospective, randomized, controlled, multicentric trial nested in a population based epidemiological survey. An intervention group (Cogmed cognitive training) and a control group (standard care management) will compare children aged 5 to 6 years, born between 24- and 34-weeks' gestational age, with a global intelligence quotient >70 and a working memory index <85. The study will include 166 children from national study EPIPAGE-2 (Epidemiological Study on Small Gestational Ages). The intervention consists of 25 sessions administered over a 5- to 8-week period. The primary endpoint will be the visuospatial processing, assessed by the score of the visuospatial index: score of the WPPSI-IV (Wechsler Preschool and Primary Scale of Intelligence). The secondary endpoints will allow to assess the executive functions, language and abilities, infant behavior, quality of life assessment, school performance and parental anxiety.
DISCUSSION: This project's primary goal is to demonstrate the necessity of early visuospatial memory assessment within the vulnerable population of very preterm children, and to prove the feasibility and efficacy of computerized cognitive training using online software programs. A better global neuropsychological development improvement (visuospatial processing and other far transfer) can be expected with an improvement in learning and decreased behavioral problems. In the long term, these improvements might also reduce those global costs linked to the consequences of extreme prematurity.
TRIAL REGISTRATION: NCT02757794 (registered on 2nd May 2016 at ClinicalTrial.gov)

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BMC Pregnancy Childbirth. 2021 Jan;21:62.

BREASTFEEDING, PRENATAL DEPRESSION AND CHILDREN'S IQ AND BEHAVIOUR: A TEST OF A MODERATION MODEL.

Amiel CR, Glover V, Ehlert U, et al.

BACKGROUND: We aimed to determine the associations between breastfeeding and children's neurodevelopment indexed by intelligence quotient (IQ) and emotional and behavioural problems through mid-childhood adjusting for prenatal and postnatal depression and multiple confounders; and to test the novel hypothesis that breastfeeding may moderate the effects of prenatal depression and anxiety on children's neurodevelopment.
METHODS: The study is based on women and their children from the longitudinal Avon Longitudinal Study of Parents and Children (n=11,096). Children's IQ was derived from standardized in-person testing;

behaviour problems were assessed according to parent-report; information on breastfeeding, prenatal depression and anxiety and multiple confounders were derived from self-report questionnaires. We conducted hierarchical multiple regression adjusting for several covariates.
RESULTS: 43% women were exclusively breastfeeding at 1 month and an additional 16.8% were engaged in mixed or partial breastfeeding. Both exclusive breastfeeding (B = 2.19; SD = 0.36, p =.00) and mixed feeding (B = 1.59; SD= 0.52; p=.00) were positively associated with IQ at 8 years of age, after adjusting for covariates. Exclusive breastfeeding was negatively associated with hyperactivity/attention deficit at 4 years (B = -.30, SD = .05; p < .01); mixed feeding was related to hyperactivity/attention deficit at age 9 (B = .20; SD = .08; p = .03) after adjustments. There was no association between breastfeeding and emotional or conduct problems. Breastfeeding did not moderate the association between prenatal depression and anxiety and children's neurodevelopment.
CONCLUSIONS: The selective association between breastfeeding and neurodevelopmental measures suggests a nutritional rather than broader beneficial psychological effect on child neurodevelopment. Breastfeeding did not moderate the associations between prenatal depression and anxiety and child neurodevelopment, suggesting separate mechanisms of action

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BMC Psychiatry. 2021 Oct;21:514.

ADHD OVERDIAGNOSIS AND THE ROLE OF PATIENT GENDER AMONG IRANIAN PSYCHIATRISTS.

Beheshti A, Chavanon ML, Schneider S, et al.

BACKGROUND: Regarding the controversy about the overdiagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) in children and adolescents there are two main directions addressed as issue of age bias and issue of gender bias. In this relation, replication of findings demonstrating significant overdiagnosis is of importance which make the systematic evaluation of such occurrence necessary.
OBJECTIVE: The seminal study by Bruchmller, Margraf & Schneider, 2012 is replicated here, although in a different cultural context, in this case Iran, as ADHS might be perceived differently there. We assessed both gender bias and the impact of potential overdiagnosis on treatment recommendations.
METHODS: A total of 344 licensed Iranian psychiatrists (mean age=45.17, SD=9.50) participated in this study. Each psychiatrist received a cover letter that introduced the study as well as a case vignette. Overall, there are eight different cases, one child with ADHD and three non-ADHD children, for both a boy (Ali) and a girl (Sara). Participants also received a questionnaire requesting their particular diagnosis, treatment recommendation and the therapist's sociodemographic information. Chi square tests and multiple logistic regression were applied for data analyses.
RESULTS: Overdiagnosis occurred in both girl and boy children, although overdiagnosis was 2.45 more likely in boys than in girls (p <0.01). With respect to the psychiatrist's gender, we detected no difference between males or females, as both overdiagnosed ADHD in boys (p(female) <0.01 and p(male) <0.01). Furthermore, ADHD overdiagnosis had a direct impact on medication prescription (p<0.01).
CONCLUSION: This study suggests that diagnosticians should strictly adhere to diagnostic criteria to minimize diagnostic error

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Brain Dev. 2021 Oct;43:904-11.

A STUDY ON THE RELATIONSHIP BETWEEN NON-EPILEPTIC FAST (40 – 200 HZ) OSCILLATIONS IN SCALP EEG AND DEVELOPMENT IN CHILDREN.

Oka M, Kobayashi K, Shibata T, et al.

Objective: Physiological gamma and ripple activities may be linked to neurocognitive functions. This study investigated the relationship between development and non-epileptic, probably physiological, fast (40–200 Hz) oscillations (FOs) including gamma (40 – 80 Hz) and ripple (80 – 200 Hz) oscillations in scalp EEG in children with neurodevelopmental disorders.
Methods: Participants were 124 children with autism spectrum disorder (ASD) and/or attention deficit/hyperactivity disorder (ADHD). Gamma and ripple oscillations were explored from 60-second-long sleep EEG data in each subject using a semi-automatic detection tool supplemented with visual confirmation and time–frequency analysis.

Results: Gamma and ripple oscillations were detected in 25 (20.2%) and 22 (17.7%) children, respectively. The observation of one or more occurrence(s) of ripple oscillations, but not gamma oscillations, was significantly related to lower age at EEG recording (odds ratio, OR: 0.727 [95% confidence interval, CI: 0.568–0.929]), higher intelligence/developmental quotient (OR: 1.041, 95% CI: 1.002–1.082), and lack of a diagnosis with ADHD (OR: 0.191, 95% CI: 0.039 – 0.937) according to a binominal logistic regression analysis that included diagnosis with ASD, sex, history of perinatal complications, history of febrile seizures, and use of a sedative agent for the EEG recording as the other non-significant parameters. Diagnostic group was not related to frequency or power of spectral peaks of FOs.
Conclusion: The production of non-epileptic scalp ripples was confirmed to be associated with brain development and function/dysfunction in childhood. Further investigation is necessary to interpret all of the information on higher brain functions that may be embedded in scalp FOs

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Brain Connectivity. 2021;11:651-62.

TOPOLOGICAL ABERRANCE OF STRUCTURAL BRAIN NETWORK PROVIDES QUANTITATIVE SUBSTRATES OF POST-TRAUMATIC BRAIN INJURY ATTENTION DEFICITS IN CHILDREN.

Cao M, Luo Y, Wu Z, et al.

Background: Traumatic brain injury (TBI)-induced attention deficits are among the most common long-term cognitive consequences in children. Most of the existing studies attempting to understand the neuropathological underpinnings of cognitive and behavioral impairments in TBI have utilized heterogeneous samples and resulted in inconsistent findings. The current research proposed to investigate topological properties of the structural brain network in children with TBI and their relationship with post-TBI attention problems in a more homogeneous subgroup of children who had severe post-TBI attention deficits (TBI-A).
Materials and Methods: A total of 31 children with TBI-A and 35 group-matched controls were involved in the study. Diffusion tensor imaging-based probabilistic tractography and graph theoretical techniques were used to construct the structural brain network in each subject. Network topological properties were calculated in both global level and regional (nodal) level. Between-group comparisons among the topological network measures and analyses for searching brain-behavioral were all corrected for multiple comparisons using Bonferroni method.
Results: Compared with controls, the TBI-A group showed significantly higher nodal local efficiency and nodal clustering coefficient in left inferior frontal gyrus and right transverse temporal gyrus, whereas significantly lower nodal clustering coefficient in left supramarginal gyrus and lower nodal local efficiency in left parahippocampal gyrus. The temporal lobe topological alterations were significantly associated with the post-TBI inattentive and hyperactive symptoms in the TBI-A group.
Conclusion: The results suggest that TBI-related structural re-modularity in the white matter subnetworks associated with temporal lobe may play a critical role in the onset of severe post-TBI attention deficits in children. These findings provide valuable input for understanding the neurobiological substrates of post-TBI attention deficits, and have the potential to serve as quantitatively measurable criteria guiding the development of more timely and tailored strategies for diagnoses and treatments to the affected individuals. This study provides a new insight into the neurobiological substrates associated with post-traumatic brain injury attention deficits (TBI-A) in children, by evaluating topological alterations of the structural brain network. The results demonstrated that relative to group-matched controls, the children with TBI-A had significantly altered nodal local efficiency and nodal clustering coefficient in temporal lobe, which strongly linked to elevated inattentive and hyperactive symptoms in the TBI-A group. These findings suggested that white matter structural re-modularity in subnetworks associated with temporal lobe may serve as quantitatively measurable biomarkers for early prediction and diagnosis of post-TBI attention deficits in children

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Brain Dev. 2021 Feb;43:186-91.

DO LOW BIRTH WEIGHT INFANTS NOT SEE EYES? FACE RECOGNITION IN INFANCY.

Yamamoto M, Konishi Y, Kato I, et al.

BACKGROUND: Progress in neonatal medicine has dramatically improved the survival rate of preterm births, but the evidence suggests that these low-birth weight infants (LBWIs) go on to develop pervasive

development disorders and attention deficit hyperactivity disorder (ADHD) at greater rates than the general population. Children with neurodevelopmental disorders are known to suffer from deficits in visual cognition, such as in face perception and attentional functions, the characteristics of which already manifest in early infancy.
PURPOSE: This study aimed to investigate visual cognition in LBWIs during infancy.
SUBJECTS: 20 LBWIs and 20 normal-birth-weight infants (NBWIs: control) of age 9-10 months (corrected age was used for LBWIs).
METHOD: Children were held seated in front of an eye tracking system by a parent, and presented with facial photos as visual stimuli. During the familiarization phase, the child was presented with two images of the same human face (familiarization stimulus) on the left and right side of a display screen (5x10 trials). Next, during the test phase, the child was presented with the same image on one side of the screen, and a photo of a different person's face (novel stimulus) on the other (2x5 trials). Gaze behavior was assessed in terms of the total time spent looking at either facial stimulus, and specifically at the eyes of the stimuli, as well as the number of attentional shifts between stimuli, and novelty preference.
RESULTS/DISCUSSION: LBWIs spent significant less time looking at facial stimuli overall, and less time at the eye region, than NBWIs. These findings seem to evidence developmental differences in functions related to visual cognition

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Brain Imaging Behav. 2021.

FUNCTIONAL ABNORMALITY IN THE SENSORIMOTOR SYSTEM ATTRIBUTED TO NRXN1 VARIANTS IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zhong Y, An L, Wang Y, et al.

Impaired sensorimotor circuits have been suggested in Attention-deficit/hyperactivity disorder (ADHD). NRXN1, highly expressed in cortex and cerebellum, was one of the candidate risk genes for ADHD, while its effects on sensorimotor circuits are unclear. In this content, we aimed to investigate the differential brain effects as functions of the cumulative genetic effects of NRXN1 variants in ADHD and healthy controls (HCs), identifying a potential pathway mapping from NRXN1, sensorimotor circuits, to ADHD. Magnetic resonance imaging, blood samples and clinical assessments were acquired from 53 male ADHD and 46 sex-matched HCs simultaneously. The effects of the cumulative genetic effects of NRXN1 variants valued by poly-variant risk score (PRS), on brain function was measured by resting-state functional connectivity (rs-FC) of cerebrocerebellar circuits. Mediation analyses were conducted to evaluate the association between NRXN1, functional abnormality, and ADHD diagnosis, as well as ADHD symptoms. The results were validated by bootstrapping and 10,000 times permutation tests. The rs-FC analyses demonstrated significant mediation models for ADHD diagnosis, and emphasized the involvement of cerebellum, middle cingulate gyrus and temporal gyrus, which are crucial parts of sensorimotor circuits. The current study suggested NRXN1 conferred risk for ADHD by regulating the function of sensorimotor circuits

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Brain Sciences. 2021;11.

IMPULSIVE AND OMISSION ERRORS: POTENTIAL TEMPORAL PROCESSING ENDOPHENOTYPES IN ADHD.

Acosta-Lopez JE, Suírez I, Pineda DA, et al.

Temporal processing (TP) is associated with functions such as perception, verbal skills, temporal perspective, and future planning, and is intercorrelated with working memory, attention, and inhibitory control, which are highly impaired in individuals with attention deficit hyperactivity disorder (ADHD). Here we evaluate TP measures as potential endophenotypes in Caribbean families ascertained from probands affected by ADHD. A total of 232 individuals were recruited and clinically evaluated using an extensive battery of neuropsychological tasks and reaction time (RT)-based task paradigms. Further, the heritability (genetic variance underpinning phenotype) was estimated as a measure of the genetics apportionment. A predictive framework for ADHD diagnosis was derived using these tasks. We found that individuals with ADHD differed from controls in neuropsycho-logical tasks assessing mental control, visual-verbal memory, verbal fluency, verbal, and semantic fluency. In addition, TP measures such as RT, errors, and variability were also affected in individuals with ADHD. Moreover, we determined that only omission and commission errors had significant

heritability. In conclusion, we have disentangled omission and commission errors as possible TP endophenotypes in ADHD, which can be suitable to assess the neurobiological and genetic basis of ADHD. A predictive model using these endophenotypes led to remarkable sensitivity, specificity, precision and classification rate for ADHD diagnosis, and may be a useful tool for patientsΓÇÖ diagnosis, follow-up, and longitudinal assessment in the clinical setting

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Brain Sciences. 2021;11.

PERINATAL ACETAMINOPHEN EXPOSURE AND CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): EXPLORING THE ROLE OF UMBILICAL CORD PLASMA METABOLITES IN OXIDATIVE STRESS PATHWAYS.

Anand NS, Raghavan R, Wang G, et al .

Oxidative stress mechanisms may explain associations between perinatal acetaminophen exposure and childhood attention-deficit hyperactivity disorder (ADHD). We investigated whether the changes in umbilical cord plasma amino acids needed to synthesize the antioxidant glutathione and in the oxidative stress biomarker 8-hydroxy-deoxyguanosine may explain the association between cord plasma acetaminophen and ADHD in the Boston Birth Cohort (BBC). MotherΓÇôchild dyads were followed at the Boston Medical Center between 1998 and 2018. Cord plasma analytes were measured from archived samples collected at birth. Physician diagnoses of childhood ADHD were obtained from medical records. The final sample consisted of 568 participants (child mean age [SD]: 9.3 [3.5] years, 315 (52.8%) male, 248 (43.7%) ADHD, 320 (56.3%) neurotypical development). Cord unmetabolized acetaminophen was positively correlated with methionine ($R = 0.33$, $p < 0.001$), serine ($R = 0.30$, $p < 0.001$), glycine ($R = 0.34$, $p < 0.001$), and glutamate ($R = 0.16$, $p < 0.001$). Children with cord acetaminophen levels >50th percentile appeared to have higher risk of ADHD for each increase in cord 8-hydroxy-deoxyguanosine level. Adjusting for covariates, increasing cord methionine, glycine, serine, and 8-hydroxy-deoxyguanosine were associated with significantly higher odds for childhood ADHD. Cord methionine statistically mediated 22.1% (natural indirect effect logOR = 0.167, SE = 0.071, $p = 0.019$) and glycine mediated 22.0% (natural indirect effect logOR = 0.166, SE = 0.078, $p = 0.032$) of the association between cord acetaminophen >50th percentile with ADHD. Our findings provide some clues, but additional investigation into oxidative stress pathways and the association of acetaminophen exposure and childhood ADHD is warranted

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Br J Psychiatry. 2021.

ASSESSMENT OF AGE-AT-ONSET CRITERION FOR ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Riglin L, Blakey R, Langley K, et al.

Summary To investigate the accuracy of the age-at-onset criterion in those who meet other DSM-5 criteria for attention-deficit hyperactivity disorder, using a prospective population cohort we compared four different approaches to asking those aged 25 years (n = 138) when their symptoms started. Receiver operating characteristic curves showed variation between the approaches ((3) = 8.99, P = 0.03); all four showed low discrimination against symptoms that had been assessed when they were children (area under the curve: 0.57-0.68). Asking adults to recall specific symptoms may be preferable to recalling at what age symptoms started. However, limitations to retrospective recall add to debate on the validity of ADHD age-at-onset assessment

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Child Adolesc Ment Health. 2021 Nov;26:303-09.

SELF-HARM AS THE FIRST PRESENTATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADOLESCENTS.

Ward JH, Curran S.

BACKGROUND: Self-harm (SH) in adolescence has previously been shown to significantly overlap with both attention deficit hyperactivity disorder (ADHD) and emotional dysregulation (ED). Our objective as such was to investigate the relationship between self-harm and ADHD in our population and consider its clinical relevance.

METHODS: This case series analysis examined 124 presentations of SH in 13- to 17 year-olds to Accident and Emergency Departments in South West London (97F:27M). Strength and Difficulties Questionnaires

(SDQs) were used to screen for ADHD/hyperactivity and ED, and scores were compared with reference data obtained from Meltzer et al. (1999, International Review of Psychiatry (Abingdon, England), 15, 185).
RESULTS: Mean SDQ ADHD/hyperactivity scores were significantly higher in our SH sample compared to reference data ($p < .0001$). Furthermore, significantly greater ED scores were found in our sample compared with the control reference data.
CONCLUSION: Our findings contribute to the evidence for an important link between ADHD and clinical presentations of SH and suggest there to be value in screening girls presenting to A&E with self-harm for ADHD. We speculate that ED plays a role in the evolution of SH in dysregulated ADHD. We recommend that clinicians assessing adolescents have self-harmed to be aware of possible ADHD symptoms and screen as appropriate; however, future research examining the temporal association between ADHD, emotional dysregulation and self-harm is required to establish causal direction

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Child Adolesc Ment Health. 2021 Nov;26:301-02.
EDITORIAL: NEW INSIGHTS INTO SELF-HARM AMONG CHILDREN AND YOUNG PEOPLE - RENEWED LINKS WITH INEQUALITY, NEW OPPORTUNITIES FOR RECOGNITION AND NEW TREATMENT OPTION.
Ani C.
Supporting children and young people (CYP) who self-harm (SH) is an important work of Child and Adolescent Mental Health Services (CAMHS). This theme is reflected in three papers in this issue. Starting with risk factors, Marraccini and colleagues found that compared with adolescents, preadolescent children with suicidal behavior were more likely to be male, from a Black ethnic background, or to have a neurodevelopmental disorder such as autism spectrum condition (ASC) or ADHD. These authors' finding of increased school-related stressors emphasizes the importance of educational adjustments in reducing the risk of SH among CYP with ASC and ADHD. Ward and Curran's study suggests that screening for ADHD symptoms among CYP who present with SH may improve early identification of those affected by ADHD-especially among females. Finally, Ramsey and colleagues found that coupling dialectical behavioral therapy (DBT) with a specific intervention targeting self-criticism reduced episodes of SH more than standard DBT alone. Given the link between SH and suicide, improving understanding of the risk factors, early identification, and new treatment options for SH remain important

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Child Adolesc Psychiatr Clin N Am. 2021 Apr;30:283-98.
WALKING ON EGGSHELLS: A PARENT'S JOURNEY RAISING AN EMOTIONALLY DYSREGULATED SON.
Pb J.
This article examines 2 themes in my 25-year journey raising a son with severe mood dysregulation, attention deficit with hyperactivity, and learning disabilities (MAL). Raising children with MAL significantly alters parents' own development, having to manage their children's chronic rages and aggression from toddlerhood through young adulthood. I propose a framework of periods parents go through, and describe a years-long progression of internal and behavioral adaptations necessary to parent these children effectively. The article suggests that more study is needed to understand how parents fare and what happens to them over time, and considers support that would improve their trajectory

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Child Adolesc Psychiatr Clin N Am. 2021 Jul;30:649-66.
THIS IS YOUR BRAIN ON IRRITABILITY: A CLINICIAN'S GUIDE TO UNDERSTANDING HOW WE KNOW WHAT WE KNOW NOW, AND WHAT WE NEED TO KNOW IN THE FUTURE, ABOUT IRRITABILITY IN CHILDREN AND ADOLESCENTS.
Dickstein DP, Barthelemy CM, Jenkins GA, et al.
Irritability is a common reason why children and adolescents are brought for psychiatric care. Although research is advancing what is known about the underlying brain and behavior mechanisms of irritability, clinicians often are shut out of that research. This article explains some of these research methods, providing brief summaries of what is known about brain/behavior mechanisms in disorders involving irritability, including bipolar disorder, disruptive mood dysregulation disorder, attention-deficit/hyperactivity disorder,

and autism spectrum disorder. Greater access to these methods may help clinicians now and in the future, with such mechanisms translated into improved care, as occurs in the treatment of childhood leukemia

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Child Adolesc Psychiatr Clin N Am. 2021 Jul;30:667-83.

CHRONIC IRRITABILITY IN YOUTH: A REPRISE ON CHALLENGES AND OPPORTUNITIES TOWARD MEETING UNMET CLINICAL NEEDS.

Leibenluft E, Kircanski K.

This commentary focuses on irritability, one subtype of emotion dysregulation. We review literature demonstrating that irritability is not a developmental phenotype of bipolar disorder, but is longitudinally associated with unipolar depression and anxiety and genetically associated with unipolar depression, anxiety, and attention-deficit hyperactivity disorder. We describe how irritability is amenable to translational research, in part because of the relevance of frustrative nonreward, a model developed in rodents, to human irritability. Last, we demonstrate how such research has suggested a novel exposure-based intervention for irritability

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Child Adolesc Psychiatr Clin N Am. 2021 Jan;30:143-57.

RESTLESS LEGS SYNDROME IN CHILDREN AND ADOLESCENTS.

DelRosso LM, Mogavero MP, Baroni A, et al.

Children with psychiatric comorbidities frequently are referred for evaluation of sleep complaints. Common sleep symptoms can include difficulty falling asleep, frequent nocturnal awakening, restless sleep, and symptoms of restless legs syndrome (RLS). The understanding of the sleep condition in relation to the psychiatric comorbidity often is a challenge to the physician and often sleep disorders remain undiagnosed, untreated, or undertreated. Restless legs syndrome has been associated with psychiatric comorbidities and with certain medications, such as antidepressants, antihistamines, and antipsychotics. This article reviews the presentation of RLS and restless sleep, the association with psychiatric comorbidities, and treatment options

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Child Adolesc Psychiatry Ment Health. 2021;15.

A RETROSPECTIVE MEDICAL CHART REVIEW OF CLINICAL OUTCOMES IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH GUANFACINE EXTENDED-RELEASE IN ROUTINE CANADIAN CLINICAL PRACTICE.

van Stralen J, Gill SK, Reaume CJ, et al.

Objective: This study evaluated clinical outcomes in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) treated with the +¦2-adrenoceptor agonist guanfacine extended-release (GXR) in routine Canadian clinical practice.

Methods: This retrospective chart review focused on patients with ADHD aged 6-17 years initiating treatment with GXR as monotherapy or adjunctive therapy. Patients were followed for up to 12 months after GXR initiation and, if they had received prior ADHD pharmacotherapy, for 12 months before GXR initiation. The primary outcome was change in ADHD symptoms and functionality based on physician assessments, classified as improvement, no change, or worsening relative to the time of GXR initiation. Treatment-emergent adverse events (TEAEs) were evaluated. Clinical outcomes were also analyzed post hoc according to whether GXR treatment was received as monotherapy or adjunctive therapy, and by select psychiatric comorbidities. Exploratory analyses were conducted in patients who had received prior ADHD pharmacotherapy to evaluate clinical outcomes after initiating GXR.

Results: Improvements in ADHD symptoms were reported for 232/330 (70.3%) patients. Functional improvements in school performance and home life were reported for 213/330 (64.5%) and 209/330 (63.3%) patients, respectively. The most frequent TEAEs (5%) were somnolence, headache, insomnia, presyncope, and decreased appetite. Improvements in ADHD symptoms were observed when GXR was received as either monotherapy (35/60 [58.3%]) or adjunctive therapy (197/270 [73.0%]). Improvements in ADHD symptoms and functionality were observed in the majority of patients with select psychiatric comorbidities.

Among patients who had experienced worsening of symptoms with prior ADHD pharmacotherapy, 44/54 (81.5%) experienced symptom improvement, 33/44 (75.0%) who had previously experienced worsening of school performance improved, and 34/48 (70.8%) who had previously experienced worsening of home life improved.
Conclusion: In Canadian routine clinical practice, most children and adolescents with ADHD treated with GXR experienced improvements in ADHD symptoms and in functionality both at school and at home

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Child Dev. 2021 Sep;92:2089-105.

IMPACT OF THE SCHOOL ENVIRONMENT ON MEDICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A POPULATION-WIDE REGISTER DATA STUDY OF SCHOOL-WIDE POSITIVE BEHAVIORAL INTERVENTIONS AND SUPPORTS.

Borgen NT, Frønes I, Raaum O.

Although attention deficit hyperactivity disorder (ADHD) is among the most heritable psychiatric childhood disorders, social and gene–environment interactions seemingly play an important role in the etiology of ADHD. Consistent with this, this study finds that School-Wide Positive Behavioral Interventions and Supports (SWPBIS) reduced the likelihood of pharmacotherapeutic treatment for ADHD at age 14–16 by 12%, using population-wide Norwegian register data and a difference-in-difference design (N = 698,364, birth cohorts 1990–2002, 48.7% girls, 5.7% immigrant background). At-risk students in schools with high fidelity of implementation are driving these intervention effects. Overall, the findings indicate that children with a genetic disposition for ADHD are more likely to avoid medical treatment in an organized and predictable school setting with a focus on positive reinforcement

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Child Neuropsychol. 2021.

THE MEDIATING ROLE OF ADHD SYMPTOMS BETWEEN EXECUTIVE FUNCTION AND SOCIAL SKILLS IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1.

Haebich KM, Dao DP, Pride NA, et al.

Children with neurofibromatosis type 1 (NF1) often experience executive dysfunction, attention deficit/hyperactivity disorder (ADHD) symptoms and poor social skills, however, the nature of the relationships between these domains in children with NF1 is unclear. This study investigated these relationships using primary caregiver ratings of executive functions, ADHD symptoms and social skills in children with NF1. Participants were 136 children with NF1 and 93 typically developing (TD) controls aged 3-15years recruited from 3 multidisciplinary neurofibromatosis clinics in Melbourne and Sydney, Australia, and Washington DC, USA. Mediation analysis was performed on primary outcome variables: parent ratings of executive functions (Behavior Rating Inventory of Executive Function, Metacognition Index), ADHD symptoms (Conners-3/Conners ADHD Diagnostic and Statistical Manual for Mental Disorders Scales) and social skills (Social Skills Improvement System-Rating Scale), adjusting for potential confounders (full scale IQ, sex, and social risk). Results revealed significantly poorer executive functions, elevated ADHD symptoms and reduced social skills in children with NF1 compared to controls. Poorer executive functions significantly predicted elevated ADHD symptoms and poorer social skills. Elevated ADHD symptoms significantly mediated the relationship between executive functions and social skills problems although did not fully account for social dysfunction. This study provides evidence for the importance of targeting ADHD symptoms as part of future interventions aimed at promoting prosocial behaviors in children with NF1

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Child Psychiatry Hum Dev. 2021 Oct;52:783-99.

PRENATAL AND POSTNATAL PREDICTIVE FACTORS FOR CHILDREN'S INATTENTIVE AND HYPERACTIVE SYMPTOMS AT 5 YEARS OF AGE: THE ROLE OF EARLY FAMILY-RELATED FACTORS.

Huhdanpää H, Morales-Muñoz I, Aronen ET, et al.

We examined several parent-reported prenatal and postnatal factors as potential risk factors for attention-deficit and hyperactivity disorder (ADHD) symptomatology in 5-year-old children. Our study is based on the CHILD-SLEEP birth cohort. Several parental questionnaires were collected prenatally (32nd pregnancy

week) and postnatally (i.e. child aged 3, 8, and 24 months and at 5 years). At 5 years of age, ADHD symptoms were assessed using questionnaires. Our main results showed that being a boy, parental depressive symptoms, more negative family atmosphere or a child's shorter sleep duration, and maternal authoritarian parenting style predicted inattentive/hyperactive symptoms. Maternal and paternal authoritative parenting style predicted less inattentive/hyperactive symptoms. Children with several risk factors together had the highest risk for inattentive/hyperactive symptoms. Our findings emphasise the need for early screening and treatment of parental mental health, and early evidence-based targeted parental support, to enable early intervention in those children at a risk of developing ADHD. (PsycInfo Database Record (c) 2021 APA, all rights reserved)

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Child Psychiatry Hum Dev. 2021 Aug;52:533-43.

ASSOCIATION BETWEEN PRESCRIBED HYPNOTICS IN INFANTS AND TODDLERS AND LATER ADHD: A LARGE COHORT STUDY FROM NORWAY.

HoldÃ¸ I, Bramness JG, Handal M, et al.

As previously indicated an association may exist between early sleep problems in infants and toddlers, and a diagnosis of attention deficit hyperactivity disorder (ADHD). The aim of this study was to study if this association could be replicated in a complete nationwide cohort of children. Prospective cohort study using national registries. All children born in Norway from January 2004 to December 2010 were included (Nâ€‰=â€‰410,555). Information on hypnotic drugs dispensed to children 0-3Â years of age outside of institutions was collected from the Norwegian Prescription Database and used as a proxy for sleep problems. The outcome ADHD (ICD-10), as diagnosed by specialists in the Child Mental Health Service, was obtained from the Norwegian Patient Registry. Data were analysed using weighted estimation in Cox regression. The unadjusted weighted hazard ratio (wHR) for a later diagnosis of ADHD in children dispensed two or more prescriptions for any hypnotic drug, compared to zero prescriptions, was 2.30 [95% confidence interval (CI) 1.63-3.23] for girls and 1.75 (95% CI 1.48-2.07) for boys. For the sedative antihistamine trimeprazine the corresponding wHR was 3.71 (95% CI 1.83-7.52) for girls and 2.78 (95% CI 2.04-3.80) for boys. After adjusting for parental ADHD and parental education the wHR for trimeprazine users was 2.81 (95% CI 1.34-5.88) for girls and 2.33 (95% CI 1.70-3.20) for boys. Infants and toddlers who were dispensed hypnotics had an increased risk of ADHD at school age. This association was most pronounced with the use of trimeprazine, a drug traditionally prescribed to toddlers for sleep problems in Norway. After adjusting for parental ADHD and educational level the risk for ADHD among the trimeprazine users was still more than twice the risk among controls

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Child Psychiatry Hum Dev. 2021 Dec;52:1131-42.

ATTENTION DEFICITS INFLUENCE THE DEVELOPMENT OF MOTOR ABNORMALITIES IN HIGH FUNCTIONING AUTISM.

Pitzianti M, Fagioli S, Pontis M, et al.

Early attentional dysfunction is one of the most consistent findings in autism spectrum disorder (ASD), including the high functioning autism (HFA). There are no studies that assess how the atypical attentional processes affect the motor functioning in HFA. In this study, we evaluated attentional and motor functioning in a sample of 15 drug-naive patients with HFA and 15 healthy children (HC), and possible link between attentional dysfunction and motor impairment in HFA. Compared to HC, HFA group was seriously impaired in a considerable number of attentional processes and showed a greater number of motor abnormalities. Significant correlations between attention deficits and motor abnormalities were observed in HFA group. These preliminary findings suggest that deficit of attentional processes can be implied in motor abnormalities in HFA

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Clin Child Fam Psychol Rev. 2020 Dec;23:577-604.

How to Improve Behavioral Parent and Teacher Training for Children with ADHD: Integrating Empirical Research on Learning and Motivation into Treatment.

Van der Oord S, Tripp G.

Attention deficit hyperactivity disorder [ADHD] is one of the most common psychiatric disorders of childhood with poor prognosis if not treated effectively. Recommended psychosocial evidence-based treatment for preschool and school-aged children is behavioral parent and teacher training [BPT]. The core elements of BPT are instrumental learning principles, i.e., reinforcement of adaptive and the ignoring or punishment of non-adaptive behaviors together with stimulus control techniques. BPT is moderately effective in reducing oppositional behavior and improving parenting practices; however, it does not reduce blinded ratings of ADHD symptoms. Also after training effects dissipate. This practitioner review proposes steps that can be taken to improve BPT outcomes for ADHD, based on purported causal processes underlying ADHD. The focus is on altered motivational processes (reward and punishment sensitivity), as they closely link to the instrumental processes used in BPT. Following a critical analysis of current behavioral treatments for ADHD, we selectively review motivational reinforcement-based theories of ADHD, including the empirical evidence for the behavioral predictions arising from these theories. This includes consideration of children's emotional reactions to expected and unexpected outcomes. Next we translate this evidence into potential ADHD-specific adjustments designed to enhance the immediate and long-term effectiveness of BPT programs in addressing the needs of children with ADHD. This includes the use of remediation strategies for proposed deficits in learning not commonly used in BPT programs and cautions regarding the use of punishment. Finally, we address how these recommendations can be effectively transferred to clinical practice

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Clin Child Psychol Psychiatry. 2021 Apr;26:518-30.

Relationship between sluggish cognitive tempo and sleep, psychological, somatic, and cognitive problems and impairment in children with autism and children with ADHD.

Mayes SD, Calhoun SL, Waschbusch DA.

Sluggish cognitive tempo (SCT) is a topic of renewed interest. Much remains to be learned about its association with symptoms and diagnoses that have received little research attention, particularly sleep disturbance, somatic complaints, and autism. Our study is the first to explore the relationship between SCT and sleep, internalizing, externalizing, somatic, and cognitive problems, impairment, and demographics in large samples of children with autism, ADHD-Combined, and ADHD-Inattentive. Mothers rated 1,436 children with autism and 1,056 with ADHD without autism, 2 to 17â€‰years, on the Pediatric Behavior Scale (PBS). Factor analysis yielded a 6-item SCT factor (sluggish/slow moving/low energy, stares/preoccupied/in own world, tires easily, in a fog/confused, drowsy/sleepy/not alert, and apathetic) plus 10 additional factors. SCT was distinct from but related to several factors and was associated with social and academic impairment. The strongest independent predictors of SCT were depression, sleeping more than normal, cognitive problems, autism, and somatic complaints. Scores on the remaining factors (sleep disturbance, attention deficit, impulsivity, hyperactivity, oppositional defiant disorder, conduct disorder, and anxiety) increased explained variance by less than 2%. Findings suggest that SCT is not simply sluggish cognitive tempo, as the name implies, and is a complex construct with behavioral, affective, emotional, cognitive, and somatic components and associations. Given that 49% of children with autism had SCT, SCT symptoms should be considered in all children being evaluated for autism, as well as for ADHD-C and ADHD-I (with SCT percentages of 31% and 40%). Assessing and treating SCT is especially important because of its association with impairment

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Clin Child Psychol Psychiatry. 2021 Jul;26:894-905.

Comorbid chronic tic disorder and Tourette syndrome in children requiring inpatient mental health treatment.

Zinna S, Luxton R, Papachristou E, et al.

OBJECTIVE: Children needing admission to an inpatient mental health unit often present with severe neuropsychiatric disorders characterised by complex psychopathology. We aimed to examine all admitted

children with comorbid chronic tic disorder (CTD) and Tourette syndrome (TS) over a 10-year period and determine the clinical significance of these diagnoses.
METHOD: A retrospective, naturalistic study was conducted, comparing children with and without CTD/TS in terms of co-morbid diagnoses, medication use, access to education, aggression contributing to the admission, duration of admission, functional outcomes and satisfaction with treatment. Data were analysed using Chi-square/Fisher's exact test and t-test for categorical and continuous variables, respectively, and subsequently with unadjusted and adjusted linear and logistic regression analyses.
RESULTS: A relatively high proportion of children had co-morbid CTD/TS (19.7%). There was a significant association with co-morbid obsessive-compulsive disorder, intellectual disability and autism spectrum disorder but not attention deficit hyperactivity disorder. CTD/TS were associated with longer admissions even after adjustments for confounding but did not seem to be independently associated with other examined clinical characteristics.
CONCLUSIONS: The prevalence of CTD/TS in children needing inpatient treatment is significant. In our sample, comorbid CTD/TS seem to represent a marker of overall symptom severity as evidenced by longer admissions

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Clin Child Psychol Psychiatry. 2021 Apr;26:505-17.

A MIXED METHODS STUDY OF CLINICIAN REPORTED CHALLENGES IN THE ASSESSMENT OF ADHD AND TREATMENT DECISIONS FOR CHILDREN WITH ADHD IN BRAZIL.

Honorio NF, Camargo AP, Polanczyk G, et al.

Objective: This ADHD national survey has obtained original data on the assessment and treatment of attention deficit hyperactivity disorder (ADHD) reported by Brazilian paediatricians and child psychiatrists; and has compared their practice.
Method: The study questionnaire was delivered to 165 neuro/community paediatricians and 272 child and adolescent psychiatrists. Quantitative and qualitative data were collected and analysed.
Results: Paediatricians assess children with a suspected ADHD, but do not feel confident to prescribe methylphenidate alone. Both paediatricians and child psychiatrists consider combined treatment of medication and psychotherapy more effective. Clinicians want to involve other professionals in the medical decisions but experience difficulties accessing specialist services, especially in public practice.
Conclusion: This study showed the impact of the public-private mix in the delivery of and access to appropriate assessment and treatment services for children with ADHD in Brazil

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Clin EEG Neurosci. 2022 Jan;53:12-23.

DETECTION OF ADHD FROM EEG SIGNALS USING DIFFERENT ENTROPY MEASURES AND ANN .

Catherine JR, Thomas GS, Albert RA, et al.

Attention deficit hyperactivity disorder (ADHD) is a prevalent behavioral, cognitive, neurodevelopmental pediatric disorder. Clinical evaluations, symptom surveys, and neuropsychological assessments are some of the ADHD assessment methods, which are time-consuming processes and have a certain degree of uncertainty. This research investigates an efficient computer-aided technological solution for detecting ADHD from the acquired electroencephalography (EEG) signals based on different nonlinear entropy estimators and an artificial neural network classifier. Features extracted through fuzzy entropy, log energy entropy, permutation entropy, SURE entropy, and Shannon entropy are analyzed for effective discrimination of ADHD subjects from the control group. The experimented results confirm that the proposed techniques can effectively detect and classify ADHD subjects. The permutation entropy gives the highest classification accuracy of 99.82%, sensitivity of 98.21%, and specificity of 98.82%. Also, the potency of different entropy estimators derived from the t-test reflects that the Shannon entropy has a higher P-value (>.001); therefore, it has a limited scope than other entropy estimators for ADHD diagnosis. Furthermore, the considerable variance found from potential features obtained in the frontal polar (FP) and frontal (F) lobes using different entropy estimators under the eyes-closed condition shows that the signals received in these lobes will have more significance in distinguishing ADHD from normal subjects

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Clin J Sport Med. 2021 Sep;31:438-41.

MIDDLE SCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER HAVE A GREATER CONCUSSION HISTORY.

Iverson GL, Kelshaw PM, Cook NE, et al.

OBJECTIVE: Examine lifetime history of concussions in middle school student athletes who have attention-deficit/hyperactivity disorder (ADHD).
DESIGN: Cross-sectional study.
SETTING: Nine middle schools in Virginia, USA.
PARTICIPANTS: A sample of 1037 middle school students (ages 11-14 years, M = 12.6, SD = 0.93; 45.8% girls) underwent baseline/preseason assessments during the 2017 to 2018 academic year and self-reported their health history, including whether or not they had been diagnosed with ADHD. Athletes were divided into 2 groups, those with ADHD (n = 71; 6.8%) and control subjects (n = 966).
INDEPENDENT VARIABLES: Self-reported diagnosis of ADHD and self-identified sex. MAIN OUTCOME MEASURES: Self-reported concussion history.
RESULTS: In the total sample, boys were more likely to report a previous history of concussion than girls [Ï‡2(1) = 10.81, P = 0.001; odds ratio (OR) = 1.92; 95% confidence interval (CI), 1.30-2.85]. The rate of previous concussion in children with ADHD (23.9%) was twice the rate of previous concussion among children without ADHD (11.4%) [Ï‡2(1) = 9.70, P = 0.002; OR = 2.45; 95% CI, 1.37-4.38]. Approximately 1 in 4 boys with ADHD (24.5%) and 1 in 5 girls with ADHD (22.2%) reported having sustained one or more previous concussions.
CONCLUSIONS: Attention-deficit/hyperactivity disorder is associated with a greater prevalence of previous concussion in middle school children. Further research is needed to understand the risk of sustaining concussion for young athletes with ADHD, as well as short- and long-term outcomes of concussion among young athletes with ADHD

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Clin J Sport Med. 2021 Jul;31:e188-e192.

PRESEASON VESTIBULAR OCULAR MOTOR SCREENING IN CHILDREN AND ADOLESCENTS.

Iverson GL, Cook NE, Howell DR, et al.

OBJECTIVES: The primary purpose of this study was to examine vestibular/ocular motor screening (VOMS) test performance in a sample of healthy youth ice hockey players. A particular focus was to investigate the potential effects of age and pre-existing health conditions, including concussion history, attention-deficit/hyperactivity disorder (ADHD), learning disability (LD), headaches/migraines, and depression/anxiety on preseason baseline VOMS performance, including the near point of convergence (NPC) distance. DESIGN: Cross-sectional cohort.
SETTING: Outpatient physiotherapy clinic.
PARTICIPANTS: Three hundred eighty-seven male youth hockey players, with an average age of 11.9 years (SD = 2.2, range = 8-17), completed the VOMS and responded to self- or parent-reported demographic and medical history questionnaires during preseason baseline assessments.
INDEPENDENT VARIABLES ASSESSED: Age, sex, and mental and physical health history including ADHD, headaches, depression, anxiety, migraine, and LD.
OUTCOME MEASURE: Vestibular/ocular motor screening.
RESULTS: The large majority of boys scored within normal limits on the VOMS, ie, they reported no symptom provocation of more than 2 points on any VOMS subset (89%) and had a normal NPC distance, ie, <5 cm (78%). The individual VOMS subtests had low abnormality rates, and demographic and pre-existing health conditions, such as age, headache or migraine history, previous neurodevelopmental conditions, or mental health problems, were not associated with clinically meaningful symptom provocation during the VOMS.
CONCLUSIONS: There was a low rate of abnormal findings for the individual VOMS subtests, with the exception of NPC distance, among male youth hockey players during preseason assessment

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Clin J Sport Med. 2021 Sep;31:e229-e234.

SEX DIFFERENCES AND REPORTING OF SCAT-5 CONCUSSION SYMPTOMS IN ADOLESCENT ATHLETES.

Bunt SC, Didehbani N, Tarkenton T, et al.

OBJECTIVE: To elucidate specific symptoms that may differ between adolescent female and male athletes after a sports-related concussion (SRC) and identify symptoms that may require greater clinical attention by medical and athletic staff.

DESIGN: Prospective.

SETTING: This study is part of a larger research project conducted at clinics in the North Texas Concussion Network (ConTex) Registry.

PARTICIPANTS: Subjects (N = 491) aged 12 to 18 years who sustained a diagnosed SRC within 30 days of clinic visit.

INDEPENDENT VARIABLES: Sex (female vs male). Covariates included age, race, current mood (anxiety and depression), learning disability/ADHD, and time to clinic.

MAIN OUTCOME MEASURES: Twenty-two individual postconcussion symptoms as measured by the Post-Concussion Symptom Scale from the Sport Concussion Assessment Tool-5 (SCAT-5).

RESULTS: Girls endorsed higher levels of anxiety and depression symptoms at initial clinic visit. analysis of covariance results revealed that girls had significantly greater symptom severity of headache, dizziness, sensitivity to light, sensitivity to noise, pressure in the head, feeling slowed down, fatigue, and drowsiness than boys. Ordinal logistic regression results also revealed that girls had significantly greater predicted odds of higher symptom severity on these 8 symptoms and in trouble concentrating than boys.

CONCLUSIONS: Closer examination of specific symptoms with attention to patients' current levels of anxiety and depression symptoms may better inform medical and athletic staff to anticipate and address symptoms that may present greater challenges for adolescent girls than boys

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Clin J Sport Med. 2021 Sep;31:e240-e244.

TEST ORDER DOES NOT AFFECT VESTIBULAR/OCULAR MOTOR SCREENING ITEM SCORES IN HIGH SCHOOL ATHLETES.

D'Amico NR, Elbin RJ, Sufrinko A, et al.

OBJECTIVE: To compare VOMS item scores between a fixed and randomized administration order in a sample of nonconcussed high school athletes.

DESIGN: Post-test only, quasi-experimental design.

SETTING: Local high schools in a mid-west region of the United States.

PATIENTS: Fifty nonconcussed high school athletes (M = 15.64; SD = 1.12 years) completed the VOMS in a randomized testing order (RANDOM), and 49 (M = 15.64; SD = 1.12 years) completed the VOMS in the fixed testing order (FIXED). The groups were matched on age, sex, learning disorder, attention-deficit/hyperactivity disorder, concussion history, and baseline concussion symptoms.

INTERVENTIONS: The Vestibular/Ocular Motor Screening (VOMS) tool comprises pretest symptoms, smooth pursuit (SP), horizontal/vertical saccade (HSAC/VSAC), average near-point of convergence (NPC) distance, convergence symptoms, horizontal/vertical vestibular ocular reflex (HVOR/VVOR), and visual motion sensitivity (VMS).

MAIN OUTCOME MEASURES: Mann-Whitney U tests were performed to examine differences between FIXED and RANDOM groups on VOMS items. RANDOM scores were rearranged in order of administration and combined with the FIXED group scores, and a Freidman test was performed for repeated measures.

RESULTS: There were no significant differences between FIXED and RANDOM groups on VOMS pretest symptoms (U = 1171, P = 0.57), SP (U = 1122.5, P = 0.35), HSAC (U = 1128.5, P = 0.44), VSAC (U = 1055.5, P = 0.16), convergence symptoms (U = 1129.0, P = 0.41), average NPC distance (U = 979.0, P = 0.06), HVOR (U = 1085.0, P = 0.25), VVOR (U = 1126.0, P = 0.41), and VMS scores (U = 1101.0, P = 0.32). When VOMS items were rearranged and the sample was combined, there were no differences for repeated measures [Ï‡2 (6) = 9.92, P = 0.13].

CONCLUSIONS: There were no significant differences on VOMS items between FIXED and RANDOM groups for repeated measures. The testing order of VOMS items does not affect VOMS scores in nonconcussed high school athletes

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Clin Linguist Phon. 2021 Jul;35:690-705.

THE EFFECT OF PICTURE SUPPORT ON NARRATIVE RETELLS IN SWEDISH ADOLESCENTS WITH ADHD.

Bergman A, Hallin AE.

ADHD is characterized by executive functioning (EF) deficits, which in turn may affect language, and therefore EF demands in language assessment tasks are important to consider. This study aims to inform clinical practice by 1) comparing and describing narrative retells in Swedish adolescents with and without ADHD, and 2) investigating the effects of picture support on narration in the two groups. Fifteen adolescents with ADHD and 31 with typical development (TD) participated. Two carefully matched narratives for retelling, one with and one without picture support were administered, transcribed, and analyzed regarding content and linguistic complexity (macro- and microlevel measures). The results showed that the ADHD group included less content than the TD group in both tasks, measured in fewer story grammar units and details. Both groups included more story grammar units in the task without picture support. The TD group had shorter retells with higher syntactic complexity in the task with picture support compared to the task without picture support. Compared to TD peers, retells without picture support from the ADHD group were significantly shorter and had a higher proportion of grammatical errors. These results show different strengths and weaknesses in the two groups and indicate that the narrative task without picture support, which places higher demands on EF, captured a linguistic vulnerability in the ADHD group. In conclusion, the choice of narrative task is important to consider in clinical practice to enable accurate descriptions of linguistic strengths and weaknesses in individuals with ADHD, and aid in differential diagnosis

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Clin Neuropharmacol. 2021 Mar;44:68-70.

ATOMOXETINE REDUCED BINGE/PURGE SYMPTOMS IN A CASE OF ANOREXIA NERVOSA BINGE/PURGE TYPE.

Wilfahrt RP, Wilfahrt LG, Matthews HA.

Psychopharmacologic treatments for eating disorders (EDs) remain unclear, particularly for anorexia nervosa. As in attention-deficit hyperactivity disorder, a dopaminergic mechanism has been implicated in EDs, prompting our use of atomoxetine in an 18-year-old woman with anorexia nervosa, binge/purge type. Atomoxetine is a highly selective norepinephrine reuptake inhibitor with nonaddictive properties and limited effects of appetite suppression. Doses followed those used in a previous trial of atomoxetine in the treatment of binge ED, and response was assessed over 4 months, with significant improvement in ED behaviors and mood. Larger-scale, randomized studies that assess the efficacy of atomoxetine in the treatment of anorexia nervosa, binge/purge type are warranted

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Clin Psychol Rev. 2021 Feb;83:101954.

COGNITIVE BEHAVIOR THERAPY FOR EXTERNALIZING DISORDERS IN CHILDREN AND ADOLESCENTS IN ROUTINE CLINICAL CARE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Riise EN, Wergeland GJH, Njardvik U, et al.

Various Cognitive Behavioral Therapy (CBT) programs for externalizing disorders in children and adolescents are supported by a substantial body of empirical evidence. Most of the research evidence comes from efficacy studies conducted in university settings, but there is less knowledge about the effect of these treatments in routine clinical care. The purpose of this meta-analysis was to investigate the effectiveness of CBT in non-university settings for Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD). Embase OVID, Ovid MEDLINE and PsycINFO were systematically searched for eligible studies published up to May 2020. In total, 51 treatment effectiveness studies involving 5295 patients were included. The average within-group effect size at post-treatment was significant (g=0.91), and there were large effect sizes for both ADHD (g=0.80) and CD/ODD (g=0.98). At post treatment, remission rates were 38% for ADHD and 48% for CD/ODD, and the overall attrition rate was 14%. Benchmarking against efficacy studies showed that CBT in routine clinical care yields remission rates, within-group effect sizes and attrition rates that are very similar to those found in university settings. The findings support the transportability of CBT for externalizing disorders from university settings to routine clinical care. PROSPERO registration: CRD42020147524

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Clin Transl Sci. 2021 Jan;14:412-21.

RETROSPECTIVE REVIEW OF PHARMACOGENETIC TESTING AT AN ACADEMIC CHILDREN'S HOSPITAL.

Roberts TA, Wagner JA, Sandritter T, et al.

There is limited evidence to support pharmacogenetic (PGx) testing in children. We conducted a retrospective review of PGx testing among 452 patients at an academic children's hospital to determine the potential utility of PGx in diseases of childhood and to identify targets for future pediatric pharmacogenetic research. An actionable gene-drug pair associated with the 28 genes tested (Clinical Pharmacogenetics Implementation Consortium (CPIC) level A or B, Pharmacogenomics Knowledge Base (PharmGKB) level 1A or B, or US Food and Drug Administration (FDA) recommendation and a PharmGKB level) was present in 98.7% of patients. We identified 203 actionable gene-drug-diagnosis groups based on the indications for each actionable drug listed in Lexicomp. Among patients with an actionable gene-drug-diagnosis group, 49.3% had a diagnosis where the drug was a therapeutic option and PGx could be used to guide treatment selection. Among patients with an associated diagnosis, 30.9% had a prescription for the actionable drug allowing PGx guided dosing. Three genes (CYP2C19, CYP2D6, and CYP3A5) accounted for all the gene-drug-diagnosis groups with matching diagnoses and prescriptions. The most common gene-drug-diagnosis groups with matching diagnoses and prescriptions were CYP2C19-citalopram-escitalopram-depression 3.3% of patients tested; CYP2C19-dexlansoprazole-gastritis-esophagitis 3.1%; CYP2C19-omeprazole-gastritis-esophagitis 2.4%; CYP2D6-atomoxetine-attention deficit hyperactivity disorder 2.2%; and CYP2C19-citalopram-escitalopram-obsessive-compulsive disorder 1.5%. PGx could be used to guide selection of current treatment options or medication dosing in almost half (48.7%) of pediatric patients tested. Mood disorders and gastritis/esophagitis are promising targets for future study of PGx testing because of the high prevalence of these diagnoses and associated actionable gene-drug pairs in the pediatric population

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Clin Case Stud. 2021.

A CONTROLLED EVALUATION OF A SPORT-SPECIFIC PERFORMANCE OPTIMIZATION PROGRAM IN AN ATHLETE DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND OPPOSITIONAL DEFIANT DISORDER WITHIN THE CONTEXT OF COVID-19.

Phrathep D, Donohue B, Kraus S, et al.

Adolescent athletes with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) experience unique challenges that impact their sport performance, such as making errors due to poor concentration. The current multiple-baseline across behaviors case trial (i.e., positive assertion and negative assertion) is an evaluation of The Optimum Performance Program in Sports in an adolescent athlete diagnosed with ADHD and ODD. Intervention skill sets were targeted sequentially in a virtual format to safeguard against COVID-19 contraction. A battery of psychological measures was administered at baseline, post-intervention, and 1-month follow-up. Results indicated negative and positive assertion skills improved, but only when targeted, and severity of ADHD and ODD symptom severity, general mental health symptoms, and factors interfering with sport performance decreased from pre- to post-intervention and these improvements were maintained at 1-month follow-up. Similar improvements occurred in relationships with coaches, teammates, and family. Treatment integrity and consumer satisfaction were high

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Cogn Process. 2021 Nov;22:659-73.

DIVERSE PATTERNS OF VULNERABILITY TO VISUAL ILLUSIONS IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Makris G, Pervanidou P, Chouliaras G, et al.

Research on how children with neurodevelopmental disorders perceive, process, and interpret visual illusions (VIs) has been extensively focused on children with autism spectrum disorder providing controversial findings. In this study, we investigated the patterns of vulnerability to a wide set of VIs comprising 23 standard text book VIs and their variations in a clinical sample of children with neurodevelopmental disorders compared to typically developing children (TD). A total of 176 children, aged between 4.6 and 13.8 years old, were distributed into four groups: high-functioning autism (HFA; N=23), attention-deficit/hyperactivity disorder (ADHD; N=42), specific learning disorder (SLD; N=70), and TD (N=41). Regression models, adjusted for sex,

age, and non-verbal IQ, showed that HFA was associated with greater responses accuracy than TD children to the full battery of VIs, to the cognitive illusions, to the distortions, and to both geometrical illusions of size/shape (cognitive distortions) and lightness contrast effects (physical distortions). The susceptibility of ADHD children was found attenuated for illusory contours and greater for paradoxical illusions in comparison with TD children. No significant differences were shown between the SLD group and the TD children. Our findings, which were adjusted for the same duration of visual working memory across groups, showed that there is a potential specific tendency of HFA children to failure of processing visual information in context. Contrarily, children with ADHD showed in general normal global processing such as children diagnosed with SLD

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Computers in Biology and Medicine. 2021;134.

EFFECTIVE CONNECTIVITY IN BRAIN NETWORKS ESTIMATED USING EEG SIGNALS IS ALTERED IN CHILDREN WITH ADHD.

Abbas AK, Azemi G, Amiri S, et al.

This study presents a methodology developed for estimating effective connectivity in brain networks (BNs) using multichannel scalp EEG recordings. The methodology uses transfer entropy as an information transfer measure to detect pair-wise directed information transfer between EEG signals within +¦, +©, +¦, +¦ and +¦-bands. The developed methodology is then used to study the properties of directed BNs in children with attention-deficit hyperactivity disorder (ADHD) and compare them with that of the healthy controls using both statistical and receiver operating characteristic (ROC) analyses. The results indicate that directed information transfer between scalp EEG electrodes in the ADHD subjects differs significantly compared to the healthy ones. The results of the statistical and ROC analyses of frequency-specific graph measures demonstrate their highly discriminative ability between the two groups. Specifically, the graph measures extracted from the estimated directed BNs in the +¦-band show the highest discrimination between the ADHD and control groups. These findings are in line with the fact that +¦-band reflects active concentration, motor activity, and anxious mental states. The reported results show that the developed methodology has the capacity to be used for investigating patterns of directed BNs in neuropsychiatric disorders

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Curr Opin Psychol. 2020 Aug;34:105-11.

SLEEP PROBLEMS, BEHAVIOR, AND PSYCHOPATHOLOGY IN AUTISM: INTER-RELATIONSHIPS ACROSS THE LIFESPAN.

Schreck KA, Richdale AL.

Across the lifespan, autistic individuals experience symptomatology concomitant with their diagnosis including increased rates of daytime behavior (e.g. stereotypy, self-injurious behavior, and aggression) and psychopathology (e.g. attention deficit hyperactivity disorder, anxiety, and depression). In addition to this inter-related behavior and psychopathology, autistic children, adolescents, and adults consistently exhibit a wide variety of sleep problems (e.g. insomnia, reduced total sleep time, increased sleep onset latency, night waking, etc.). Early research and current research continue to describe the inter-relatedness among these daytime behaviors, psychopathology, and sleep problems for autistic individuals. Although descriptions of these issues appear in research, only preliminary suggestions exist for the causes and contributors toward the sleep problems or the interactions of sleep problems with psychopathology, although current research suggests a possible biopsychosocial interaction

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Curr Psychol. 2021 25;1-17.

INVESTIGATING THE EFFECTS OF COVID-19 LOCKDOWN ON ITALIAN CHILDREN AND ADOLESCENTS WITH AND WITHOUT NEURODEVELOPMENTAL DISORDERS: A CROSS-SECTIONAL STUDY.

Termine C, Dui LD, Borzaga L, et al.

We conducted a cross-sectional study to compare the impact of social distancing and lifestyle changes that occurred during Corona Virus Disease 2019 (COVID-19) lockdown on children and adolescents with and without Neurodevelopmental Disorders (NDDs). An online questionnaire was administered in order to investigate the effects of NDD condition, socio-demographic status, familiar/home environment and COVID-

19 exposure on their lives during a two months period of social isolation. We used logistic regression, focusing on five endpoints (remote learning, lifestyle, stress/anxiety, sociality, scolding) to define the extent of these effects. Most questions were paired up to parents and children, to verify the occurrence of agreement. 8305 questionnaires were analyzed, 1362 of which completed by NDDs and 6943 by controls. Results showed that the presence of a NDD, compared to controls, had a significant impact on: Remote Learning (i.e. subjects with NDDs experienced more difficulties in attending online classes and studying), Sociality (i.e. subjects with NDDs missed their schoolmates less), Scolding (i.e. subjects with NDDs were scolded more often) and Anxiety (i.e. subjects with NDDs were perceived by their parents as more anxious). Substantial agreement between parents and children arose from questions concerning Remote learning, Lifestyle and Scolding. The current study actually points out that having a NDD gives account for a stronger influence on school performance and on behavioral and psychological aspects, during a two months lockdown. Such results may provide useful information to governments and school authorities on how carrying through supportive strategies for youth affected by NDDs.
Supplementary information: The online version contains supplementary material available at 10.1007/s12144-021-02321-2

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Cytokine. 2020 Sep;133:155152.

CYTOKINE EXPRESSION PROFILES IN AUTISM SPECTRUM DISORDER: A MULTI-CENTER STUDY FROM TURKEY.

Kutuk MO, Tufan E, Gokcen C, et al.

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in communication and social interaction as well as restricted interests and repetitive behaviors. The pathogenesis of ASD is not completely understood, but a growing body of research has demonstrated that the immune response may be a contributing factor in the etiology and/ or ontogeny of ASD. The aim of this study was to determine the expression levels of IL-1Î², IL-1Î±, IL-4, IL-6, IL-17, TNF-Î± and TGF-Î² in peripheral blood mononuclear cells of children with ASD and healthy controls in order to determine the contributions of cytokines to ASD. Within the study timeframe, 195 children with ASDs (80.5% male) and 162 controls (73.6% male) were enrolled. Most children with ASD had a comorbid disorder (n=114, 58.5%), with the most common diagnoses as Intellectual Developmental Disorder (IDD, n=64, 32.8%) and ADHD (n=64, 32.8%). The majority of children with ASD had severe autistic symptoms as evaluated via Childhood Autism Rating Scale (CARS, n=130, 64.6%). The mean CARS score in the ASD sample was 40.8 (S.D.=7.6). The patients with ASD were found to have significantly higher levels of IL-6 ($p<0.001$) and significantly lower levels of IL-17 ($p<0.05$, all Bonferroni corrected). Treatment tended to affect IL-4 levels. Lastly, discriminant function analysis (DFA) revealed that a combination of IL-6, IL-17 and IL-1Î± correctly classified 56.6% of cases. Despite extensive immunological evidence suggesting immune system aberrations, further research is required to clarify the relationship between immune profiles and ASD symptoms

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Dev Med Child Neurol. 2021 Aug;63:954-62.

MENTAL HEALTH, NEURODEVELOPMENTAL, AND FAMILY PSYCHOSOCIAL PROFILES OF CHILDREN BORN VERY PRETERM AT RISK OF AN EARLY-ONSET ANXIETY DISORDER.

Morris AR, Bora S, Austin NC, et al.

AIM: To compare the mental health and neurodevelopmental profiles of school-age children born very preterm, with and without an anxiety disorder, and to identify neonatal medical, psychosocial, and concurrent neurodevelopmental correlates.
METHOD: A regional cohort of 102 (51 males, 51 females) children born very preterm (mean [SD] gestation at birth=28wks [2], range=23-31wks) was studied from birth to age 9Â years alongside a comparison group of 109 (58 males, 51 females) children born at term (mean [SD] gestation at birth=40wks [1], range=38-41wks). At age 9Â years, all children underwent a neurodevelopmental evaluation while parents were interviewed using the Development and Well-Being Assessment to diagnose a range of DSM-IV childhood psychiatric disorders. Detailed information was also available about the children's neonatal medical course and postnatal psychosocial environment, including maternal mental health and parenting.

RESULTS: At age 9 years, 21% (n=21) of very preterm and 13% (n=14) of term-born children met diagnostic criteria for an anxiety disorder. Clinically-anxious children born very preterm were characterized by higher rates of comorbid mental health (odds ratio [OR]=11.5, 95% confidence interval [CI]=3.8-34.7), social (OR=6.2, 95% CI=2.1-18.4), motor (OR=4.4, 95% CI=1.6-12.2), and cognitive (OR=2.6, 95% CI=1.0-7.0) problems than those without an anxiety disorder. Concurrent maternal mental health and child social difficulties were the strongest independent correlates of early-onset child anxiety disorders.
INTERPRETATION: Children born very preterm who developed an early-onset anxiety disorder were subject to high rates of comorbid problems. Findings highlight the importance of addressing both maternal and child mental health issues to optimize outcomes in this high-risk population. What this paper adds One out of five school-age children born very preterm are likely to meet DSM-IV diagnostic criteria for an anxiety disorder. Half of these children born very preterm with an early-onset anxiety disorder have comorbid attention-deficit/hyperactivity disorder. Other neurodevelopmental correlates of early-onset anxiety disorders include lower cognitive ability, motor problems, and peer social difficulties. Concurrent maternal mental health and child social adjustment problems were the strongest correlates of early-onset anxiety disorder risk among children born very preterm

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Dev Psychol. 2021 Aug;57:1359-71.

GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO CO-OCCURRING ADHD AND EMOTIONAL PROBLEMS IN SCHOOL-AGED CHILDREN.

Gustavson K, Torvik FA, Eilertsen EM, et al.

Children with attention deficit hyperactivity disorder (ADHD) often experience co-occurring emotional problems. ADHD with this comorbidity is associated with poorer outcomes than ADHD without comorbidity. Better understanding of the etiology of comorbidity could improve prevention of negative outcomes for children with ADHD. The sample consisted of 567 twin pairs, 3,632 sibling pairs, and 2,340 cousin pairs from the Norwegian Mother, Father and Child Cohort Study. Mothers rated offspring symptoms of ADHD, anxiety, and depression at 8 years of age. Biometric modeling was performed to examine genetic and environmental contributions to co-occurring symptoms of ADHD and emotional problems in the children. We fitted four variable (inattention, hyperactivity/impulsivity, anxiety, and depression) covariance matrices of additive genetic, common environmental, twin- and individual-specific environmental effects. Genetic, shared environmental, and individual-specific environmental factors contributed to the correlation between ADHD and depression. The pattern was similar for both inattention and hyperactivity/impulsivity. Familial risk factors (genetic and shared environment), but not individual-specific environmental factors contributed to the positive correlations between each of the two ADHD subdomains and anxiety. The genetic contributions to ADHD-depression comorbidity only partly overlapped with genetic contributions to ADHD-anxiety comorbidity. Our findings indicate that shared risk factors for ADHD and comorbid depression were familial as well as individual-specific, while shared risk factors for ADHD and comorbid anxiety were primarily familial

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Dev Psychopathol. 2021 Oct;33:1351-67.

CHILDHOOD PREDICTORS AND MODERATORS OF LIFETIME RISK OF SELF-HARM IN GIRLS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Meza JI, Owens EB, Hinshaw SP.

Attention-deficit/hyperactivity disorder (ADHD) is associated with self-harm during adolescence and young adulthood, especially among females. Yet little is known about the developmental trajectories or childhood predictors/moderators of self-harm in women with and without childhood histories of ADHD. We characterized lifetime risk for nonsuicidal self-injury (NSSI), suicidal ideation (SI), and suicide attempts (SA), comparing female participants with (n = 140) and without (n = 88) childhood ADHD. We examined theory-informed childhood predictors and moderators of lifetime risk via baseline measures from childhood. First, regarding developmental patterns, most females with positive histories of lifetime self-harm engaged in such behaviors in adolescence yet desisted by adulthood. Females with positive histories of self-harm by late adolescence emanated largely from the ADHD-C group. Second, we found that predictors of NSSI were early externalizing symptoms, overall executive functioning, and father's negative parenting; predictors of SI were

adverse childhood experiences and low self-esteem; and predictors of SA were early externalizing symptoms, adverse childhood experiences, and low self-esteem. Third, receiver operating characteristics analyses helped to ascertain interactive sets of predictors. Findings indicate that pathways to self-harm are multifaceted for females with ADHD. Understanding early childhood predictors and moderators of self-harm can inform both risk assessment and intervention strategies

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Dev Cognitive Neurosci. 2021;52.

PREDICTING MULTISCAN MRI OUTCOMES IN CHILDREN WITH NEURODEVELOPMENTAL CONDITIONS FOLLOWING MRI SIMULATOR TRAINING.

Simhal AK, Filho JOA, Segura P, et al.

Pediatric brain imaging holds significant promise for understanding neurodevelopment. However, the requirement to remain still inside a noisy, enclosed scanner remains a challenge. Verbal or visual descriptions of the process, and/or practice in MRI simulators are the norm in preparing children. Yet, the factors predictive of successfully obtaining neuroimaging data remain unclear. We examined data from 250 children (6ΓÇô12 years, 197 males) with autism and/or attention-deficit/hyperactivity disorder. Children completed systematic MRI simulator training aimed to habituate to the scanner environment and minimize head motion. An MRI session comprised multiple structural, resting-state, task and diffusion scans. Of the 201 children passing simulator training and attempting scanning, nearly all (94%) successfully completed the first structural scan in the sequence, and 88% also completed the following functional scan. The number of successful scans decreased as the sequence progressed. Multivariate analyses revealed that age was the strongest predictor of successful scans in the session, with younger children having lower success rates. After age, sensorimotor atypicalities contributed most to prediction. Results provide insights on factors to consider in designing pediatric brain imaging protocols

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Epilepsy Res. 2020 Nov;167:106351.

NEUROCOGNITIVE PROFILES OF PEDIATRIC PATIENTS WITH ESES, GENERALIZED EPILEPSY, OR FOCAL EPILEPSY.

Ng R, Hodges E.

To date, the neurocognitive profile and comorbid psychiatric risks associated with ESES, a syndrome that commonly coincides with a seizure disorder, in contrast to generalized or partial/focal epilepsy without ESES remains unclear. Accordingly, this preliminary study aimed to characterize the neurocognitive differences across pediatric patients with ESES, generalized or focal epilepsy, and risk for comorbid diagnoses (mood disorder, autism, intellectual disability, learning disability, ADHD). We included data from a total of 79 pediatric patients, including those with recently diagnosed ESES (N = 12), generalized epilepsy (GE, N = 25), left focal epilepsy (LFE; N = 20), or right focal epilepsy (RFE; N = 22). All patients completed a neurocognitive evaluation as part of their medical workup and treatment for epilepsy. Cognitive domains assessed include intellectual functioning, verbal/non-verbal reasoning, working memory, processing speed, receptive language, learning and memory. Results showed that children with GE performed more poorly across intellectual functioning, verbal and non-verbal reasoning, working memory, processing speed, and receptive vocabulary; whereas, these areas were most preserved among those with RFE. Working memory and processing speed among those recently diagnosed with ESES was also modestly stronger compared to the GE group. A greater proportion of patients with GE met diagnostic criteria for a learning disability relative to other epilepsy types, although the rates of ADHD, autism spectrum, intellectual disability, and mood disorder were comparable across groups. Findings provide supporting evidence that GE may be associated with greater cognitive risks when refractory to treatment, highlighting the need for earlier intervention services to circumvent adverse effects on adaptive and behavioral functioning. Neuropsychological differences between ESES versus other epilepsy subtypes may emerge as a late-effect of the neurological condition and/or related medication treatment, implicating a greater need for developmentally focused investigations

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Epilepsy Res. 2020 Dec;168:106489.

CHILDHOOD-ONSET SEIZURES: A LONG-TERM COHORT STUDY OF USE OF ANTIEPILEPTIC DRUGS, AND DRUGS FOR NEUROPSYCHIATRIC CONDITIONS.

Ãndell E, Tomson T, et al.

OBJECTIVE: We conducted a long-term follow-up of a cohort of children with newly diagnosed unprovoked seizures to assess treatment with antiepileptic drugs (AEDs), neuroleptics, antidepressants and medication for attention deficit hyperactivity disorder (ADHD) with special attention to the impact of comorbidities on the use of such medication.

METHODS: Our study cohort comprised 769 children (28 days-18 years), living in Stockholm Sweden, with a first unprovoked seizure identified between 2001 and 2006. Information on neurodevelopmental comorbidities and Cerebral Palsy (CP) at seizure onset was collected from medical records. Information on treatment with AEDs, neuroleptics, antidepressants and ADHD medication was retrieved by linkage to the Swedish National Prescription Registry between 2005 and 2014. The association between comorbidities and drug treatments was assessed by odds ratios (OR) with 95 % confidence intervals (CI), adjusted for age and sex.

RESULTS: Eight years after the index seizure, 31 % of the children were on AEDs, and this was more common among children with any of the comorbidities studied (OR; 4.0 95 % CI 2.9-5.6) compared to those without such comorbidities, and within this group of comorbidities particularly for those with CP (OR; 5.2 95 % CI: 2.9-9.3). Children with neurodevelopmental comorbidity or CP at baseline were more likely to receive neuroleptics (ORs 8 years after the index seizure; 6.9, 95 % CI: 2.4-19.8), antidepressants (OR; 2.3, 95 % CI: 1.0-5.5) and ADHD medication (OR; 3.6, 95 % CI: 1.8-7.2) than children without the studied comorbidities.

CONCLUSION: Children with seizures in combination with neurodevelopmental comorbidities or CP, especially CP, have a more frequent use of AEDs, neuroleptics, antidepressants, and ADHD medication up to 13 years following the initial seizure than children without comorbidity. Our data highlight the treatment burden in children with epilepsy and comorbidities

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Eur Child Adolesc Psychiatry. 2021 Nov;30:1671-94.

IS THERE A DYSBIOSIS IN INDIVIDUALS WITH A NEURODEVELOPMENTAL DISORDER COMPARED TO CONTROLS OVER THE COURSE OF DEVELOPMENT? A SYSTEMATIC REVIEW.

Jurek L, Sevil M, Jay A, et al.

Many scientific papers reported that an unbalanced gut microbiota could lead to or worsen neurodevelopmental disorders (NDD). A dysbiosis may then be observed in the course of development and mark a dysfunction within what is called the gut-brain axis. The aim of this systematic review is to investigate potential evidence of dysbiosis in children and young adults with NDD compared to controls. Using the PRISMA guidelines we systematically reviewed studies that compared the gut microbiota in NDD participants (with an age inferior to thirty) to the gut microbiota of controls, regardless of the data analysis methods used. The MEDLINE, Scopus and PsycINFO databases were searched up to September 2018. 31 studies with a total sample size of 3002 ASD (Autism Spectrum Disorder) and 84 ADHD (Attention Deficit Hyperactivity Disorder) participants were included in this systematic review. Independent data extraction and quality assessment were conducted. The quality of the studies was rated from low to high. Population characterization and experimental methods were highly heterogeneous in terms of the data available, selection of criteria, and dysbiosis measurement. A dysbiosis was reported in 28 studies in terms of either diversity, bacterial composition or metabolome dysfunction. Due to heterogeneity, a quantitative synthesis was not applicable. In this paper, we discuss the different biases to understand the complexity of microbiota and neurodevelopmental disorders to provide leads for future cohort studies looking to answer the questions raised by the trillions of microorganisms that inhabit key body niches

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Eur Child Adolesc Psychiatry. 2021 Aug;30:1251-62.

MENTAL DISORDERS IN REFERREDÂ 0-3-YEAR-OLD CHILDREN: A POPULATION-BASED STUDY OF INCIDENCE, COMORBIDITY AND PERINATAL RISK FACTORS.

Koch SV, Andersson M, Hvelplund C, et al.

The epidemiology of mental disorders in early childhood is still under-researched. We aim to explore the incidence, comorbidities and risk factors of mental disorders in 0-3-year-olds referred to hospital settings. In a national cohort of 918,280 children born in 1997-2010, we calculated incidence rates per 1,000 person-years (IR) of first-time mental and developmental disorders diagnosed in hospitals before four years of age. Data were obtained from Danish population registries. We used logistic regression to analyse co-morbidity and Cox proportional hazard models to evaluate the influence of pre- and perinatal risk factors.Â A total of 16,164 children (1.76%) were diagnosed with a mental (0.90%) or developmental disorder (1.05%). Pervasive developmental disorders (PDD) and disorders of hyperactivity and inattention (ADHD) were increasingly diagnosed with age. Feeding and eating disorders and disorders of social functioning were most frequent among the youngest children. Comorbidity was found in 18%, e.g., between PDD and ADHD (OR 135.8; 95% CI 112.0-164.7) or between ADHD and disorders of social functioning (OR 148.0; 95% CI 106.4-205.7). Young maternal age, old paternal age, maternal smoking in pregnancy, boy sex, premature birth and being small for gestational age were associated with highly increased risk of mental and developmental disorders. Mental and developmental disorders diagnosed within the first four years of life show increasing incidence rates and a complex pattern of comorbidities. Study findings point to the need of clinical and research attention towards the manifestations of developmental psychopathology in very young children

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Eur Child Adolesc Psychiatry. 2021 Nov;30:1825-28.

PRENATAL INFLAMMATION DOES NOT INCREASE THE RISK FOR SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN OFFSPRING.

Jallow J, Halt AH, Ã–hman H, et al.

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Eur J Epidemiol. 2021 Oct;36:993-1004.

PRENATAL AND POSTNATAL EXPOSURE TO ACETAMINOPHEN IN RELATION TO AUTISM SPECTRUM AND ATTENTION-DEFICIT AND HYPERACTIVITY SYMPTOMS IN CHILDHOOD: META-ANALYSIS IN SIX EUROPEAN POPULATION-BASED COHORTS.

Alemany S, Avella-GarcÃ-a C, Liew Z, et al.

The potential etiological role of early acetaminophen exposure on Autism Spectrum Conditions (ASC) and Attention-Deficit/Hyperactivity Disorder (ADHD) is inconclusive. We aimed to study this association in a collaborative study of six European population-based birth/child cohorts. A total of 73,881 mother-child pairs were included in the study. Prenatal and postnatal (up to 18Â months) acetaminophen exposure was assessed through maternal questionnaires or interviews. ASC and ADHD symptoms were assessed at 4-12Â years of age using validated instruments. Children were classified as having borderline/clinical symptoms using recommended cutoffs for each instrument. Hospital diagnoses were also available in one cohort. Analyses were adjusted for child and maternal characteristics along with indications for acetaminophen use. Adjusted cohort-specific effect estimates were combined using random-effects meta-analysis. The proportion of children having borderline/clinical symptoms ranged between 0.9 and 12.9% for ASC and between 1.2 and 12.2% for ADHD. Results indicated that children prenatally exposed to acetaminophen were 19% and 21% more likely to subsequently have borderline or clinical ASC (OR=1.19, 95% CI 1.07-1.33) and ADHD symptoms (OR=1.21, 95% CI 1.07-1.36) compared to non-exposed children. Boys and girls showed higher odds for ASC and ADHD symptoms after prenatal exposure, though these associations were slightly stronger among boys. Postnatal exposure to acetaminophen was not associated with ASC or ADHDÂ symptoms. These results replicate previous work and support providing clear information to pregnant women and their partners about potential long-term risks of acetaminophen use

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Eur J Neurol. 2021 Nov;28:3805-08.

RAPID ONSET OF FUNCTIONAL TIC-LIKE BEHAVIOURS IN YOUNG ADULTS DURING THE COVID-19 PANDEMIC.

Pringsheim T, Martino D.

BACKGROUND AND PURPOSE: Clinicians have reported an increase in functional tic-like behaviours in children and youth during the COVID-19 pandemic. We describe adults developing rapid onset of functional tic-like behaviours between May 2020 and June 2021.

METHODS: Data were analysed from the Adult Tic Disorders Registry, a single-site,12-month prospective cohort study that began enrolment in January 2021. We compared clinical features of participants with Tourette syndrome or persistent motor/vocal tic disorder to participants with rapid onset tic-like behaviours.

RESULTS: Thirty-three participants registered between January and June of 2021; nine had rapid onset tic-like behaviours, and 24 had Tourette syndrome or persistent motor tic disorder. Participants with rapid onset tic-like behaviours were younger (19.9 vs. 38.6 years, p=0.003), had older age at onset (15.3 vs. 10.1, p=0.0009), and were more likely female (p<0.0001). They had higher motor and vocal tic severity and impairment scores (all p<0.01) and were more likely to have complex arm/hand motor tics (p<0.0001), complex vocal tics (p<0.0001), and coprolalia (p=0.004). They had significantly higher scores on all mental health symptom self-report measures (all p<0.05) and were significantly more likely to be diagnosed with depression (p=0.03).

CONCLUSIONS: The clinical features that help differentiate rapid onset tic-like behaviours from Tourette syndrome or persistent motor tic disorder include their phenomenology, onset age, and clinical course. Rapid onset tic-like behaviours are a distinct subtype of functional neurological disorder that has emerged during the COVID-19 pandemic in young people and appears to be strongly socially influenced

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Eur Child Adolesc Psychiatry. 2021.

A POST HOC ANALYSIS OF THE EFFECT OF VILOXAZINE EXTENDED-RELEASE CAPSULES ON LEARNING AND SCHOOL PROBLEMS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Faraone SV, Gomeni R, Hull JT, et al.

Improvement in attention-deficit/hyperactivity disorder (ADHD) symptoms vs. placebo was reported in a series of pediatric clinical trials of viloxazine extended-release capsules (viloxazine ER; QelbreeΓäó). This post hoc analysis of those studies evaluated the effect of viloxazine ER on learning and school problems (LSPs). We used data from four Phase 3 placebo-controlled trials of 100ΓÇô600-ámg/day viloxazine ER (N = 1354; 6-17-áyears of age). LSPs were evaluated using the School domain of the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P-S) and the Learning Problems content scale of the Conners 3rd Edition-Parent Short Form (C3PS-LP) at baseline and end of study (Week 6). ADHD symptoms were assessed weekly using the ADHD Rating Scale 5th Edition. The analyses were performed using the general linear mixed model with participant as a random effect. The responder analyses were performed using the Chi-square test. Viloxazine ER demonstrated significantly greater improvements in WFIRS-P-S (p < 0.0001) and C3PS-LP (p = 0.0113) scores vs. placebo. The response rate for the WFIRS-P-S was significantly greater for viloxazine ER vs. placebo (p = 0.001), and the number needed to treat (NNT) was 10.3 (effect size 0.7). Conversely, response rates for C3PS-LP did not differ between groups (p = 0.9069). In addition to ADHD symptoms improvement demonstrated in previous studies, viloxazine ER significantly reduced LSPs in pediatric subjects with ADHD. The responder analyses and NNT estimates indicate that a substantial number of children and adolescents with ADHD treated with viloxazine ER improved in clinically assessed LSPs

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Eur Child Adolesc Psychiatry. 2021.

THE MANAGEMENT OF ADHD IN CHILDREN AND ADOLESCENTS: BRINGING EVIDENCE TO THE CLINIC: PERSPECTIVE FROM THE EUROPEAN ADHD GUIDELINES GROUP (EAGG).

Coghill D, Banaschewski T, Cortese S, et al.

ADHD is the most common neurodevelopmental disorder presenting to child and adolescent mental health, paediatric, and primary care services. Timely and effective interventions to address core ADHD symptoms and co-occurring problems are a high priority for healthcare and society more widely. While much research

has reported on the benefits and adverse effects of different interventions for ADHD, these individual research reports and the reviews, meta-analyses and guidelines summarizing their findings are sometimes inconsistent and difficult to interpret. We have summarized the current evidence and identified several methodological issues and gaps in the current evidence that we believe are important for clinicians to consider when evaluating the evidence and making treatment decisions. These include understanding potential impact of bias such as inadequate blinding and selection bias on study outcomes; the relative lack of high-quality data comparing different treatments and assessing long-term effectiveness, adverse effects and safety for both pharmacological and non-pharmacological treatments; and the problems associated with observational studies, including those based on large national registries and comparing treatments with each other. We highlight key similarities across current international clinical guidelines and discuss the reasons for divergence where these occur. We discuss the integration of these different perspective into a framework for person/family-centered evidence-based practice approach to care that aims to achieve optimal outcomes that prioritize individual strengths and impairments, as well as the personal treatment targets of children and their families. Finally, we consider how access to care for this common and impairing disorder can be improved in different healthcare systems

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Eur J Paediatr Neurol. 2021;35:74-81.

NEONATAL HYPOXIC-ISCHAEMIC ENCEPHALOPATHY: MOTOR IMPAIRMENT BEYOND CEREBRAL PALSY.

Erdi-Krausz G, Rocha R, Brown A, et al .

Background: Research investigating neuromotor function in the absence of cerebral palsy (CP) for children who had neonatal HIE is limited.

Aims: To investigate school-age neurological and neuromotor function, and correlations with attention, neonatal Magnetic Resonance Imaging (MRI), and neuromotor assessments at toddler age.

Methods: Twenty-seven children with neonatal HIE without CP who underwent hypothermia treatment and a comparison group of 20 children were assessed at age 5ΓÇô7 years for Minor Neurological Dysfunction (MND; simplified Touwen), motor skills (Movement Assessment Battery for Children-2; MABC-2), parental concern over motor function (MABC Checklist), general cognition (Wechsler Preschool and Primary Scale of Intelligence-IV, WPPSI), and attention (DuPaul ADHD Rating Scale). Neurological examination and motor development, using Bayley-3 scales, at age 24-months was extracted from the clinical database. Clinical neonatal MRI was assessed for hypoxic-ischaemic injury.

Results: In the HIE group, MND was more prevalent (p = 0.026) and M-ABC performance (total score p = 0.006; balance subtest p = 0.008) was worse; parents were more concerned about children's motor function (p = 0.011). HIE group inattention scores were higher (p = 0.032), which correlated with lower MABC-2 scores (rs = ΓêÆ0.590, p = 0.004). Neurological examination at 24-months correlated with MND (rs = 0.437, p = 0.033); Bayley-3 motor scores did not correlate with M-ABC-2 scores (rs = 368, p = 0.133). Neonatal MRI findings were not associated with school-age MND (rs = 0.140, p = 0.523) or MABC-2 (rs = 0.300, p = 0.165).

Conclusions: Children with neonatal HIE, without CP, treated with hypothermia may be more likely to develop MND and motor difficulties than typically developing peers. Inattention may contribute to motor performance. In the absence of CP, neonatal MRI and toddler age assessment of motor development have limited predictive value for school-age outcome. Since this was an exploratory study with a small sample size, findings should be confirmed by a definite larger study

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Eur J Pediatr. 2021.

NEUROLOGICAL AND NEURODEVELOPMENTAL SYMPTOMS IN CHILDREN WITH FAMILIAL MEDITERRANEAN FEVER AND THEIR SIBLINGS.

Biro O, Gileles-Hillel A, Dor-Wollman T, et al.

Familial Mediterranean fever is a common autoinflammatory disease characterized by periodic attacks of fever and serositis.-áThere are few reports describing neurological symptoms in patients with FMF. The aim of this study was to systematically assess the neurologic and developmental involvement in pediatric patients with FMF. Between the years 2016 and 2019, parents of children with FMF were asked to complete a questionnaire regarding the presence of neurological and developmental symptoms in their children with and

without FMF. Demographic data, clinical characteristics, and disease course of FMF patients were collected from the medical charts. Neurodevelopmental manifestations were compared between the children with FMF and their siblings. A total of 205 children were enrolled (11.6 -¦ 4.7-áyears of age): 111 children with FMF and 94 healthy siblings in the control group. Neurological morbidity was frequently reported in children with FMF: 44 (40%) had recurrent headaches, 31 (28%) ADHD symptoms, 27 (24%) learning disabilities, and 10 (9%) febrile convulsions. Headaches and febrile convulsions were significantly more prevalent in children with FMF as compared to their siblings (ps < 0.05). ADHD and learning disabilities were associated with poor adherence to colchicine treatment. Conslusions: The present study found an increased prevalence of ADHD, learning disabilities, headaches, and febrile seizures in children with FMF. The findings underscore the importance of addressing the neurodevelopmental domain in children with FMF. In addition, detection and treatment of ADHD and learning disabilities could improve adherence with therapy and control of the underlying disease.What is Known:ΓÇó-áFamilial Mediterranean fever (FMF) is the most common inherited auto-inflammatory disease, characterized by recurrent attacks of fever, serositis, and arthritis.ΓÇó-áSome previous case reports also described rare neurological manifestations in children with FMF.What is New:ΓÇó-áThe study found an increased prevalence of headaches, febrile seizures, ADHD, and learning disabilities, in children with FMF.ΓÇó-áThe findings underscore the importance of addressing the neurological domain in this population, which could potentially improve adherence with therapy and control of the underlying disease

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Eur Neuropsychopharmacol. 2021;51:e149-e150.

W6. IMPACTS OF GENETICS AND PRENATAL DIET QUALITY ON ADHD SYMPTOMS ACROSS CHILDHOOD – A LONGITUDINAL STUDY IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT.

Solberg B, Kvalvik LG, Instanes JI, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) symptoms are dimensional traits that are generally attributed to a combination of multiple genetic and environmental factors. It has been reported that ADHD symptoms are associated with the quality of the diet, which may be a target for the prevention/intervention of this disorder. In genetics, ADHD polygenic risk score (ADHD PRS) has been shown to be associated with the ADHD symptoms. We aimed to examine the effects of common genetic variants (ADHD PRS) and prenatal overall diet quality on the development of ADHD symptoms in childhood (3-8 years of age).

Methods: This study utilized the data collected by the Norwegian Mother, Father and Child Cohort Study (Moba). We examined 2,463 mother-father-child trios with the following information available: a) ADHD PRS from child and both parents that were calculated using MoBa genetic data and the largest genome-wide association study of clinically diagnosed ADHD to date (20,183 cases and 35,191 controls) and b) maternal fiber intake during pregnancy (proxy for diet quality) from the Moba food frequency questionnaire in gestational weeks 17-22. The examined phenotype was a constructed ADHD score for offspring at either 3, 5 or 8 years of age, utilizing information from several instruments reflecting child's behavior collected through Moba questionnaires. The effects of genetics and maternal prenatal diet on ADHD scores were examined by means of structural equation modeling in two models: 1) the effects of genetics and maternal fiber intake on the overall levels of ADHD scores at 3, 5 or 8 years of age and 2) the effects of genetics and maternal fiber intake on the change in offspring's ADHD scores during the examined ages of 3 to 8 years.

Results: Model 1: The child's own ADHD PRS was associated with ADHD scores at 5 and 8 years of age (unstandardized regression coefficient, bADHD5=0.32, p=0.016 and b8=0.47, p=0.003), but not at age 3. Higher ADHD PRS from the father was associated with a lower ADHD score at 8 years of age (b8=-0.30, p=0.03). Further, higher intake of fiber during pregnancy was associated with a lower level of ADHD symptoms at 3 and 5 years of age (b3=-0.02, p=0.002, and b5=-0.01, p=0.015), but not at 8 years of age (b8=-0.001, p=0.84). The contribution of all exposures, including covariates, explained 1.3-1.9% of variability in ADHD scores at the examined three timepoints. Model 2: The change in ADHD scores over time showed positive correlation with child's PRS and negative correlation with both maternal and paternal PRSes, although only the latter was significant (b5-8 = -0.28, p = 0.045) at 8 years of age only.

Discussion: We found that genetic effects of common variants associated with clinically diagnosed ADHD (captured by PRS) showed correlation with ADHD symptoms in children in general population, and that child's PRS showed positive correlation with the change in ADHD symptoms across the examined ages. Further,

our results indicate that maternal prenatal diet rich in fiber is associated with lower ADHD scores in offspring. We will repeat the analyses in a larger sample (Γê+40,000 trios, ready by end of June 2021) and will present the updated results at WCPG in October. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e94.

TU1. POLYGENIC RISK SCORE ANALYSES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TRAJECTORIES IN ADULTS.

Bandeira CE, Grevet EH, Vitola ES, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) trajectories may be influenced by different genetic backgrounds whether evaluated from childhood to adulthood or during adulthood. In this study, we explore if Polygenic Risk Scores (PRS) for ADHD are associated with persistence or remission of symptoms during adulthood, in a 13-years follow-up of a clinical sample. In addition, PRS for disorders frequently comorbid and with a shared genomic background with ADHD (e.g. Major Depressive Disorder - MDD, Bipolar Disorder - BD and Schizophrenia) were also evaluated.

Methods: The target sample was composed of 174 cases diagnosed with ADHD during adulthood and followed until middle-age that were evaluated and classified according to their ADHD trajectory: 127 persisters (45.7% males, mean age of 46.0 years) fulfilled ADHD diagnostic criteria in all the assessments points available (two or three), and 47 remitters (59.6% males, mean age of 43.0 years) presented full or partial remission of the symptoms at least in one assessment. DNA was isolated from blood samples and genotyped with the Illumina PsychChip array. PRS analyses were conducted on PRSice-2 through clumping and threshold approach (P thresholds - Pt: 5e-08, 5e-06, 0.05, 0.1, 0.5 and 1). Clumping was performed with PRSice default options, and sex, age and the first five principal components were included as covariates. Discovery samples were summarized data from ADHD, MDD, BP and Schizophrenia GWAS.

Results: Persisters presented higher MDD-PRS than remitters (Pt = 0.05, R-¦=0.167, P=0.010). For the PRS derived for ADHD, BD and Schizophrenia, there were no significant between-groups differences.

Discussion: Our results suggest a possible shared genetic background between MDD and ADHD trajectories during adulthood. Although we did not observe associations for the other disorders tested, MDD GWAS presented the largest sample size (N=500,199), and, consequently, the greatest statistical power to detect any associations between genetic liability and ADHD persistence/remission in adulthood. For ADHD, the lack of significance might be due to the fact that most individuals from the GWAS sample were children. Once childhood and adulthood share genetic similarities, but also differences, a PRS computed based on adult samples (as MDD sample) would be more adequate to capture the genetic similarities and smooth differences between persistence and remission trajectories in adulthood. Yet, these results are preliminary and need to be explored in a more detailed view. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e11-e12.

CLUSTERING OF GENETIC EFFECTS ON BRAIN MORPHOLOGY AND CONTRIBUTIONS TO PSYCHIATRIC DISORDERS.

Makowski C, Van Der Meer D, Dong W, et al.

Background: Incorporation of genetically informed brain atlases in genome-wide association studies (GWAS) of the cerebral cortex holds potential in discovering meaningful genetic variants and functional pathways that could be altered in psychiatric disorders.

Methods: Here we apply genetically-informed atlases of 12 surface area and 12 cortical thickness phenotypes in GWAS studies of 39,898 adults from the UK Biobank and 9136 children from the Adolescent Brain Cognitive Development (ABCD) Study. Given that significant GWAS loci of both cortical and mental health phenotypes are often disproportionately found in non-coding/regulatory regions of the genome, we utilized information from cell-type specific accessible chromatin sites obtained from human motor cortex tissue to assess overlap with the genetic architecture of our cortical phenotypes. We calculated genetic correlations between our cortical phenotypes and nine psychiatric disorders based on PGC summary statistics, and applied Mendelian randomization to selected psychiatric disorder-brain phenotype pairs.

Results: We uncovered 440 genome-wide significant loci in the discovery cohort and 800 from a post-hoc combined meta-analysis. Many of these genetic variants are linked to neurodevelopment in early life, which

is supported by the correspondence in GWAS results between UK Biobank and ABCD, despite the different ages of these samples. Association regions of the cortex important for higher-order functions, such as the prefrontal and inferior parietal cortices, were significantly enriched for regulatory genomic regions. Genetic correlations between our brain phenotypes and psychiatric disorders revealed the strongest association between Attention Deficit Hyperactivity Disorder (ADHD) and total surface area, with nominally significant genetic correlations between ADHD and fronto-parietal thickness, where one of these regions (medial prefrontal thickness) was also found to be enriched for accessible chromatin sites in excitatory Layer 6 neurons. Mendelian randomization uncovered a putative causal relationship of reduced anteromedial temporal area, a region linked to accessible chromatin sites in inhibitory neurons, giving rise to ASD. Associations between polygenic scores informed by our GWAS analyses on genetically-informed brain regions and various measures of psychopathology in the ABCD cohort will also be discussed.
Discussion: Analyses with genetically-informed atlases confirmed the complex polygenic architecture of the cortex and substantially enhanced discovery of significant loci compared to previous cortical GWAS. Incorporation of cell-type specific accessible chromatin sites provided an additional layer of information that can help us better understand how seemingly small tweaks in regulation can have large effects on cortical patterning. Alterations in the strongly regulated patterning of the cortex may give rise to psychiatric disorders, particularly those with neurodevelopmental origins, such as ADHD and ASD. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e54-e55.

27. USING A TRIO-BASED GENETIC DESIGN FOR INVESTIGATING THE AETIOLOGY OF ATTENTION DEFICIT HYPERACIVITY DISORDERS (ADHD).

Martin J, Wray M, Agha SS, et al.

Background: Unique properties of the parent-offspring trio design enable testing hypotheses related to transmitted and non-transmitted genetic risks. We applied this design to ADHD to test whether: a) children with ADHD disproportionately inherit psychiatric disorder and low cognition polygenic liability, b) non-transmitted parental polygenic liability differs compared to controls, and c) there are ascertainment biases of using the trio design, in terms of clinical and genetic differences between complete and incomplete trios.
Methods: We calculated polygenic scores for ADHD, autism, depression, anxiety, schizophrenia, bipolar disorder and cognitive ability, in a sample of clinically ascertained UK (European ancestry) children with a diagnosis of ADHD, their biological parents, the non-transmitted parental alleles, and population-matched controls. We used the polygenic transmission disequilibrium test to assess whether polygenic variation was over- or under-transmitted from parents to probands (N=328 trios). Next, we tested whether the non-transmitted alleles from parents (N=328) differed from population controls (N=503). Finally, we tested for clinical and genetic differences in complete parent-offspring trios (where both biological parents provided DNA and were confirmed to be related to the proband, N=367) and incomplete trios (where DNA was missing from one or both biological parents, N=454).
Results: Results suggest that polygenic liability for ADHD (mean(SE)=0.30(0.06), p=1.3 +ù 10-7) and lower cognitive ability (mean(SE)=-0.33(0.05), p=2.1 +ù 10-9), but not other psychiatric disorder liability (all p>0.05), was over-transmitted in children with ADHD. Non-transmitted alleles from parents of ADHD probands were also enriched for ADHD (OR=1.27(1.01-1.60), p=0.042) and (lower) cognitive ability (OR=0.76(0.61-0.94), p=0.013) polygenic risk compared to controls. Children from incomplete trios had more hyperactive-impulsive (mean(SE)=7.82(0.07) vs 7.65(0.08), p=0.019) and conduct disorder (mean(SE)=1.53(0.08) vs 1.16(0.09), p=0.012) symptoms, lower IQ (mean(SE)=82.9(0.67) vs 85.5(0.71), p=0.041), lower family socioeconomic status (% low: 59.9% vs 39.1%, p=1.1 +ù 10-7), and higher polygenic risk for bipolar disorder (p=0.0032), compared to those from complete trios. There were no group differences in other child or maternal polygenic scores (all p>0.05). Replication analyses are ongoing.
Discussion: The results demonstrate that clinical recruitment for childhood ADHD may result in a sample with a polygenic liability pattern characterised by higher polygenic risk for ADHD and low cognitive ability in children (excess over-transmission), as well as parents (non-transmitted parental alleles). Despite known widespread shared genetic risks across psychiatric disorders, this was not observed for polygenic liability for other disorders. Also, ascertainment of complete parent-offspring ADHD trios may be non-random, with some greater phenotypic severity observed in children from incomplete trios. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e53-e54.

25. THE ROLE OF DELETERIOUS RARE VARIANTS IN ADHD RISK.

Demontis D, Duan J, Satterstrom F, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable childhood behavioural disorder affecting 3-6% of school-age children, and has a heritability of around 0.74. The amount of risk attributed to common genetic variation has been estimated to be 0.22 and we have previously established the role of rare coding variants in ADHD, where we found that ADHD and autism spectrum disorder have similar significant excesses of constrained rare protein truncating variants compared to controls, and that these variants occur in similar sets of genes.

Methods: Here we present results from updated analyses of rare coding variants in ADHD. The study is based on whole-exome sequencing of two cohorts: 1) a Danish cohort with samples from the Danish Newborn Screening Biobank (DNSB) comprising Γê+8,900 cases and 9,000 controls (DNSB samples) and 2) a sample consisting of 1,100 clinically ascertained cases from Germany and the Netherlands and 1,700 controls with German and Dutch ancestry (clinical samples), bringing our total sample to 10,000 cases and 10,700 controls.

Results: Preliminary results of DNSB samples demonstrate a significant overrepresentation of rare protein truncating variants (rPTVs) in cases compared to controls (OR = 1.24; P = 3.8 +ù 10-15) in evolutionarily constrained genes intolerant to loss of function variation (pLI > 0.9). A comparable effect size was found for rare damaging (MPC > 3) missense variants (rDMVs) (OR = 1.28; P=0.0045). For comparison, counts of rare synonymous variants in highly constrained genes showed no difference between cases and controls (OR = 0.99; P = 0.34). Similar enrichment of deleterious variants in constrained genes in ADHD cases was observed in the clinical samples. For gene-discovery we combined counts of rPTVs+rDMVs in DNSB samples with counts in non-psych non-Finnish European individuals from gnomAD (N = 44,779) and identified the first three genes exome-wide significantly associated with ADHD (P < 2.5 +ù 10-6). When considering all genes with P < 5 +ù 10-4 (13 genes) we found these genes have a significant down regulation in late childhood in BrainSpan data (P = 2.27 10-4).

Discussion: Our preliminary results support the idea that rPTVs and rDMVs play a considerable role in ADHD risk, especially when located in evolutionary constrained genes. Additionally, we will present results from gene-set analyses (e.g. genes highly expressed in brain), evaluate whether ADHD risk genes identified based on common variant analyses also carry an increased burden of rare deleterious variants and estimate the combined effect of common variants and rPTVs+rDMVs on ADHD risk. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e195.

TH3. SCHOOLS MODERATE THE EFFECTS OF ADHD GENETIC RISK ON EDUCATIONAL ACHIVEMENT.

Cheesman R, Ayorech Z, Eilertsen EM, et al.

Background: Young people at greater genetic risk for ADHD achieve lower school grades. It is unknown whether this relationship is the same in every context, or whether schools act as moderators. Such interactions (GxE) are challenging to study, due to the difficulties of measuring relevant aspects of schools and of accounting for gene-environment correlation (rGE; arising from social sorting), and population stratification.

Methods: We link register data on young people's standardised test results for Mathematics, Reading and English at ages 10-14, and schools (2,422 schools within 428 municipalities) to the Norwegian Mother, Father and Child Cohort Study (MoBa), which includes 30,000 genotyped parent-child trios. First, we estimate associations between ADHD symptoms and an achievement composite based on three core subjects, and examine how associations vary across schools using random slope models. Second, we introduce polygenic scores to investigate the effect of ADHD genetic risk on achievement. We include random slopes to assess how this association varies across schools (GxE), while remaining agnostic to the relevant features of school environments. Adjusting for parental polygenic scores allows us to estimate this latent GxE while accounting for rGE and population stratification. Third, we test the extent that measured characteristics of schools can explain any school-level moderation of the effect of ADHD genetic risk on achievement.

Results: Symptoms of inattention are more predictive of lower achievement in fifth grade (beta= -0.19; 95%CI -0.20,-0.18) than are hyperactivity symptoms (beta= -0.07; 95%CI -0.08,-0.06). The association between inattention and achievement varies considerably across schools (SD of slopes across schools=0.07;chisq=32.5; df=2; p<0.001). School-level moderation of the effect of hyperactivity on achievement is weaker (SD of slopes=0.04;chisq=6.2; df=2; p=0.045). Polygenic scores for ADHD have been constructed and GxE analyses are underway.
Discussion: To our knowledge, this is the first study to investigate interactions between genetic risk for ADHD and schools. This research therefore represents an empirical advance in our understanding of how genetic risk for neurodevelopmental problems works together with environmental factors at the school level to shape educational outcomes in childhood and adolescence. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e177.

W62. THE ROLE OF GENETIC NURTURING EFFECTS IN CHILDHOOD PSYCHOPATHOLOGY

Middeldorp CM, Jami E, Sallis H, et al.

Background: It is well established that parental characteristics, such as parental mental disorders or parenting style, are associated with offspring psychopathology. As parents both transmit their genes and create part of the environment for their offspring, only genetically informative designs can identify the mechanisms underlying parent-offspring associations. The availability of cohorts with genetic data collected in parents and their offspring now provides the opportunity to test whether genetic nurture, i.e., the environment that is created by parents but is also related to their genotype, plays a role in childhood psychopathology.
Methods: Applying two different methods, we have studied genetic nurture effects on depression, ADHD and externalizing symptoms measured in children aged 8 years. Firstly, we analyzed data collected in the Norwegian Mother, Father and child cohort Study (MoBa) from 5,990 mother-child dyads and 6,222 father-child dyads using m-GCTA. Secondly, we tested whether parental polygenic risk scores based on transmitted and non-transmitted genetic variants for wellbeing were associated with these three traits collected in 10,613 children from the Netherlands Twin Register (NTR) and the Avon Longitudinal Study of Parents and Children (ALSPAC).
Results: The m-GCTA analyses did not yield significant genetic nurture effects. Estimates for the variance explained by maternal and paternal genetic nurture effects on depression were 2.9% and 9.8% with an additional 7.6% correlation between maternal and offspring genetic effects. Maternal, but not paternal, genetic nurturing effects explained 8.4% of the variance in ADHD symptoms. The parental wellbeing PRS analyses did not show any evidence of genetic nurturing effects explaining the association between parental wellbeing and childhood depression, adhd or externalizing symptoms.
Discussion: In line with the finding of common environmental effects on depression in children below 12 years, we found suggestive evidence of genetic nurturing effects. The results of the parental wellbeing PRS analyses showed that these effects are not related to parental wellbeing. With parental and childhood phenotypes becoming more and more available, we will be able to gain more insight in parent-offspring associations which is also important from a clinical perspective as it may provide leads for modifiable environmental factors. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e147.

W2. THE EFFECT OF POLYGENIC RISCK SCORE OF INSOMNIA, SLEEP DURATION AND CHRONOTYPE ON ADHD GENETIC SUSCEPTIBILITY IN CHILDREN FROM A BRAZILIAN SAMPLE.

Fraga BB, Martins-Silva T, Carpena MX, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder highly comorbid with insomnia, short sleep duration and preference for the nocturnal chronotype. However, the underlying mechanisms explaining this relationship are still poorly understood. The genetic architecture of the relationship between ADHD and sleep phenotypes appears to be multifactorial and, therefore, studies that investigate the entire genome and assess the polygenic character of this relationship are needed. The

aim of the present work is to analyze the additive effect of genetic markers associated with sleep duration, insomnia and chronotype from recently published GWAS studies and ADHD in a Brazilian sample.
Methods: We performed a family-based study, using 259 Brazilian probands with ADHD and their biological parents, from Porto Alegre, Brazil. The sample is essentially of European ancestry. Their DNA samples were genotyped using the Infinium PsychArray-24 BeadChip (Ilumina). Additional markers were imputed using the Ricopili. The family design was converted to a case-pseudo-control approach for association analyses. Summary statistics from GWAS studies of insomnia (Lane et al., 2019), sleep duration (Dashti et al., 2019) and chronotype (Jones et al., 2019) were used as discovery sample to create a weighted Polygenic Risk Score (PRS) using four p-value thresholds (Pt): 5 +ù 10-8, 5 +ù 10-6, 0.05, and 0.5. The PRS was created using PRSice v.2.2.1 software. The association between each PRS and ADHD was tested through logistic regression using STATA v.14.0. Bonferroni was used to correct for multiple tests (four tests, corresponding to the number of Pt tested). Significant association was considered when p-value < 0.0125.
Results: Our sample is composed of a majority of boys (76.4%), with a mean age of 10.42 years (range: 4-17 years) and a majority with white skin color (83.4%). We found a suggestive association of the polygenic insomnia risk score at the PT = 0.05 (p = 0.02; pseudo-R-¦ = 0.007; OR = 1.228; 95% CI 1.030 - 1.462). We did not find an association between the PRS of sleep duration and chronotype with ADHD at any threshold.
Discussion: This is the first study assessing PRS of sleep phenotypes in a sample of ADHD children. Our findings suggest that insomnia and ADHD may share a genetic component. The set of alleles that contribute to the increased risk of insomnia apparently also increase the risk for ADHD in our sample, which is in agreement with other evidences. We did not find association between PRS of sleep duration and chronotype with ADHD, suggesting that both phenotypes may have lower genetic influence on ADHD, and insomnia might represent an important sleep phenotype for ADHD, as previously reported. Further studies are needed to clarify the genetic architecture of the relationship between sleep-related phenotypes and ADHD. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e56.

29. MAPPING ASSOCIATIONS BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER GENETIC LIABILITY, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS, AND BEHAVIORAL AND NEUAL CORRELATES OF RESPONSE INHIBITION.

Saracaydin G, Ruisch H, van Rooij D, et al.

Background: Dysfunctional response inhibition (RI) and aberrant neural activity commonly present in not only people with attention-deficit/hyperactivity disorder (ADHD) but also their unaffected first-degree relatives, proposing impaired RI as a candidate endophenotype in ADHD. This study aimed (1) to explore whether polygenic risk score for ADHD (PRS-ADHD) was associated with ADHD symptoms, and behavioral performance and brain activation during RI; (2) to explore whether behavioral performance and brain activation during RI was associated with ADHD symptoms; and (3) to determine whether behavioral performance and brain activation during RI mediated the association between PRS-ADHD and ADHD symptoms.
Methods: Event-related functional magnetic resonance imaging data (fMRI) during a performance-adjusted stop-signal task and genetic data were available for 454 participants (age: 8-29, 178 with ADHD). Summary statistics from the genome-wide association study of ADHD (19,099 cases, 34,194 controls) conducted by the Psychiatric Genomics Consortium were used as the discovery set to calculate PRS-ADHD. We examined the following three contrasts of interest: successful inhibition>go, failed inhibition>go, and failed inhibition>successful inhibition. Brain activations elicited by the contrasts of interest were cluster thresholded with a voxel thresholded of Z=2.3, and a family-wise error rate-corrected cluster significance threshold of p=0.05 across the whole brain. Mean reaction time (MRT), intra-individual coefficient of variation of reaction time (ICV) and stop-signal reaction time were calculated as behavioral outcomes of the task. Inattention and hyperactivity-impulsivity symptoms of ADHD were assessed using Conners' Parent Rating Scale. The associations between PRS-ADHD, ADHD symptoms, task outcomes, and RI-related neural activity were tested using linear mixed regression. Mediation analyses of the linear mixed regression models were conducted to explore the effects of possible mediators. We included age, sex, genetic principal components, recruitment center as confounding factors, and familial relations as random-effect term. Finally, we used false-discovery-rate (q<=0.05) to correct for multiple comparisons.

Results: Significant associations between PRS-ADHD and ADHD symptoms were partially mediated by MRT and ICV. PRS-ADHD was associated with hypoactivation in the left inferior frontal gyrus (IFG) during successful inhibition, hyperactivation in the left temporal pole and parahippocampal gyrus and right putamen during failed inhibition, and hyperactivation in the left IFG and right basal ganglia during failed versus successful inhibition. The association between PRS-ADHD and symptoms of hyperactivity-impulsivity was partially mediated by the left temporal pole and parahippocampal activity during failed inhibition.
Discussion: Our findings support the polygenic nature of ADHD and further corroborate RI-related neural activity as a possible endophenotype of ADHD. Mediation analyses indicated that common genetic risk variants of ADHD were associated with RI-related neural activity which in turn mediated their relation with hyperactivity-impulsivity symptoms. Besides, the significant associations of MRT and ICV with PRS-ADHD, and their mediatory effects on the relation between PRS-ADHD and ADHD symptoms suggest that genetic liability to ADHD might influence attention regulation on the behavioral level. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e56-e57.

30. GENETIC AND EARLY ENVIROLMENTAL FACTORS ASSOCIATED WITH TRAJECTORIES OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS SYMPTOMS INTO ADULTHOOD.

Blakey R, Stergiakouli E, Tilling K, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) symptoms typically onset in childhood and behave as continuous traits in the population. The course of ADHD is not static and a developmental perspective is essential. Higher polygenic risk scores (PRS) for ADHD and broader psychopathology are associated with greater likelihood of ADHD diagnosis, yet how they impact the developmental course of ADHD symptoms is unclear. There is evidence that both individual and maternal genetic liability for psychopathology, alongside early environmental exposures, may be associated with age-dependent developmental changes in ADHD symptoms. It is also possible that genetic liability for compensatory executive functions may underpin typical developmental decreases in ADHD symptoms through the life-course.
Methods: We used data from over 8000 mothers and children from the Avon Longitudinal Parent And Child (ALSPAC) study. ADHD symptoms were measured using the Strengths and Difficulties Questionnaire (SDQ) across 8 measurement occasions between ages 3 to 25. We fit multilevel linear spline models to examine the impacts of individual and maternal psychiatric PRS (ADHD, autism spectrum disorder, broad depression, major depressive disorder, anxiety), PRS of executive functions, and early environmental risks (low birth weight, maternal age at delivery, maternal paracetamol intake, maternal lead exposure) on ADHD symptom development.
Results: Our main findings included that both individual and maternal psychiatric PRS scores were more strongly associated with developmental symptom changes (trajectory slopes) than initial symptom levels (trajectory intercepts). Higher individual PRS for ADHD were associated with shallower ADHD symptom decline in early life 0.10 SDQ (95% CI: 0.05, 0.15), p = 0.007 (trajectory slope 3-8 years), but not later in development. PRS for major depression showed the reverse pattern, with no evidence of associations early in development (3 -16 years), but evidence of increased ADHD symptoms with increased genetic liability for major depression between ages 16 and 25, 0.08 SDQ (0.00, 0.15), p = 0.0386 (trajectory slope 16-25 years).
Discussion: Our results expand our understanding of genetic liability as salient to symptom changes through development, as opposed to simply incidence of disease. Together, our findings reinforce the importance of a developmental, and intergenerational, perspective on the course of ADHD symptoms. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2021;51:e194-e195.

TH2. CAFFEINE-RELATED GENES INFLUENCE ANXIETY DISORDERS IN CHILDREN AND ADULTS WITH ADHD.

Fraporti T, Bandeira CE, Tovo-Rodrigues L, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders (AD) frequently co-occur, increasing morbidity and challenging treatment. Caffeine is a central nervous system stimulant and acts in the brain through adenosine receptors, influencing attention, alertness, and anxiety.

Methods: In the present study, we performed a gene-set analysis to verify if genes related to caffeine response are associated with anxiety disorders in 240 children and 406 adults with ADHD.
Results: We demonstrated an association between the gene-set with AD in children (P=0.0054) and with the number of anxiety disorders in adults (P=0.0197). In order to test if this effect is a result of anxiety in general or is related to AD comorbid with ADHD, we evaluated the association between caffeine gene-set with AD in an adult control sample. The gene-set was neither associated with the AD presence (P=0.3008) nor with the number of AD (P=0.5594) in this control sample. We also test this gene-set with ADHD (n=55,374) and AD (n=18,186) GWAS summary statistics, and we did not observe significant results with ADHD (P=0.5587) or AD (P=0.3930). Discussion: Our findings suggest that genes related to caffeine response influence the presence of AD in the context of ADHD, likely being more relevant for a subgroup of patients that present both disorders. The genes related to this biological pathway may be markers of a shared genetic background between these disorders, and it could help to better understand the heterogeneity found in psychiatric nosology and treatment response. Further studies should be performed to better address this possible relationship.
Disclosure: Nothing to disclose

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Exp Neurol. 2021 Aug;342:113723.
GENETIC MOSAICISM, INTRAFAMILIAL PHENOTYPIC HETEROGENEITY, AND MOLECULAR DEFECTS OF A NOVEL MISSENSE SLC6A1 MUTATION ASSOCIATED WITH EPILEPSY AND ADHD.
Poliquin S, Hughes I, Shen W, et al.
BACKGROUND: Mutations in SLC6A1, encoding Î³-aminobutyric acid (GABA) transporter 1 (GAT-1), have been recently associated with a spectrum of neurodevelopmental disorders ranging from variable epilepsy syndromes, intellectual disability (ID), autism and others. To date, most identified mutations are de novo. We here report a pedigree of two siblings associated with myoclonic astatic epilepsy, attention deficit hyperactivity disorder (ADHD), and ID.
METHODS: Next-generation sequencing identified a missense mutation in the SLC6A1 gene (c.373G > A(p.Val125Met)) in the sisters but not in their shared mother who is also asymptomatic, suggesting gonadal mosaicism. We have thoroughly characterized the clinical phenotypes: EEG recordings identified features for absence seizures and prominent bursts of occipital intermittent rhythmic delta activity (OIRDA). The molecular pathophysiology underlying the clinical phenotypes was assessed using a multidisciplinary approach including machine learning, confocal microscopy, and high-throughput (3)H radio-labeled GABA uptake assays in mouse astrocytes and neurons.
RESULTS: The GAT-1(Val125Met) mutation destabilizes the global protein conformation and reduces transporter protein expression at total and cell surface. The mutant transporter protein was localized intracellularly inside the endoplasmic reticulum (ER) in both HEK293T cells and astrocytes which may directly contribute to seizures in patients. Radioactive (3)H-labeled GABA uptake assay indicated the mutation reduced the function of the mutant GAT-1(Val125Met) to ~30% of the wildtype.
CONCLUSIONS: The seizure phenotypes, ADHD, and impaired cognition are likely caused by a partial loss-of-function of GAT-1 due to protein destabilization resulting from the mutation. Reduced GAT-1 function in astrocytes and neurons may consequently alter brain network activities such as increased seizures and reduced attention

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Folia Med (Plovdiv). 2021 Feb;63:138-41.
16P11.2 DUPLICATION SYNDROME - A CASE REPORT.
Levkova M, Stoyanova M, Staneva R, et al.
16p11.2 duplication syndrome is a rare disorder, often associated with intellectual disability, attention deficit, hyperactivity disorder, and a predisposition to epilepsy and schizophrenia. There are no specific dysmorphic features for this genetic condition, but micro-cephaly, micrognathia and hypertelorism could be present. We report a case of 16p11.2 duplication syndrome which has the typical clinical presentation - slight facial dysmorphism, impaired intellectual development, and autistic behavior. Whole-exome sequencing was performed, but no pathogenic or likely pathogenic mutations were identified. Array comparative genomic

hybridization analysis established the diagnosis of 16p11.2 duplication syndrome, which illustrates the importance of this method when diagnosing children with unexplained intellectual disability

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Frontiers in Genetics. 2018;9.

COMT VAL158MET POLYMORPHISM AND SOCIAL IMPAIRMENT INTERACTIVELY AFFECT ATTENTION-DEFICIT HYPERACTIVITY SYMPTOMS IN HEALTHY ADOLESCENTS.

Millenet SK, Nees F, Heintz S, et al.

The dopaminergic system has been shown to have substantial effects on the etiology of attention-deficit hyperactivity disorder (ADHD). However, while some studies found a significant direct effect, others did not. In this context, social behavior might play an important role as a factor that is related both to the dopaminergic system and ADHD. In a large epidemiological sample of adolescents (N = 462; 16ΓÇô17 years), we assessed the level of ADHD symptoms using the Strengths and Difficulties Questionnaire, social behavior using the Social Responsiveness Scale, and the allelic distribution of the dopaminergic catechol-O-methyltransferase (COMT) Val158Met polymorphism. We found a significant association between COMT and social impairment, insofar as Met-allele carriers showed increased levels of social impairment. Moreover, social impairment significantly determined an association between COMT and ADHD (explained variance: 19.09%). This effect did not significantly differ between males and females. COMT and social impairment might interactively affect ADHD symptomatology, and could thus represent significant gene-phenotypic risk factors for ADHD symptomatology. This might have interesting implications for prevention and intervention strategies with a focus on social behavior in genetically at-risk individuals

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Front Human Neurosci. 2021;15.

DIFFERENCES IN DISRUPTED DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY AMONG CHILDREN, ADOLESCENTS, AND ADULTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A RESTING-STATE FMRI STUDY.

Agoalikum E, Klugah-Brown B, Yang H, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most widespread mental disorders and often persists from childhood to adulthood, and its symptoms vary with age. In this study, we aim to determine the disrupted dynamic functional network connectivity differences in adult, adolescent, and child ADHD using resting-state functional magnetic resonance imaging (rs-fMRI) data consisting of 35 children (8.64 -¦ 0.81 years), 40 adolescents (14.11 -¦ 1.83 years), and 39 adults (31.59 -¦ 10.13 years). We hypothesized that functional connectivity is time-varying and that there are within- and between-network connectivity differences among the three age groups. Nine functional networks were identified using group ICA, and three FC-states were recognized based on their dynamic functional network connectivity (dFNC) pattern. Fraction of time, mean dwell time, transition probability, degree-in, and degree-out were calculated to measure the state dynamics. Higher-order networks including the DMN, SN, and FPN, and lower-order networks comprising the SMN, VN, SC, and AUD were frequently distributed across all states and were found to show connectivity differences among the three age groups. Our findings imply abnormal dynamic interactions and dysconnectivity associated with different ADHD, and these abnormalities differ between the three ADHD age groups. Given the dFNC differences between the three groups in the current study, our work further provides new insights into the mechanism subserved by age difference in the pathophysiology of ADHD and may set the grounds for future case-control studies in the individual age groups, as well as serving as a guide in the development of treatment strategies to target these specific networks in each age group

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Frontiers in Neuroscience. 2021;15.

Dynamic Functional Connectivity Reveals Abnormal Variability in the Amygdala Subregions of Children With Attention-Deficit/Hyperactivity Disorder.

Yang Y, Yang B, Zhang L, et al.

Objective: This study investigates whether the dynamic functional connectivity (dFC) of the amygdala subregions is altered in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: The dFC of the amygdala subregions was systematically calculated using a sliding time window method, for 75 children with ADHD and 20 healthy control (HC) children.
Results: Compared with the HC group, the right superficial amygdala exhibited significantly higher dFC with the right prefrontal cortex, the left precuneus, and the left post-central gyrus for children in the ADHD group. The dFC of the amygdala subregions showed a negative association with the cognitive functions of children in the ADHD group.
Conclusion: Functional connectivity of the amygdala subregions is more unstable among children with ADHD. In demonstrating an association between the stability of functional connectivity of the amygdala and cognitive functions, this study may contribute by providing a new direction for investigating the internal mechanism of ADHD

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Frontiers in Neuroscience. 2021;15.
ALTERED VARIABILITY AND CONCORDANCE OF DYNAMIC RESTING-STATE FMRI INDICES IN PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Lou F, Tao J, Zhou R, et al.
Objective: Attention deficit hyperactivity disorder (ADHD) is a commonly diagnosed neuropsychiatric disorder in children, which is characterized by inattention, hyperactivity and impulsivity. Using resting-state functional magnetic resonance imaging (R-fMRI), the alterations of static and dynamic characteristics of intrinsic brain activity have been identified in patients with ADHD. Yet, it remains unclear whether the concordance among indices of dynamic R-fMRI is altered in ADHD.
Methods: R-fMRI scans obtained from 50 patients with ADHD and 28 healthy controls (HC) were used for the current study. We calculated the regional dynamic changes in brain activity indices using the sliding-window method and compared the differences in variability of these indices between ADHD patients and HCs. Further, the concordance among these dynamic indices was calculated and compared. Finally, the relationship between variability/concordance of these indices and ADHD-relevant clinical test scores was investigated.
Results: Patients with ADHD showed decreased variability of dynamic amplitude of low-frequency fluctuation (dALFF) in the left middle frontal gyrus and increased one in right middle occipital gyrus, as compared with the HCs. Besides, ADHD patients showed decreased voxel-wise concordance in the left middle frontal gyrus. Further, lower voxel-wise concordance in ADHD's left middle frontal gyrus was associated with more non-perseverative errors in Wisconsin Card Sorting Test, which reflects worse cognitive control.
Conclusion: Our findings suggest that variability and concordance in dynamic brain activity may serve as biomarkers for the diagnosis of ADHD. Further, the decreased voxel-wise concordance is associated with deficit in cognitive control in ADHD patients

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Frontiers in Neuroscience. 2021;15.
DRD1 AND DRD2 RECEPTOR POLYMORPHISMS: GENETIC NEUROMODULATION OF THE DOPAMINERGIC SYSTEM AS A RISK FACTOR FOR ASD, ADHD AND ASD/ADHD OVERLAP.
Mariggiò MA, Palumbi R, Vinella A, et al.
The dopaminergic system (DS) is one of the most important neuromodulator systems involved in complex functions that are compromised in both autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), conditions that frequently occur in overlap. This evidence suggests that both disorders might have common neurobiological pathways involving the DS. Therefore, the aim of this study was to examine the DRD1 and DRD2 dopamine receptor single nucleotide polymorphisms (SNPs) as potential risk factors for ASD, ADHD, and ASD/ADHD overlap. Genetic data were obtained from four groups: 75 ASD patients, 75 ADHD patients, 30 patients with ASD/ADHD overlap, and 75 healthy controls. All participants were between 2 and 17 years old. We compared the genotypic and allelic frequency of 18 SNPs among all of the study groups. Moreover, in the case of statistically significant differences, odds ratios (OR) were obtained to evaluate if the presence of SNPs might be a risk factor of developing a specific clinical phenotype. This study found that DRD1 and DRD2 receptors SNPs might be considered as potential risk factors for ASD and ADHD. However, only DRD2-12 (rs7131465) was significantly associated with a higher risk for the

ASD/ADHD overlap. These data support the hypothesis of the genetic neuromodulation of the DS in the neurobiology of these conditions

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Frontiers in Neuroscience. 2021;15.

MULTIMODAL MR IMAGES-BASED DIAGNOSIS OF EARLY ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER USING MULTIPLE KERNEL LEARNING.

Zhou X, Lin Q, Gui Y, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common brain diseases among children. The current criteria of ADHD diagnosis mainly depend on behavior analysis, which is subjective and inconsistent, especially for children. The development of neuroimaging technologies, such as magnetic resonance imaging (MRI), drives the discovery of brain abnormalities in structure and function by analyzing multimodal neuroimages for computer-aided diagnosis of brain diseases. This paper proposes a multimodal machine learning framework that combines the Boruta based feature selection and Multiple Kernel Learning (MKL) to integrate the multimodal features of structural and functional MRIs and Diffusion Tensor Images (DTI) for the diagnosis of early adolescent ADHD. The rich and complementary information of the macrostructural features, microstructural properties, and functional connectivities are integrated at the kernel level, followed by a support vector machine classifier for discriminating ADHD from healthy children. Our experiments were conducted on the comorbidity-free ADHD subjects and covariable-matched healthy children aged 9ΓÇô10 chosen from the Adolescent Brain and Cognitive Development (ABCD) study. This paper is the first work to combine structural and functional MRIs with DTI for early adolescents of the ABCD study. The results indicate that the kernel-level fusion of multimodal features achieves 0.698 of AUC (area under the receiver operating characteristic curves) and 64.3% of classification accuracy for ADHD diagnosis, showing a significant improvement over the early feature fusion and unimodal features. The abnormal functional connectivity predictors, involving default mode network, attention network, auditory network, and sensorimotor mouth network, thalamus, and cerebellum, as well as the anatomical regions in basal ganglia, are found to encode the most discriminative information, which collaborates with macrostructure and diffusion alterations to boost the performances of disorder diagnosis

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Front Psychiatry. 2021;12.

LOW LEVEL OF PERFECTIONISM AS A POSSIBLE RISK FACTOR FOR SUICIDE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Katzenmajer-Pump L, Farkas BF, Varga BA, et al.

Introduction: Suicide is one of the leading causes of death among adolescents. Although it is known that both perfectionism and attention-deficit/hyperactivity disorder (ADHD) are important risk factors for suicide, there are no studies that have investigated the relationship between suicidal behavior and perfectionism among people with ADHD.

Aim: The current study investigates the association between perfectionism and suicide in adolescents with ADHD.

Method: Subjects included 88 adolescents with ADHD and 96 non-clinical control adolescents. We used the Multidimensional Perfectionism Scale to evaluate perfectionism as well as its separate traits, and the Mini International Neuropsychologic Interview Kid to evaluate psychiatric disorders and suicidal behavior. Differences between the groups were statistically evaluated using t-tests, a Poisson regression analysis with suicide as a discrete variable, and a logistic regression analysis with suicide as a binary variable.

Results: Compared to the control group, the ADHD group showed a significantly lower level on the adaptive Organization trait of perfectionism, but not on any other trait, and a significantly higher level of suicidal behavior. Logistic regression results indicated a significant association for perfectionism in general (OR = 0.93, p = 0.003), and for the Personal Standards trait (OR: 0.82, p = 0.039). Poisson regression analysis also showed a significant association with perfectionism in general (IRR = 0.90; p < 0.001) and with the Personal standards trait model (IRR = 0.81, p = 0.019).

Discussion: Our results indicate that a low level of perfectionism, in particular Personal standards, may be a risk factor for suicidal behavior in adolescents with ADHD. We recommend that psychoeducation and

therapy of adolescents with ADHD should consider focusing on adaptive perfection as a possible risk factor for suicide as well

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Front Psychiatry. 2021;12.

ASSOCIATION BETWEEN HYPERACTIVITY SYMPTOMS AND SOMATIC COMPLAINTS: MEDIATING AND MODERATING MECHANISMS IN CHILDHOOD TRAUMA AND LIFE EVENTS AMONG CHINESE MALE ADOLESCENTS.

Wu S, Yang T, He Y, et al.

Background: Prior research has found that attention deficit/hyperactivity disorder (ADHD) particularly hyperactivity symptoms is associated with various somatic complaints. The present study further tests the relationship between hyperactivity symptoms and somatic complaints in Chinese male adolescents and explores the underlying moderating and mediating mechanisms.

Methods: Our sample included 1,586 males (age = 12-16) recruited as part of an epidemiological study of child and adolescent mental disorders from April to July, 2014. Hyperactivity symptoms and somatic complaints were assessed with Achenbach's Child Behavior Checklist (CBCL), and the Childhood Trauma Questionnaire Short Form (CTQ-SF) and Adolescent Life Events Scale (ASLEC) were used to assess exposure to childhood trauma and recent life events.

Results: Adolescents with hyperactivity symptoms experienced more emotional abuse, physical abuse, life events, and reported more somatic complaints symptoms ($p < 0.0083$ or $p < 0.05$). Linear regression analysis showed that hyperactivity, total childhood trauma score/emotional abuse and sexual abuse and ASLEC score significantly predicted somatic complaints (all $p < 0.05$). Emotional abuse and life events mediated the relationship between hyperactivity symptoms and somatic complaints. Furthermore, childhood trauma moderated the path between hyperactivity symptoms and ASLEC in the moderation mediation model for predicting somatic complaints ($p < 0.05$).

Conclusions: Hyperactivity symptoms had a significant impact on somatic complaints among Chinese male adolescents. Furthermore, childhood trauma and life events affected the relationship between hyperactivity symptoms and somatic complaints. Interventions for somatic complaints in male adolescents with hyperactivity symptoms should thus consider history of childhood trauma and life events

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Games Health J. 2021 Aug;10:283-92.

A VIRTUAL REALITY SERIOUS VIDEOGAME VERSUS ONLINE CHESS AUGMENTATION IN PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RANDOMIZED CLINICAL TRIAL.

Rodrigo-Yanguas M, Martin-Moratinos M, Menendez-Garcia A, et al.

Objective: Serious videogames and virtual reality (VR) have gained increasing interest for treating attention deficit hyperactivity disorder (ADHD). "The Secret Trail of Moon" (TSTM) study is a clinical trial devoted to testing the efficacy of TSTM, a VR serious videogame developed to train in five major cognitive skills usually compromised in patients with ADHD. This study is a three-arm nonequality trial comparing TSTM to online chess training and a control group (CG). This study aims to demonstrate that augmentation with either TSTM or online chess is efficacious in clinically drug-stable patients with ADHD.

Materials and Methods: This study is prospective, unicentric, and randomized with a CG. One hundred five patients with ADHD, ages 12-22 years old, and pharmacologically stable were enrolled. Patients were randomized into three groups: TSTM group, online chess group (therapeutic chess [TC]), and CG. Objective and subjective measures of the patient and parents are included. Patient visits differ for each group. TSTM group patients have 15 face-to-face visits: preinclusion visit, inclusion visit, 12 training visits, and final visit. TC and CG patients have 3 face-to-face visits (preinclusion, initial visit, and final visit) and 12 e-mail or phone communications during training (TC) or follow-up (CG group). This study was approved by the local Institutional Review Board (IRB).

Results: Not applicable. This is a study protocol.

Conclusion: This is the first study testing an augmentation strategy using either a serious videogame or chess in clinically drug-treated patients with ADHD. Using VR serious videogames present with several advantages over traditional videogames.
Trial Registration: NCT04355065

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Gen Hosp Psychiatry. 2021;73:9-15.

FIFTEEN YEARS' EXPERIENCE WITH METHYLPHENIDATE FOR ATTENTION-DEFICIT DISORDER DURING PREGNANCY: EFFECTS ON BIRTH WEIGHT, APGAR SCORE AND CONGENITAL MALFORMATION RATES.

Damer EA, Edens MA, van der Loos MLM, et al.

Background: Methylphenidate (MPD) is increasingly prescribed to fertile women with Attention-Deficit Disorder (AD(H)D), with or without hyperactivity, despite advice for discontinuation during pregnancy. Few studies report on results concerning safety after methylphenidate exposure during pregnancy for the offspring. Aim: Safety for the offspring of exposure to MPD during pregnancy.
Methods: This is an observational retrospective cohort study in a population of pregnant women and their offspring, treated with MPD for ADHD in the Psychiatry-Gynaecology-Pediatrics outpatient clinic between 1 January 2005 and 1 June 2020 at Isala hospital. The primary endpoints were birth weight and Apgar score in offspring exposed to MPD during pregnancy, compared to offspring unexposed to MPD. Birth weight was analysed using linear mixed model analysis. Apgar score and (secondary endpoint) neonatal malformations, at 20 week ultrasound, were analysed using basic univariate statistical analysis.
Results: MPD continuation, compared to discontinuation, was associated with higher neonatal birth weight (p = 0.049), but lost statistical significance after incorporating covariates (p = 0.079). There were no significant differences in Apgar scores and congenital malformations between neonates exposed and unexposed to MPD.
Conclusions: MPD does not seem to affect birth weight, Apgar score and the frequency of neonatal malformations at the 20 week ultrasound

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Genet Epidemiol. 2021 Oct;45:710-20.

IDENTIFYING GENETIC RISK VARIANTS ASSOCIATED WITH BRAIN VOLUMETRIC PHENOTYPES VIA K-SAMPLE BALL DIVERGENCE METHOD.

Hu Y, Tan H, Li C, et al.

Regional human brain volumes including total area, average thickness, and total volume are heritable and associated with neurological disorders. However, the genetic architecture of brain structure and function is still largely unknown and worthy of exploring. The Pediatric Imaging, Neurocognition, and Genetics (PING) data set provides an excellent resource with genome-wide genetic data and related neuroimaging data. In this study, we perform genome-wide association studies (GWAS) of 315 brain volumetric phenotypes from the PING data set including 1036 samples with 539,865 single-nucleotide polymorphisms (SNPs). We introduce a nonparametric test based on K-sample Ball Divergence (KBD) to identify genetic risk variants that influence regional brain volumes. We carry out simulations to demonstrate that KBD is a powerful test for identifying significant SNPs associated with multivariate phenotypes although controlling the type I error rate. We successfully identify nine SNPs below a significance level of 5â€‰Ã—â€‰10(-5) for the PING data. Among the nine identified genetic variants, two SNPs rs486179 and rs562110 are located in the ADRA1A gene that is a well-known risk factor of mental illness, such as schizophrenia and attention deficit hyperactivity disorder. Our study suggests that the nonparametric test KBD is an effective method for identifying genetic variants associated with complex diseases in large-scale GWAS of multiple phenotypes

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Health Econ. 2021 Nov;30:2905-20.

GENETIC RISKS, ADOLESCENT HEALTH, AND SCHOOLING ATTAINMENT.

Amin V, Behrman JR, Fletcher JM, et al.

We provide new evidence on the effect of adolescent health behaviors/outcomes (obesity, depression, smoking, and attention deficit hyperactivity disorder [ADHD]) on schooling attainment using the National

Longitudinal Study of Adolescent to Adult Health. We take two different approaches to deal with omitted variable bias and reverse causality. Our first approach attends to the issue of reverse causality by estimating the effect of health polygenic scores (PGSs) on schooling. Second, we estimate the effect of adolescent health using sibling fixed-effects models that control for unmeasured genetic and family factors shared by siblings. We use the PGSs as additional controls in the sibling fixed-effects models to reduce concerns about residual confounding from sibling-specific genetic differences. We find consistent evidence across both approaches that being genetically predisposed to smoking and smoking regularly in adolescence reduces schooling attainment. Estimates for depression are more imprecise, but also suggest that a high genetic risk of depression and adolescent depression reduce schooling attainment. We find mixed evidence for ADHD. Our estimates suggest that having a high genetic risk for ADHD reduces grades of schooling, but we do not find any statistically significant negative effects of ADHD. Finally, we find no consistent evidence for a detrimental effect of obesity on schooling attainment

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Health Sociol Rev. 2021 Jul;30:188-203.

SOCIAL CLASS, TEACHERS, AND MEDICALISATION LAG: A QUALITATIVE INVESTIGATION OF TEACHERS' DISCUSSIONS OF ADHD WITH PARENTS AND THE EFFECT OF NEIGHBOURHOOD-LEVEL SOCIAL CLASS.

Simoni Z.

While medical sociologists have explored how teachers aid the medicalisation process of Attention Deficit Hyperactivity Disorder (ADHD), there is a paucity of work investigating the role of neighbourhood-level social class. This paper has two main aims. First, to explore how teachers discuss ADHD with parents, and second, to understand how these discussions differ based upon neighbourhood-level social class. To achieve these aims, I utilise grounded theory and interviews with thirty-four elementary school teachers. Emergent themes describe the following process: (a) reifying biological causation of ADHD, (b) evidence gathering, and (c) furtive diagnosis. Findings suggest teachers in upper-class areas skipped steps in the process or easily managed each step while discussing ADHD with parents. Teachers in lower-class areas were met with barriers that affected the likelihood of children receiving a furtive diagnosis from teachers, thus reducing the likelihood of meeting with a medical professional and receiving medical intervention. Findings explain disparities in medication use for ADHD by neighbourhood-level social class and help to explain the social reproduction of social class. By building on the literature regarding cultural capital and mental health literacy, I conceptualise 'medicalisation lag' as integral to the medicalisation process and to the social reproduction of social class

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Health Technol Assess. 2021 May;25:1-84.

A VIDEO-FEEDBACK PARENTING INTERVENTION TO PREVENT ENDURING BEHAVIOUR PROBLEMS IN AT-RISK CHILDREN AGED 12-36 MONTHS: THE HEALTHY START, HAPPY START RCT .

O'Farrelly C, Barker B, Watt H, et al.

Background: Behaviour problems emerge early in childhood and place children at risk for later psychopathology.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of a parenting intervention to prevent enduring behaviour problems in young children.

Design: A pragmatic, assessor-blinded, multisite, two-arm, parallel-group randomised controlled trial.

Setting: Health visiting services in six NHS trusts in England.

Participants: A total of 300 at-risk children aged 12-36 months and their parents/caregivers.

Interventions: Families were allocated in a 1 : 1 ratio to six sessions of Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline (VIPP-SD) plus usual care or usual care alone.

Main outcome measures: The primary outcome was the Preschool Parental Account of Children's Symptoms, which is a structured interview of behaviour symptoms. Secondary outcomes included caregiver-reported total problems on the Child Behaviour Checklist and the Strengths and Difficulties Questionnaire. The intervention effect was estimated using linear regression. Health and social care service use was recorded using the Child and Adolescent Service Use Schedule and cost-effectiveness was explored using the Preschool Parental Account of Children's Symptoms.

Results: In total, 300 families were randomised: 151 to VIPP-SD plus usual care and 149 to usual care alone. Follow-up data were available for 286 (VIPP-SD, n = 140; usual care, n = 146) participants and 282 (VIPP-SD, n = 140; usual care, n = 142) participants at 5 and 24 months, respectively. At the post-treatment (primary outcome) follow-up, a group difference of 2.03 on Preschool Parental Account of Children's Symptoms (95% confidence interval 0.06 to 4.01; p = 0.04) indicated a positive treatment effect on behaviour problems (Cohen's d = 0.20, 95% confidence interval 0.01 to 0.40). The effect was strongest for children's conduct [1.61, 95% confidence interval 0.44 to 2.78; p = 0.007 (d = 0.30, 95% confidence interval 0.08 to 0.51)] versus attention deficit hyperactivity disorder symptoms [0.29, 95% confidence interval -1.06 to 1.65; p = 0.67 (d = 0.05, 95% confidence interval -0.17 to 0.27)]. The Child Behaviour Checklist [3.24, 95% confidence interval -0.06 to 6.54; p = 0.05 (d = 0.15, 95% confidence interval 0.00 to 0.31)] and the Strengths and Difficulties Questionnaire [0.93, 95% confidence interval -0.03 to 1.9; p = 0.06 (d = 0.18, 95% confidence interval -0.01 to 0.36)] demonstrated similar positive treatment effects to those found for the Preschool Parental Account of Children's Symptoms. At 24 months, the group difference on the Preschool Parental Account of Children's Symptoms was 1.73 [95% confidence interval -0.24 to 3.71; p = 0.08 (d = 0.17, 95% confidence interval -0.02 to 0.37)]; the effect remained strongest for conduct [1.07, 95% confidence interval -0.06 to 2.20; p = 0.06 (d = 0.20, 95% confidence interval -0.01 to 0.42)] versus attention deficit hyperactivity disorder symptoms [0.62, 95% confidence interval -0.60 to 1.84; p = 0.32 (d = 0.10, 95% confidence interval -0.10 to 0.30)], with little evidence of an effect on the Child Behaviour Checklist and the Strengths and Difficulties Questionnaire. The primary economic analysis showed better outcomes in the VIPP-SD group at 24 months, but also higher costs than the usual-care group (adjusted mean difference £1450, 95% confidence interval £619 to £2281). No treatment- or trial-related adverse events were reported. The probability of VIPP-SD being cost-effective compared with usual care at the 24-month follow-up increased as willingness to pay for improvements on the Preschool Parental Account of Children's Symptoms increased, with VIPP-SD having the higher probability of being cost-effective at willingness-to-pay values above £800 per 1-point improvement on the Preschool Parental Account of Children's Symptoms.
Limitations: The proportion of participants with graduate-level qualifications was higher than among the general public.
Conclusions: VIPP-SD is effective in reducing behaviour problems in young children when delivered by health visiting teams. Most of the effect of VIPP-SD appears to be retained over 24 months. However, we can be less certain about its value for money.
Trial registration: Current Controlled Trials ISRCTN58327365.
Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 25, No. 29. See the NIHR Journals Library website for further project information

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Inquiry. 2021 Jan;58:469580211049065.

Online Learning Performances of Children and Adolescents With Attention Deficit Hyperactivity Disorder During the COVID-19 Pandemic.

He S, Shuai L, Wang Z, et al.

To investigate attention deficit hyperactivity disorder (ADHD) core symptoms that impair executive function (EF), emotional state, learning motivation, and the family and parenting environment of children and adolescents with ADHD, both with and without severe difficulties. This will be explored within an online learning environment during the period of COVID-19 pandemic. A total of 183 ADHD children diagnosed using DSM-V criteria were selected and divided into 2 groups high difficulties during online learning (HDOL) and low difficulties during online learning (LDOL) according to the answer of Home Quarantine Investigation of the Pandemic (HQIP). The participants filled out a set of questionnaires to assess their emotional state and learning motivation, and their parents also filled out the questionnaires about ADHD core symptoms, EF, and family and parenting environment. Compared with ADHD children in the LDOL group, the children in the HDOL group had significant symptoms of inattention, hyperactivity, oppositional defiant, behavioral and emotional problems according to the Swanson, Nolan, and Pelham Rating Scale (SNAP). They also had more severely impaired EF according to the Behavior Rating Inventory of Executive Function (BRIEF), more difficulties and disturbances in the family by the Chinese version of Family Environment Scale (FES-CV), and lower parenting efficacy and satisfaction by Parenting Sense of Competence (PSOC). With regard to the

self-rating questionnaires of children and adolescents, the HDOL group reported lower learning motivation according to the Students Learning Motivation Scale (SLMS). By Screening for Child Anxiety-Related Emotional Disorders and Depression Self-Rating Scale for Children (DSRSC), those in HDOL presented more negative emotions. The HDOL group spent significantly more time on both video games and social software per day and significantly less time on multiple activities per week, when compared to those in the LDOL group. This study demonstrated that ADHD children and adolescents with HDOL had more inattention-related behaviors, more severe emotional problems and EF impairment, weaker learning motivation, and poorer family and parenting environment. Meanwhile, digital media use should be supervised and appropriate extracurricular activities should be encouraged by parents and schools

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Int J Eat Disord. 2021 May;54:785-93.

ONE SIZE DOES NOT FIT ALL. GENOMICS DIFFERENTIATES AMONG ANOREXIA NERVOSA, BULIMIA NERVOSA, AND BINGE-EATING DISORDER.

HÃbel C, Abdulkadir M, Herle M, et al.

OBJECTIVE: Genome-wide association studies have identified multiple genomic regions associated with anorexia nervosa. No genome-wide studies of other eating disorders, such as bulimia nervosa and binge-eating disorder, have been performed, despite their substantial heritability. Exploratively, we aimed to identify traits that are genetically associated with binge-type eating disorders.

METHOD: We calculated genome-wide polygenic scores for 269 trait and disease outcomes using PRSice v2.2 and their association with anorexia nervosa, bulimia nervosa, and binge-eating disorder in up to 640 cases and 17,050 controls from the UK Biobank. Significant associations were tested for replication in the Avon Longitudinal Study of Parents and Children (up to 217 cases and 3,018 controls).

RESULTS: Individuals with binge-type eating disorders had higher polygenic scores than controls for other psychiatric disorders, including depression, schizophrenia, and attention deficit hyperactivity disorder, and higher polygenic scores for body mass index.

DISCUSSION: Our findings replicate some of the known comorbidities of eating disorders on a genomic level and motivate a deeper investigation of shared and unique genomic factors across the three primary eating disorders

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Int J Environ Res Public Health. 2021 Sep;18.

EMPATHY QUOTIENT AND SYSTEMIZING QUOTIENT IN ELEMENTARY SCHOOL CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A COMPARATIVE STUDY.

Lasmono A, Ismail RI, Kaligis F, et al.

This study compares the Empathy Quotient (EQ) and Systemizing Quotient (SQ) scores of elementary school children with and without ADHD. The study also examined their brain types and, because sex plays a big role in empathy and systemizing ability, compared the results of the boys and girls. This cross-sectional study involved 122 participants, including 61 parents of children with ADHD and 61 parents of children without ADHD. The EQ, SQ and brain types were obtained using the Empathy and Systemizing Quotient in children (EQ-/SQ-C), validated in the Indonesian language. Data was analyzed using the SPSS program version 20 for Windows, with a p-value < 0.05 for statistical significance. There was a significant difference in EQ between children with and without ADHD, the score being lower in children with ADHD. There was also a significant difference in SQ among girls with and without ADHD, but not in boys. The brain types in both groups were not significantly different. The results indicate that children with ADHD have a lower ability to empathize compared to children without ADHD. Systemizing abilities were significantly lower in girls with ADHD than in girls without. Therefore, an intervention program focusing on improving empathy and systemizing ability needs to be developed in the community

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Int J Environ Res Public Health. 2021 Sep;18.

EVALUATING THERAPEUTIC EFFECTS OF ADHD MEDICATION OBJECTIVELY BY MOVEMENT QUANTIFICATION WITH A VIDEO-BASED SKELETON ANALYSIS.

Ouyang CS, Chiu YH, Chiang CT, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder in children. Several scales are available to evaluate ADHD therapeutic effects, including the Swanson, Nolan, and Pelham (SNAP) questionnaire, the Vanderbilt ADHD Diagnostic Rating Scale, and the visual analog scale. However, these scales are subjective. In the present study, we proposed an objective and automatic approach for evaluating the therapeutic effects of medication in patients with (ADHD). The approach involved using movement quantification of patients' skeletons detected automatically with OpenPose in outpatient videos. Eleven skeleton parameter series were calculated from the detected skeleton sequence, and the corresponding 33 features were extracted using autocorrelation and variance analysis. This study enrolled 25 patients with ADHD. The outpatient videos were recorded before and after medication treatment. Statistical analysis indicated that four features corresponding to the first autocorrelation coefficients of the original series of four skeleton parameters and 11 features each corresponding to the first autocorrelation coefficients of the differenced series and the averaged variances of the original series of 11 skeleton parameters significantly decreased after the use of methylphenidate, an ADHD medication. The results revealed that the proposed approach can support physicians as an objective and automatic tool for evaluating the therapeutic effects of medication on patients with ADHD

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Int J Environ Res Public Health. 2021 Sep;18.

TRENDS OF MENTAL DISORDERS AND TREATMENT CONTINUITY PREDICTORS OF NEW PATIENTS IN THE PAEDIATRIC PSYCHIATRY CLINIC OF A UNIVERSITY HOSPITAL.

Lee AR, Bahn GH.

This study analysed trends of first-time patients visiting the paediatric psychiatry clinic in a university hospital. The medical records from 2009 to 2016 of first-time patients visiting the Kyung Hee University Hospital were reviewed, focusing on children in grades 1-12. We analysed the clinical diagnosis rate of mental disorders per 100,000 in the general population by gender and grade, and the characteristics of patients who sought outpatient care more than three times. The study included 1467 participants, of which 931 were males (63.5%). The number of male patients per 100,000 population significantly decreased from 4.14 in 2009 to 2.03 in 2016. While hyperkinetic disorders had the highest prevalence in males, neurotic disorders were most frequent in females. The rate of disruptive behaviour disorders in males and mental retardation in females decreased significantly during the data collecting period. The factors affecting treatment continuity were being female, 7th-12th graders, and diagnosis of depressive, hyperkinetic, and tic disorders. Physicians should consider the new paediatric patients' gender, grade, and expected diagnosis from their first visit to improve treatment compliance

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Int J Environ Res Public Health. 2021 Sep;18.

RELATIONSHIP BETWEEN BULLYING VICTIMIZATION AND QUALITY OF LIFE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN TAIWAN: MEDIATION OF THE EFFECTS OF EMOTIONAL PROBLEMS AND ADHD AND OPPOSITIONAL DEFIANT SYMPTOMS.

Lin CW, Lee KH, Hsiao RC, et al.

This cross-sectional study investigated the mediating effects of emotional problems including depression, anxiety, attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) symptoms on the association between bullying victimization and quality of life (QoL) among adolescents with ADHD in Taiwan. A total of 171 adolescents diagnosed as having ADHD participated in this study. Adolescents completed the School Bullying Experience Questionnaire, the Taiwanese Quality of Life Questionnaire for Adolescents, the Taiwanese version of the Children's Depression Inventory and the Multidimensional Anxiety Scale for Children. Caregivers completed the Chinese version of the Swanson, Nolan, and Pelham Version IV Scale. Structural equation modeling (SEM) was used to examine the relationships among the variables. The results of SEM revealed that bullying victimization indirectly correlated with QoL through the mediation

of emotional problems in adolescents with ADHD, whereas ADHD and ODD symptoms did not mediate the association between bullying victimization and QoL. Bullying victimization should be actively prevented and intervened on to ensure better QoL in adolescents with ADHD. Moreover, emotional problems should be alleviated among adolescents with ADHD with bullying victimization experience to maintain their QoL

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Int J Hyg Environ Health. 2021 Mar;232:113686.

PROXIMITY TO TRAFFIC AND EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS IN RELATION TO ATTENTION DEFICIT HYPERACTIVITY DISORDER AND CONDUCT DISORDER IN U.S. CHILDREN.

Kim SS, Vuong AM, Dietrich KN, et al.

BACKGROUND: Traffic related air pollution (TRAP) and its component polycyclic aromatic hydrocarbons (PAHs) may be neurotoxic in children. There is limited research on postnatal exposure to TRAP and PAHs and child neurodevelopment.

METHODS: We linked data from the U.S. NHANES 2001-2004 with the National Highway Planning Network 2005 to examine the proximity to major roads (highway or urban/rural principal arterials), urinary PAH metabolites, and diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and Conduct Disorder (CD) based on Diagnostic Interview Schedule for Children (C-DISC) in 1253 children aged 8-15 years. We calculated odds ratios (ORs) and 95% Confidence Intervals (CIs) for ADHD and CD by traffic proximity and PAH exposures using logistic regression adjusted for confounders.

RESULTS: Higher ADHD prevalence was observed among children living <500Â m (9.86%) compared to those 500m (3.84%) from a major road. Prevalence of children with CD was comparable (<500m: 2.51% and 500m: 2.43%). We found little difference in urinary PAH metabolite levels between children living near major roads and those who did not. Children living <500 m from a major road had a non-significant OR of 2.06 (95% CI 0.85-5.03) for ADHD diagnosis. Children living on 2 major roads within 500m of a highway had a non-significant OR of 2.27 (95% CI 0.71-7.26) for ADHD diagnosis. There was no association between proximity to major roads and CD diagnosis.

CONCLUSION: We found living close to a major road was not associated with increased PAH levels. We did not find statistically significant relation between proximity to a major road or urinary PAH metabolite levels and ADHD or CD diagnosis in this cross-sectional analysis. Prospective studies are needed for the investigation of postnatal TRAP exposure and ADHD and CD diagnosis

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Int J Methods Psychiatr Res. 2020 Dec;29:1-14.

ASSESSMENT OF A CONCEPTUALLY INFORMED MEASURE OF EMOTION DYSREGULATION: EVIDENCE OF CONSTRUCT VALIDITY VIS A VIS IMPULSIVITY AND INTERNALIZING SYMPTOMS IN ADOLESCENTS WITH ADHD.

Monopoli WJ, Evans SW, Benson K, et al.

OBJECTIVES: Despite advances in understanding associations among attention-deficit hyperactivity disorder (ADHD), emotion dysregulation (ED), and related outcomes, there is incongruity between ADHD-relevant conceptualizations of ED and available measures of ED. To assess the psychometric properties of a parent-report questionnaire of ED conceptualized as deficits in the ability to modulate the (a) speed/degree of emotion escalation; (b) expression intensity; and (c) speed/degree of de-escalation.

METHODS: Participants were 209 adolescents with ADHD (78% male; 13.5-17.8years old [M = 15.2 SD = 0.91]). Questionnaire items were selected from parent-report scales of ED and oppositional defiant disorder and subjected to exploratory factor analysis (EFA) and validity analyses.

RESULTS: The EFA revealed two factors, with speed/degree of escalation combined with intensity as factor one, and speed/degree of de-escalation as factor two. Factor one scores were related to ADHD impulsivity symptoms but not to anxiety and depression symptoms and they remained predictors of impulsivity even in the presence of self-report ED, evincing convergent, discriminant, and incremental validity. Factor two scores were related to anxiety and depression but not impulsivity, evincing convergent and discriminant validity.

CONCLUSION: These results inform our understanding of ADHD-relevant ED in adolescence and offer avenues for future research in measurement development, as well as for understanding ED and ADHD-related impairment

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Int J Methods Psychiatr Res. 2020 Sep;29:e1837.

LIFETIME TREATMENT OF DSM-IV MENTAL DISORDERS IN THE SAUDI NATIONAL MENTAL HEALTH SURVEY.

Al-Subaie AS, Altwaijri YA, Al-Habeeb A, et al.

OBJECTIVES: To estimate lifetime treatment rates of mental disorders in the Saudi National Mental Health Survey (SNMHS).

METHODS: The SNMHS is a face-to-face community epidemiological survey in a nationally representative household sample of citizens ages 15-65 in the Kingdom of Saudi Arabia (KSA) (n = 4,004). The World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) was used to produce estimates of lifetime prevalence and treatment of common DSM-IV mental disorders.

RESULTS: Lifetime treatment ranged from 52.2% for generalized anxiety disorder to 20.3% for attention deficit/hyperactivity disorder, had a median (interquartile range) of 35.5% (30.6-39.5%) across disorders, and was 28.3% for people with any lifetime DSM-IV/CIDI disorder. Half (49.0%) of patients received treatment in the mental health specialty sector, 35.9% in the general medical sector, 35.2% in the human services sector, and 15.7% in the complementary-alternative medical sector. Median (interquartile range) delays in help-seeking after disorder onset among respondents who already sought treatment were 8 (3-15) years. Odds of seeking treatment are positively related to age-of-onset and comorbidity.

CONCLUSIONS: Unmet need for treatment of lifetime mental disorders is a major problem in KSA. Interventions to ensure prompt help-seeking are needed to reduce the burdens and hazards of untreated mental disorders

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Int J Environ Res Public Health. 2021;18.

STRUCTURAL EQUATION MODELING (SEM): CHILDHOOD AGGRESSION AND IRRITABLE ADHD ASSOCIATED WITH PARENTAL PSYCHIATRIC SYMPTOMS.

Tzang RF, Chang YC, Chang CH.

Background: Children with attention deficit hyperactivity disorder (ADHD) co-occurring with Oppositional Defiant Disorder (ODD) further present aggressive behavior and may have a depressive parent. A child with co-occurring ADHD and ODD has differentially higher levels of behavioral and emotional difficulties. Little is known about how the irritable subtype of ADHD in children mediates the development of parental symptomatology. This study aims to elucidate the direct or indirect influence of childhood disruptive ADHD with aggressive behavior on their parental symptom using Structural Equation Modeling (SEM).

Methods: A total of 231 ADHD children and their parents completed the Swanson, Nolan, and Pelham Version IV questionnaire for symptoms of ADHD, Oppositional Defiant Disorder (ODD) scale for irritable symptoms, Child Behavior Check List (CBCL) for aggression, and Symptom Checklist (SCL) for parental symptom.

Results: The three-factor confirmatory factor analysis (CFA) model found symptoms of inattention, hyperactivity/impulsivity, irritable ODD, and aggression were inter-related. Mediational analyses demonstrated ODD mediates symptoms directly predicting the risk of increasing ADHD severity. Disruptive child symptoms (ADHD + ODD + aggression) may increase the risk of depression-related symptoms in the parent. When the child's aggression increases by one standard deviation (SD), parental psychiatric symptoms increase by 0.235 SD ($p < 0.001$).

Conclusions: By this SEM pathway analysis, there is the correlation between the disruptive, more aggressive subtype of ADHD in children/adolescents and the existence of psychopathological symptomatology of their parents. ADHD + ODD + aggression in children should be classified as an irritable subtype of ADHD, warranting early diagnosis and intensive treatment

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Int J Psychophysiol. 2021;170:59-66.

EFFECTS OF HEMOENCEPHALOGRAPHIC BIOFEEDBACK WITH VIRTUAL REALITY ON SELECTED ASPECTS OF ATTENTION IN CHILDREN WITH ADHD.

Skalski S, Konaszewski K, Pochwatko G, et al.

For children with attention deficit/hyperactivity disorder (ADHD), a reduction of inattention by biofeedback has been shown in several studies. As evidenced by previous reports, biofeedback (BFB) with virtual reality

(VR) allows for controlling distractors, providing an environment that captures participants' attention. The purpose of this study was to evaluate the effects of hemoencephalographic (HEG) BFB with VR in treating deficits in vigilance (assessed using the short form of the Mackworth Clock Task), visual search (the Visual Search Task), and divided attention (Multitasking Test) among children with ADHD. Data subjected to analysis were collected from 87 participants aged 9ΓÇô15 years. Children were assigned to one of three groups (standard 2D BFB in the lab, VR BFB with a limited visual scene, VR BFB with a complex visual scene) and were subjected to ten HEG BFB sessions. Children in the VR BFB groups exhibited a bigger regional cerebral blood oxygenation slope during BFB and better performance in cognitive tests following the experiment compared to children in the 2D BFB group. The data obtained suggest that HEG BFB with VR may have a more beneficial effect in treating attention deficits compared to standard 2D HEG BFB. We believe that the strong effects of HEG BFB with VR stem from the increased commitment and motivation in individuals, rather than from manipulation with regard to visual scene complexity

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J Abnorm Child Psychol. 2020 Jun;48:783-95.

PLACENTAL GENE EXPRESSION AND OFFSPRING TEMPERAMENT TRAJECTORIES: PREDICTING NEGATIVE AFFECT IN EARLY CHILDHOOD.

Finik J, Buthmann J, Zhang W, et al.

Exposure to prenatal stress increases offspring risk for long-term neurobehavioral impairments and psychopathology, such as Attention Deficit Hyperactivity Disorder (ADHD). Epigenetic regulation of glucocorticoid pathway genes may be a potential underlying mechanism by which maternal conditions 'program' the fetal brain for downstream vulnerabilities. The present study aims to investigate whether mRNA expression of glucocorticoid pathway genes in the placenta predict offspring negative affect during early childhood (between 6 and 24 months). Participants include 318 mother-child dyads participating in a longitudinal birth cohort study. Placental mRNA expression of glucocorticoid pathway genes (HSD11B1, HSD11B2, NR3C1, NCOR2) were profiled and negative affect traits of the offspring were measured at 6, 12, 18, and 24 months. HSD11B1 mRNA expression significantly predicted negative affect (β = -.09, SE = .04; p = .036), and Distress to Limitations trajectories (β = -.13, SE = .06; p = .016). NCOR2 mRNA expression significantly predicted Distress to Limitations (β = .43, SE = .21; p = .047), and marginally predicted Sadness trajectories (β = .39, SE = .21; p = .068). HSD11B2 and NR3C1 did not predict trajectories of Negative Affect or subscale scores. Infant negative affect traits were assessed via maternal self-report, and deviated from linearity across follow-up. mRNA expression of glucocorticoid pathway genes in the placenta may be a potentially novel tool for early identification of infants at greater risk for elevated negative affect. Further study is needed to validate the utility of mRNA expression of glucocorticoid pathway genes in the placenta

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J Abnorm Child Psychol. 2020 Dec;48:1591-601.

SLUGGISH COGNITIVE TEMPO AND DEPRESSIVE SYMPTOMS IN CHILDREN AND ADOLESCENTS PREDICT ADULTHOOD PSYCHOPATHOLOGY.

Smith ZR, Zald DH, Lahey BB.

Sluggish cognitive tempo (SCT) is characterized by behavioral symptoms reflecting slowness and lethargy (e.g., sluggishness, appearing sleepy) and inconsistent alertness/mental confusion (e.g., daydreaming, fogginess). SCT is substantially correlated with the inattentive symptoms of attention-deficit/hyperactivity disorder (ADHD) and may be part of that domain, but in cross-sectional data, SCT is also strongly associated with both inattention and depression. To date, no study has examined the prospective associations of SCT symptoms in childhood/adolescence with symptoms of ADHD and internalizing problems in adulthood. Using a sample of 449 twin children and adolescent pairs, prospective multiple regression analyses examined whether self- and parent-reported SCT, depression, and parent-reported symptoms of ADHD predicted symptoms in adulthood 12Â years later. SCT and depression at time one were strongly correlated (self-reported SCT and depression r=0.84; parent-reported SCT and depression r=0.78). When adult outcomes were separately regressed on each youth symptom dimension, self-reported SCT ($Î²$=0.26, p<0.0001) and depression ($Î²$=0.13, p<0.0001) each predicted adult symptoms of depression and self-reported SCT predicted inattention ($Î²$=0.12, p=0.0026). Parent-reported depression, but not parent-reported SCT,

predicted self-reported adult depression symptoms (Î²=0.17, p=0.0003). In contrast, when each adult outcome was regressed simultaneously on youth self-reported SCT and depression, neither predicted adulthood inattention or depression. These findings indicate that SCT in childhood and adolescence is strongly associated concurrently and predictively with both inattention and depression. Theoretical and clinical applications of the construct of SCT must take its robust association with both inattention and depression into account

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J Abnorm Child Psychol. 2020 Sep;48:1197-210.

NEUROCOGNITIVE CORRELATES OF RUMINATION RISK IN CHILDREN: COMPARING COMPETING MODEL PREDICTIONS IN A CLINICALLY HETEROGENEOUS SAMPLE.

Harmon SL, Kistner JA, Kofler MJ.

The current study examined associations between rumination and executive function difficulties in preadolescent youth, using predictions outlined in the attentional scope and multiple systems models of rumination. This study aimed to (a) extend current conceptual models of rumination to youth, (b) clarify disparate model predictions regarding working memory updating ("updating"), inhibition, and shifting abilities, and (c) examine differential neurocognitive predictions between two forms of rumination, sadness and anger. One hundred and fifty-nine youths oversampled for ADHD and other forms of child psychopathology associated with executive dysfunction (aged 8-13; 53.5% male; 59.1% Caucasian) completed a battery of assessments, including self-report measures of rumination and computerized neurocognitive tasks. Multiple regression analyses were conducted assessing relations between rumination and each executive function, controlling for both sadness and anger rumination to assess their unique associations. Sadness rumination was associated with poorer updating (β = -0.18, p = 0.046) and shifting abilities (β = 0.20, p = 0.03) but not inhibition (β = -0.04, p = 0.62), offering partial support to the attentional scope and multiple systems models. In contrast, anger rumination was associated with better updating abilities (β = 0.20, p = 0.03) but not shifting (β = -0.15, p = 0.11) or inhibition (β = 0.08, p = 0.35). Together, these results suggest (a) developmental differences in the neurocognitive correlates associated with rumination risk in youth compared to findings from the adult literature, and (b) that the executive function correlates of children's responses to negative emotions are affect-specific, such that sadness rumination is associated with difficulties replacing negative thoughts and shifting between mental sets, while anger rumination is associated with a better ability to maintain negative thoughts

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J Abnorm Child Psychol. 2020 Jul;48:923-33.

PHYSIOLOGICAL CORRELATES OF SLUGGISH COGNITIVE TEMPO IN CHILDREN: EXAMINING AUTONOMIC NERVOUS SYSTEM REACTIVITY DURING SOCIAL AND COGNITIVE STRESSOR TASKS.

Becker SP, McQuade JD.

It is important to establish correlates of sluggish cognitive tempo (SCT) across units of analysis and to better understand how SCT may be conceptualized in models of psychopathology. The current study examined SCT symptoms in relation to automatic nervous system reactivity during social and cognitive stressor tasks. Participants were 61 children ages 8-12 years with a full range of attention-deficit/hyperactivity disorder (ADHD) symptom severity. Parents provided ratings of SCT and parents and teachers completed measures that were used to create composite indices of ADHD symptoms. Children were administered standardized peer rejection and impossible puzzle tasks, during which their respiratory sinus arrhythmia (RSA) and skin conductance level (SCL) reactivity were recorded. Regression analyses indicated that SCT symptoms were unassociated with RSA reactivity to either task. Greater SCT symptoms were significantly associated with greater SCL reactivity to peer rejection. Greater SCT symptoms were not significantly associated with SCL reactivity to the impossible puzzle task. The pattern of findings was unchanged in sensitivity analyses that controlled for ADHD symptoms, internalizing symptoms, medication status, or sex. This study provides the first evidence that SCT symptoms are associated with sympathetic nervous system reactivity. These findings suggest that SCT symptoms may be associated with greater behavioral inhibition system activation, and reactivity may be especially pronounced in social challenges

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J Abnorm Child Psychol. 2020 Dec;48:1555-68.

TRAJECTORIES OF OVERPROTECTIVE PARENTING AND HYPERACTIVITY-IMPULSIVITY AND INATTENTION AMONG MODERATE-LATE PRETERM CHILDREN: A POPULATION-BASED STUDY.

Faleschini S, Matte-GagnÃ© C, Luu TM, et al.

Parents of preterm children are more likely to adopt non-optimal parenting behaviors than parents of full-term (FT) children. However, there is a lack of studies on parents of children born moderate to late preterm (MLP; 32-36 gestational weeks). In this study, we aimed to examine: (1) the association between MLP birth status and the trajectory of parental overprotection throughout preschool years, and (2) the role of parental overprotection, MLP birth status, and their interaction in the prediction of the trajectories of hyperactivity-impulsivity and inattention throughout childhood. Data comes from a Canadian representative population-based cohort including 2028 FT, 100 MLP children, and their parents. Overprotective parenting was measured when children were 5, 17, and 29Â months old. Hyperactivity-impulsivity and inattention symptoms were measured repeatedly from 4 to 8Â years of age. Trajectories of parents' overprotectiveness and children's hyperactivity-impulsivity and inattention were modeled. MLP birth status was associated with an increase in parental overprotectiveness across the preschool period. MLP birth status and parental overprotection were both found to be associated with higher levels of hyperactivity-impulsivity symptoms across childhood. No interaction was found between birth status and parental overprotection. The results suggest that parents of MLP children become more overprotective across time compared to parents of FT children and that children born MLP and/or exposed to higher levels of parental overprotection demonstrated higher levels of hyperactivity-impulsivity symptoms across childhood

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J Abnorm Child Psychol. 2020 Dec;48:1543-53.

Real-World Changes in Adolescents' ADHD Symptoms within the Day and across School and Non-school Days.

Pedersen SL, Kennedy TM, Joseph HM, et al.

Research on attention-deficit/hyperactivity disorder (ADHD) points to the possibility that contextual factors (e.g., time of day, school vs. home) may be related to symptoms and impairment. This prior research has relied on laboratory-based or retrospective, global approaches which has limited ecological validity. The present study substantively contributes to the extant literature by examining adolescents' ADHD symptoms in the real world across the day on both school and non-school days to test whether symptoms worsened throughout the day and were higher on school days relative to non-school days. As part of a larger study, 83 adolescents taking stimulant medication for ADHD (M(age)â€‰=â€‰14.7, 66% identified as boys/men, 78% White) completed a 17-day ecological momentary assessment protocol that included wake-up and bedtime reports and two reports in the afternoon and evening. These assessments asked about ADHD symptoms and stimulant medication usage since the last report. Hypotheses were tested using multilevel modeling. Accounting for demographic covariates and medication usage, ADHD symptoms worsened quadratically, peaking by the afternoon report and subsequently declining, across school days but not non-school days. Mean-level ADHD symptoms were also worse on school days relative to non-school days. Results did not differ across gender. In conclusion, our study is the first to examine important environmental factors (school, time of day) in real time in relation to level of naturalistically occurring ADHD symptoms. Our findings highlight the importance of advancing treatments to support adolescents with ADHD on school days and in the afternoon

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J Abnorm Child Psychol. 2020 Jul;48:881-94.

APPLICATION OF THE BIFACTOR S - 1 MODEL TO MULTISOURCE RATINGS OF ADHD/ODD SYMPTOMS: AN APPROPRIATE BIFACTOR MODEL FOR SYMPTOM RATINGS.

Burns GL, Geiser C, Servera M, et al.

The symmetrical bifactor model is often applied to attention-deficit/hyperactivity disorder (ADHD)-hyperactive/impulsive (HI), ADHD-inattentive (IN), and oppositional defiant disorder (ODD) symptoms, but this model frequently yields anomalous or inadmissible results. An alternative model, the bifactor S - 1 model, is more appropriate for examining the hierarchical structure of ADHD/ODD symptoms. Both models were

applied to ADHD-HI, ADHD-IN, and ODD symptom ratings by mothers, fathers, and teachers for 2142 Spanish children (49.49% girls; ages 8-13Â years). The symmetrical bifactor model yielded the typical anomalous loadings, with a weakly defined ADHD-HI specific factor and difficult to interpret associations of general and specific factors with correlates. In contrast, the bifactor S - 1 model with ADHD-HI symptoms as general reference factor produced clearly interpretable results. For mothers and fathers, slightly more than 50% of true score variance in ADHD-IN and ODD symptoms represented specific residual variance not shared with the general ADHD-HI reference factor. For teachers, approximately 69% and 39% of true score variance in ADHD-IN and ODD symptoms, respectively, represented specific residual variance not shared with the general ADHD-HI reference factor. The general ADHD-HI reference factor and specific ADHD-IN and ODD residual factors showed convergent and discriminant validity across sources, along with unique associations with peer rejection, social impairment, and academic impairment factors. The bifactor S - 1 model also yielded results consistent with predictions from trait-impulsivity theory of ADHD/ODD development. Researchers should use the bifactor S - 1 model rather than the symmetrical bifactor model if hypotheses involve the latent hierarchical structure of ADHD/ODD symptoms

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J Abnorm Child Psychol. 2020 Nov;48:1425-37.

DO PARENTS' ADHD SYMPTOMS AFFECT TREATMENT FOR THEIR CHILDREN? THE IMPACT OF PARENTAL ADHD ON ADHERENCE TO BEHAVIORAL PARENT TRAINING FOR CHILDHOOD ADHD.

Friedman LM, Dvorsky MR, McBurnett K, et al.

Nearly half of all youth with Attention-Deficit Hyperactivity Disorder (ADHD) have at least one parent who also meets criteria for the disorder, and intergenerational ADHD is a significant risk factor for poor outcomes following evidence-based behavioral parent training (BPT) programs. Given that BPT is predicated on consistent parental involvement, symptoms of ADHD in parents may be a significant barrier to effective engagement with BPT treatment. In the present investigation, we examine the effect of parental ADHD symptoms on BPT treatment engagement for children with ADHD-predominantly inattentive presentation (N=148, ages 7-11). We examine the following parent- and clinician-rated treatment engagement domains: between-session skill adherence, in-session participation, perceived skill understanding, treatment-engagement attitudes, and session attendance. Parent- and clinician-rated between-session adherence was the only treatment engagement domain related significantly to parental ADHD symptoms. This finding was robust and remained even after accounting for symptoms of parental anxiety and depression, child ADHD symptom severity, and various sociodemographic factors (parental education level, household income, employment status, and being a single parent). These findings suggest that targeting parental ADHD symptoms in the context of parenting interventions may be a promising approach for improving adherence and treatment outcomes for BPT interventions

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J Abnorm Child Psychol. 2020 Sep;48:1115-28.

MODERATING THE RISK FOR ATTENTION DEFICITS IN CHILDREN WITH PRE-ADOPTIVE ADVERSITY: THE PROTECTIVE ROLE OF SHORTER DURATION OF OUT OF HOME PLACEMENT AND CHILDREN'S ENHANCED ERROR MONITORING.

Frenkel TI, Donzella B, Frenn KA, et al.

Early institutional-deprivation has been found to increase risk for inattention/hyperactivity (ADHD). Notably, studies suggest that children with a history of adversity evidencing an enhanced ERP (the error-related-negativity; ERN) may be protected against attention problems. However, such protective effects of the ERN have been studied in children whom typically experienced residential instability. It is unknown whether error-monitoring is similarly protective for children with stable post-deprivation placements. The present study examined the protective effect of the ERN in a sample of children who experienced at least 3-years of stable, relatively enriched caregiving after being internationally-adopted as infants/toddlers from institutional-care. We included two groups of children adopted internationally before age three, one group adopted from institutional-care (PI:n = 80) and one comparison group adopted from foster-care (FC;n = 44). A second comparison group consisted of non-adopted children (NA;n = 48) from demographically comparable families. At five-years of age, we assessed child ADHD symptoms (parent-report) and behavioral performance and neural correlates of error-monitoring (Go/No-Go task). PI children displayed lower Go/No-Go accuracy

relative to FC children, and higher levels of ADHD symptoms relative to NA controls. In both FC and PI groups, longer duration of pre-adoptive out-of-home placement was associated with inattention, especially for children with deficits in error-monitoring. Enhancing cognitive control in the form of error monitoring might be a useful intervention target to protect children from some of the negative outcomes associated with adverse early care. Furthermore, results underscore that regardless of type of pre-adoptive care, we should aim to place children in stable/permanent homes as early as possible

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J Adolesc Health. 2021 Nov;69:806-14.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATION ADHERENCE IN THE TRANSITION TO ADULTHOOD: ASSOCIATED ADVERSE OUTCOMES FOR FEMALES AND OTHER DISPARITIES .

Rao K, Carpenter DM, Campbell CI.

PURPOSE: The purpose of this study was to assess the association between attention-deficit/hyperactivity disorder (ADHD) medication adherence and adverse health outcomes in older adolescents transitioning to adulthood.

METHODS: In a cohort of 17-year-old adolescents with ADHD at Kaiser Permanente Northern California, we assessed medication adherence (medication possession ratio 70%) and any medication use and associations with adverse outcomes at 18 and 19 years of age. We conducted bivariate tests of association and multivariable logistic regression models.

RESULTS: Adherence declined from 17 to 19 years of age (36.7%-19.1%, p < .001). Non-white race/ethnicity, lower estimated income, and male sex were associated with nonadherence. Model results show nonadherent females experienced several adverse outcomes: Adherence at 18 years of age (referent: nonadherence) was associated with lower odds of pregnancy (adjusted odds ratio [AOR]: .13, 95% confidence interval [CI]: .03-.54). Any use (referent: nonuse) at 18 years of age was associated with lower odds of sexually transmitted infections among females (AOR: .39, 95% CI: .19-.83), pregnancies (AOR: .26, 95% CI: .13-.50), emergency department visits (AOR: .69, 95% CI: .55-.85), and greater odds of injuries (AOR: 1.16, 95% CI: 1.02-1.32). Adherence at 19 years of age was associated with lower odds of pregnancy (AOR: .13, 95% CI: .02-.95). Any use at 19 years of age was associated with lower odds of injury in females (AOR: .77, 95% CI: .60-.99) pregnancy (AOR: .35, 95% CI: .16-.78), and, in both sexes, substance use (AOR: .71, 95% CI: .55-.92).

CONCLUSIONS: Late adolescence is associated with decline in ADHD medication use and adherence. ADHD medication adherence and any ADHD medication use is associated with fewer adverse health outcomes, particularly in females

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J Affect Disord. 2021 Dec;295:1474-81.

SWITCHES AND EARLY DISCONTINUATIONS OF ANTIDEPRESSANT MEDICATION IN YOUNG ADULTS WITH DEPRESSION.

Lampela P, Tanskanen A, LÃ¤hteenvuo M, et al.

BACKGROUND: Receiving treatment for depression is increasingly common among young adults. Antidepressants (AD) are important in depression treatment and modification of medication is common. We examined switches and discontinuations of ADs among young Finnish adults aged 18-29 years.

METHODS: All persons diagnosed with depression in inpatient or specialized outpatient care or having received sickness absence or disability pension due to depression at age of 18-29 years during 2004-17 were included (N = 110761). Among them, we focused on incident AD users (N = 52855, 47.7%) who were identified with a 6 month washout before AD initiation. The follow-up was 2 years.

RESULTS: The majority (76.3%) initiated with selective serotonin reuptake inhibitors (SSRIs). The initial AD was switched in 17.4% of cases. Switching was most common when treatment was initiated with tricyclic antidepressants (TCA) or polytherapy, and least common when initiated with SSRIs or serotonin-noradrenaline reuptake inhibitors. Factors associated with switch included initiation with polytherapy, TCA or mirtazapine, and use of benzodiazepines or Z-drugs at baseline. During the first 3 months, 27.6% discontinued AD use, and only 14.1% used AD for 2 years. Factors associated with discontinuation included substance abuse, ADHD, previous suicide attempt and initiation with mirtazapine. SSRIs had the longest time to discontinuation (median 144 days, IQR 64-302).

LIMITATIONS: Our data sources lack those treated in primary care only, without receiving a sick leave of 2 weeks. In addition, we do not have data on severity of depression, social factors or psychotherapy.
CONCLUSIONS: Special emphasis should be paid to persons with increased risk of discontinuation, including those with previous self-harm/suicide attempt or substance abuse

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J Affect Disord. 2021 Dec;295:1153-60.
ADHD IN ADULTS WITH RECURRENT DEPRESSION.
Powell V, Agha SS, Jones RB, et al.
BACKGROUND: Depression is highly heterogeneous in its clinical presentation. Those with attention deficit/hyperactivity disorder (ADHD) may be at risk of a more chronic and impairing depression compared to those with depression alone according to studies of young people. However, no studies to date have examined ADHD in recurrently depressed adults in mid-life.
METHOD: In a sample of women in mid-life (n=148) taken from a UK based prospective cohort of adults with a history of recurrent depression, we investigated the prevalence of ADHD and the association of ADHD with clinical features of depression.
RESULTS: 12.8% of the recurrently depressed women had elevated ADHD symptoms and 3.4% met DSM-5 diagnostic criteria for ADHD. None of the women reported having a diagnosis of ADHD from a medical professional. ADHD symptoms were associated with earlier age of depression onset, higher depression associated impairment, a greater recurrence of depressive episodes and increased persistence of subthreshold depression symptoms over the study period, higher levels of irritability and increased risk of self-harm or suicide attempt. ADHD symptoms were associated with increased risk of hospitalisation and receiving non-first-line antidepressant medication.
LIMITATIONS: ADHD was measured using a questionnaire measure. We focussed on mothers in a longitudinal study of recurrent depression, so the findings may not apply to males or other groups.
CONCLUSIONS: Higher ADHD symptoms appear to index a worse clinical presentation for depression. Clinical implications include that in women with early onset, impairing and recurrent depression, the possibility of underlying ADHD masked by depression needs to be considered

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J Altern Complement Med. 2021 Aug;27:678-87.
THE HORSE AS A THERAPIST: EFFECTS OF AN EQUINE PROGRAM WITHOUT "THERAPY" ON THE ATTENTION AND BEHAVIOR OF YOUTH DISENGAGED FROM TRADITIONAL SCHOOL.
Norwood MF, Lakhani A, Maujean A, et al.
Background: Equine-assisted therapy may promote positive behavior change in young people "at risk." However, it is not always clear what therapeutic content is involved and if a trained therapist is included. The therapeutic effects of the key part of the "therapy," the horse, are not understood.
Objectives: To investigate the impact of an equine program without a therapist on attention and behavioral outcomes of young people "at risk." Design: A within subjects pre-post design. A small sample also completed a control period. Setting/location: A small riding center in a rural area of outer Brisbane, Australia. Subjects: Twelve- to 17-year olds (N = 50; 20 girls; mean age 13.88), attending nontraditional flexischool. Intervention: A 5-week program of 2-h long sessions of equine activities that did not include a trained therapist or specific therapeutic content. Outcome measures: Teacher-report measures of externalizing and internalizing behavior were reported before and after the program through the Behavioral Rating Inventory of Executive Function (BRIEF) and the Strength and Difficulties Questionnaire (SDQ).
Results: A paired samples t test resulted in the statistically significant reduction of the BRIEF Global Executive Score between pre and post participation in the equine program (mean difference = -5.89), t(36) = -3.377, p = 0.002 and the SDQ Hyperactivity score (mean difference = -0.727), t(43) = -2.244, p = 0.030. Equine activities may reverse a trajectory of worsening problems. This may especially affect symptoms related to attention deficit hyperactivity disorder.
Conclusion: Equine programs may offer an alternative method to reduce poor behavior and improve attention in young people. Benefits in attention may occur even without specific therapeutic content or

therapist involvement. It is proposed that some of these benefits come directly from the horse and the interactions with the horse; others are contextual

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J Am Acad Child Adolesc Psychiatry. 2021 Oct;60:1319.

OF TRIGGERS, TIGERS, AND TACTICS: MANAGING EMOTIONAL DYSREGULATION.

Chua J, Usher C.

The frustration of defining, understanding, and addressing irritability in child psychiatry and the difficulties that children with emotion dysregulation face on a daily basis can be seen as parallel processes. We know that irritability is one of the most common reasons for which children are referred for evaluation.(1) We also know that the stakes are extremely high, with persistent irritability associated with suicidality.(2) Despite this, we do not have a readily available nosological paradigm. Our current clinical approach remains muddled by outbursts' transdiagnostic nature. We find ourselves listing things such as posttraumatic stress disorder, disruptive mood dysregulation disorder, attention-deficit/hyperactivity disorder, anxiety, and depressive disorders in the chart, but feeling that we have not fully captured the unique neurobiological and subjective essence of a child's irritability syndrome.(3) Furthermore, despite extensive research, we lack accessible diagnostic tools or effective treatment protocols to implement on a community-wide basis. So, we (JC, CU) think we have every right to be irritable as we experience frustrative non-reward (thinking and focusing on this issue with blocked goal attainment) and face existential threat (desperately wanting children and families to enjoy better developmental trajectories, and wanting it now!).(4)

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J Appl Lab Med. 2021 Jan;6:125-41.

HEALTH DISPARITIES AMONG AUSTRALIA'S REMOTE-DWELLING ABORIGINAL PEOPLE: A REPORT FROM 2020.

Davey RX.

BACKGROUND: Australia has 2 distinct indigenous groups, Torres Strait Islanders and Aborigines. The Aborigines, described in this report, first colonized the continent 65 millennia ago. Those still living in the Northern Territory (NT) retain much ancestrally derived genetic complement but also are the most health-challenged by environment and lifestyle in 21st century. Reports providing overviews of these disparities are, as yet, rare.

CONTENT: This review defines the studied population and then describes and attempts to explain contemporary clinical findings among Australia's remote-dwelling Aborigines, principally in the NT. The report is structured by life stage and then by organ system. Finally, a brief synthesis is advanced concerning the disparities that Australia's Aboriginals face.

SUMMARY: In 2015-2017, NT aboriginal life expectancy for people then born was 66.6 years for men and 69.9 years for women compared with 78.1 and 82.7 years, respectively, among nonindigenous Territorians. Principal causes of the reduced longevity, with nonindigenous comparisons, include adolescent pregnancy, with maternal use of alcohol and tobacco (each 7-fold greater); fetal alcohol spectrum disorder and attention deficit hyperactivity disorder; skin infections, both scabies and impetigo (50-fold greater); rheumatic heart disease (260-fold greater); premature acute myocardial infarction (9-fold greater); bronchiectasis (40-fold greater); lung cancer (2-fold greater); diabetes mellitus (10-fold greater); renal failure (30-fold greater); and suicide (2-fold greater). Some disease has genetic roots, secondary to prolonged genetic drift. Much arises from avoidable stressors and from contemporary environmental disparities in housing. The Europid diet is also not helpful

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J Atten Disord. 2021 Sep;25:1564-77.

A DOUBLE-BLIND, RANDOMIZED STUDY OF EXTENDED-RELEASE MOLINDONE FOR IMPULSIVE AGGRESSION IN ADHD.

Ceresoli-Borroni G, Nasser A, Adewole T, et al.

Objective: To evaluate efficacy and safety of SPN-810 (extended-release molindone) in a Phase-2b, randomized, double-blind, placebo-controlled, dose-ranging study of children (6-12 years) with ADHD and persistent impulsive aggression (IA).

Method: After lead-in, children were randomized to (a) placebo (N = 31); (b) low-dose (N = 29, 12/18 mg/day); (c) medium-dose (N = 30, 24/36 mg/day); and (4) high-dose (N = 31, 36/54 mg/day) groups. Treatment included ~2.5-week titration, 3-week maintenance, and 1-week tapering/conversion, alongside existing monotherapy (stimulants/nonstimulants) and behavioral therapy. The primary endpoint was change in Retrospective-Modified Overt Aggression Scale (R-MOAS) score at end of study, with safety monitored.
Results: A total of 95 (78.5%) children completed the study. Aggression (R-MOAS) improved with low and medium doses (low dose: p = .031; medium dose: p = .024; high dose: p = .740). The most common adverse events were headache (10.0%), sedation (8.9%), and increased appetite (7.8%).
Conclusion: These results suggest SPN-810 may be effective in reducing residual IA behaviors in children with ADHD. Research is still needed to support the benefit-risk profile of SPN-810 in pediatric populations

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J Atten Disord. 2021 Oct;25:1640-56.

META-ANALYSIS OF SEX DIFFERENCES IN ADHD SYMPTOMS AND ASSOCIATED COGNITIVE DEFICITS.

Loyer CM, Demers M, Bigras M, et al.

Objective: A meta-analysis was carried out to determine whether there are sex differences among children and adolescents with ADHD on the primary symptoms of ADHD and on executive and attentional functioning.
Method: Studies published from 1997 to 2017 comparing boys and girls with a valid ADHD diagnosis were retained.
Results: The meta-analysis found boys with ADHD to be more hyperactive than girls with ADHD and boys to have more difficulties in terms of motor response inhibition and cognitive flexibility. Results also confirm that youths with ADHD have more executive deficits than non-ADHD peers have, but there is no sex difference in this regard.
Conclusion: Results show that there are sex differences in the behavioral expression of the difficulties related to ADHD. This highlights the importance of pursuing research to refine the profile of girls with ADHD and to develop diagnostic criteria adapted to each sex

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J Atten Disord. 2021 Nov;25:1801-17.

CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER GROWN UP: AN 18-YEAR FOLLOW-UP AFTER MULTIMODAL TREATMENT.

Dahpfner M, Mandler J, Breuer D, et al.

OBJECTIVE: ADHD treatment has positive effects on behavioral symptoms and psychosocial functioning, but studies that follow children treated for ADHD into adulthood are rare.
METHOD: This follow-up study assessed symptom severity and functional outcomes of adults (n=70) who had received individualized ADHD treatment in the Cologne Adaptive Multimodal Treatment (CAMT) Study at ages 6 to 10years.
RESULTS: Despite symptomatic improvement, participants reported poorer educational and occupational outcomes than expected (e.g., currently unemployed: 17%). They had also been in contact with the justice system more often than expected (e.g., lifetime convictions: 33%) and were impaired on health-related outcomes (e.g., substance use problems: 15%). Several social outcomes were favorable (e.g., long-term relationship/married: 63%).
CONCLUSION: Compared to the general population or norm samples, CAMT participants had a higher relative risk (RR) of functional impairments, demonstrating the need for continued support for a substantial proportion of the young adults

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J Atten Disord. 2021 Oct;25:1699-711.

Do ADHD Symptoms and Relationship Quality With Mothers and Best Friends Across High School Predict Depressive Symptoms for Adolescents?

Meinzer MC, Felton JW, Oddo LE, et al.

Objective: Symptoms of ADHD place adolescents at increased risk for depression. The transition from middle to high school may magnify depression risk. This study examined whether changes in adolescents'

negative relationship quality with their mothers and best friends from eighth to 12th grades mediated the longitudinal relations between ADHD and depressive symptoms.
Method: 368 adolescents (48.5% male) were initially recruited.
Results: Boys with elevated ADHD symptoms in the eighth grade reported steeper increases in negative relationship quality with their mothers relative to girls, and that this trajectory mediated the relation between ADHD and depressive symptoms. ADHD symptoms were also associated with increases in negative friendship quality across high school for boys; however, this did not mediate the relation between ADHD and depressive symptoms for either sex.
Conclusion: Growth in mother-adolescent negative relationship quality may be one mechanism that explains the development of depressive symptoms in adolescent boys with elevated ADHD symptoms

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J Atten Disord. 2021 Oct;25:1720-30.
COMT BY DRD3 EPISTATIC INTERACTION IN MODULATING BEHAVIORS IN CHILDREN WITH ADHD: A PHARMACO-DYNAMIC BEHAVIORAL APPROACH.
Fageera W, Grizenko N, Sengupta SM, et al.
OBJECTIVE: Examining the joint effect of two functional variants in two dopamine-related genes (DRD3 and COMT) on ADHD-relevant behaviors under three experimental conditions (EC).
METHOD: 362 children with ADHD were assessed by parents and teachers during a week of baseline evaluation, followed by 1 week of MPH and placebo, administered in a double-blind crossover design.
RESULTS: Statistically significant 3-way (DRD3-by-COMT-by-EC; p = .004) and 2-way interactions (COMT by EC; p = .002) were observed on Conners'-Teachers scores. Children with the COMT Met/Met genotype had lower scores at baseline and on placebo compared to the other genotype groups. Furthermore, stratifying the children according to their COMT genotypes helped to detect statistically significant and biologically meaningful effects of DRD3 genotype.
CONCLUSIONS: These findings suggest that COMT and DRD3 genetic variants may together play a role in ADHD symptomatology and response to treatment through gene-gene interaction

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J Atten Disord. 2021 Sep;25:1544-53.
EXPLORING THE EFFICACY OF A MINDFULNESS PROGRAM FOR BOYS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND OPPOSITIONAL DEFIANT DISORDER.
Muratori P, Conversano C, Levantini V, et al.
Objective: This study was the first attempt to explore the efficacy of a mindfulness protocol for children with attention-deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), and their parents.
Method: Fifty male children with ADHD and ODD diagnosis, aged 8 to 12, were randomly assigned to the mindfulness intervention (n = 25) or the wait-list (n = 25) group. Outcome measures included children, parents', and teachers' reports and objective measures of attention.
Results: Children from the intervention group had a greater reduction in hyperactive behaviors in the school context (effect size [ES] = 0.59) and a greater improvement in visual sustained attention (ES = 0.77) and in Avoidance and Fusion Questionnaire scores (ES = 0.43) than those in the wait-list control group. No significant effect of the intervention on aggressive behaviors was revealed.
Conclusion: A mindfulness intervention for children and their parents showed partial beneficial effects in children with ADHD + ODD

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J Atten Disord. 2021 Oct;25:1765-77.
MINDFULNESS-ENHANCED BEHAVIORAL PARENT TRAINING FOR CLINIC-REFERRED FAMILIES OF CHILDREN WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.
Mah JWT, Murray C, Locke J, et al.
Objective: This study evaluated the efficacy of a mindfulness-enhanced behavioral parent training (BPT) group program compared to standard BPT in families of children with ADHD.

Method: Parents (N = 63) of children (aged 6-11) diagnosed with ADHD were randomly assigned to either mindful or standard BPT, and participated in 12 weekly 2-hr group sessions. Parents completed a series of questionnaires assessing mindful parenting, parenting stress, harsh discipline practices, behavioral dysregulation, and child ADHD symptoms, before and after completing the group intervention.
Results: Parents in the mindful group had decreased harsh discipline practices and improved self-regulation compared to parents in the standard group. Both groups improved in parenting sense of competence and child ADHD symptoms. No significant group differences were found in mindful parenting or parenting stress.
Conclusion: There are some important parental benefits to enhancing BPT with mindfulness

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J Atten Disord. 2021 Nov;25:1818-33.

PREVALENCE AND EPIDEMIOLOGICAL CHARACTERISTICS OF ADHD IN PRE-SCHOOL AND SCHOOL AGE CHILDREN IN THE PROVINCE OF TARRAGONA, SPAIN.

Canals SJ, Morales HP, et al.

Objective: To report the ADHD estimated prevalence in Spain, considering differences in sex, age, presentation, and severity.
Method: This study has a two-phase design and forms part of the Neurodevelopmental Disorders Epidemiological Research Project (EPINED). The ADHD screening was conducted through parent (N=3,727) and teacher (N=6,894). To perform ADHD diagnosis (DSM-5), screen positive and a subsample of the screen negative children and their parents were assessed using neuropsychological tests and a semi-structured psychiatric interview.
Results: The ADHD overall estimate prevalence was 5.5% (7.7% in school-age children; 3.0% in pre-schoolers) and 3.5% for subclinical conditions. The combined presentation and mild severity were the most common, while 18.2% were highly impaired. Previous diagnoses were found in 12% of pre-schoolers and 41% school-aged.
Conclusion: The prevalence found in Spain is higher than other European reports. The low ratio of prior-diagnoses indicates a need to provide resources for assessment in school and clinical settings

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J Atten Disord. 2021 Sep;25:1511-18.

MEDICATION USE FOR ADHD AND THE RISK OF DRIVING CITATIONS AND CRASHES AMONG TEENAGE DRIVERS: A POPULATION-BASED COHORT STUDY.

Winterstein AG, Li Y, Gerhard T, et al.

Objectives: To evaluate the real-world effectiveness of ADHD medications on adverse driving outcomes in teenage drivers with ADHD.
Method: We retrospectively followed 15- to 20-year-old ADHD patients with valid driver's license to compare the risk for crashes and citations between periods with and without ADHD medication use, using Florida Medicaid records linked to Department of Motor Vehicles data from 1999 to 2004. Patient-level demographic, clinical, and driver licensing characteristics as well as county-level crash and traffic statistics were adjusted in Cox models.
Results: A total of 2,049 patients had 67 crashes and 319 citations. Adjusted hazard ratios comparing ADHD medication use versus no use were 1.22 (95% confidence interval [CI] = [0.66, 1.90]) and 0.89 (95% CI = [0.69, 1.13]) for crashes and citations, respectively.
Conclusion: Our study showed no evidence that ADHD medication use was associated with a reduced risk of adverse driving outcomes among teenage drivers enrolled in Medicaid programs. Limitations in interpreting this finding are presented

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J Atten Disord. 2021 Sep;25:1623-31.

TRANSCRANIAL DIRECT CURRENT STIMULATION IMPROVES REWARD PROCESSING IN CHILDREN WITH ADHD.

Nejati V, Sarraj KA, Nitsche MA.

Objective: Individuals with ADHD have deficits in reward processing and related cognitive tasks such as delay discounting and risky decision-making. The ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC) are two distinct cortical areas that are involved in reward processing.

Methods: Twenty children with ADHD received transcranial direct current stimulation (tDCS) in three separate sessions with one of three montages each, including anodal/cathodal tDCS over the left dlPFC and right vmPFC respectively, the reversed montage, and a sham stimulation condition. During stimulation, in each session, participants performed the balloon analogue risk taking and chocolate delay discounting tasks.

Results: A significant effect of stimulation condition on emotional processing was observed. Specifically, anodal tDCS over the right vmPFC, coupled with cathodal tDCS over the left dlPFC, reduced risky decision-making and delay discounting.

Conclusion: These results imply that the left dlPFC and right vmPFC are involved in reward processing in children with ADHD. This finding is discussed in the light of the delay aversion theory of ADHD

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J Atten Disord. 2021 Nov;25:1859-70.

PRESCRIPTION STIMULANT NONMEDICAL USE AMONG ADOLESCENTS EVALUATED FOR SUBSTANCE USE DISORDER TREATMENT (CHAT™).

Vosburg SK, Faraone SV, Newcorn JH, et al.

Objective: The purpose of the present study was to characterize prescription stimulant non-medical use (NMU) in adolescents between the ages of 13 and 18 years seeking treatment for substance use disorder (SUD) with the Comprehensive Health Assessment Tool for Teens (CHAT™).

Method: Adolescents being evaluated for SUD treatment between Q1 2010 and Q3 2017 (n = 20,189) completed the CHAT™.

Results: About 4.3% of the sample (N = 867) of adolescents in SUD treatment reported past 30-day prescription stimulant NMU. Compared to those without past 30-day prescription stimulant NMU, more reported a lifetime diagnosis of learning disorder or ADHD, more took medication for emotional, behavioral, or learning disorders, received past-month inpatient treatment, or were currently not enrolled in school. Prescription stimulants were most often taken orally for NMU, however, approximately half reported using alternate routes of administration, the most prominent of which was intranasal use.

Conclusion: About 4.3% of adolescents in SUD treatment evaluation reported past 30-day prescription stimulant NMU. Greater percentages of lifetime learning disorder, medication use, past-month inpatient treatment, school unenrollment, and overall substance misuse were associated with prescription stimulant NMU, as were alternate routes of administration. These data reveal an ongoing, persistent level of past-30-day NMU of prescription stimulants among adolescents being evaluated for SUD treatment

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J Atten Disord. 2021 Oct;25:1754-64.

WHICH CHILD WILL BENEFIT FROM A BEHAVIORAL INTERVENTION FOR ADHD? A PILOT STUDY TO PREDICT INTERVENTION EFFICACY FROM INDIVIDUAL REWARD SENSITIVITY.

van Langen MJM, van Hulst BM, Douma M, et al.

Objective: This article aims to assess whether individual differences in reward sensitivity can be used to predict which children with attention-deficit/hyperactivity disorder (ADHD) will benefit most from behavioral interventions that include reinforcement.

Methods: A 12-week behavioral intervention was offered to 21 children with ADHD and their parents. Reward sensitivity was assessed prior to the intervention using a combination of psychological and physiological measures. ADHD symptoms were assessed pre- and posttreatment using the Strengths and Weaknesses of ADHD and Normal behavior (SWAN) rating scale.

Results: Lower scores on one of the questionnaire scales were associated with greater pre/posttreatment differences in ADHD symptoms.

Conclusion: We found that pre/posttreatment change was associated with one measure of parent-rated reward sensitivity. Children with low impulsive negative behavior toward gaining reward improved most during treatment. This result suggests that aspects of reward-related behaviors in ADHD may be useful to predict the effectiveness of treatment

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J Atten Disord. 2021 Oct;25:1657-64.

PREVALENCE OF ADHD SYMPTOMATOLOGY IN ADULT POPULATION IN THE CZECH REPUBLIC-A NATIONAL STUDY.

Vaukov M, et al.

Background: Attention deficit/hyperactivity disorder is a common neurodevelopmental disorder frequently diagnosed between the ages 7 and 10years. We measured ADHD symptomatology in a representative sample of the Czech population.

Material and Methods: Data collection was performed in January 2019 through the European National Panel. The respondents completed a demographic questionnaire focusing on ADHD history and a standardized questionnaire, the Adult ADHD Self-Report Scale (ASRS) screener for ADHD symptomatology in adulthood.

Results: From the sample of 1,518 respondents, 3% of the respondents reported having been diagnosed with ADHD/hyperkinetic disorder in their lifetime. According to ASRS scoring, 119 respondents were classified as suspected ADHD. Overall, more males than females reported ADHD symptomatology. Age was also significantly associated with ASRS. Education status yielded no significant results.

Conclusion: Our study documents that the prevalence of ADHD symptomatology in adults is comparable with that in Western countries despite the different historical and health care backgrounds

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J Atten Disord. 2021 Oct;25:1676-86.

DEPENDENT STRESS MEDIATES THE RELATION BETWEEN ADHD SYMPTOMS AND DEPRESSION.

Rychik N, Fassett-Carman A, Snyder HR.

Objective: Depression and attention-deficit hyperactivity disorder (ADHD) are prevalent and highly comorbid. ADHD symptoms are associated with specific dependent (i.e., self-generated) stressors in children, and there is a strong link between dependent stress and depression. Despite continued comorbidity of ADHD and depressive symptoms into adulthood, it is unknown whether stress generation mediates the relation between ADHD and subsequent depressive symptoms in emerging adulthood, a period of heightened stress.

Method: We tested this mediation model in a semester-long longitudinal study of 224 college students (aged 18-23 years). We additionally tested whether this model differed between inattentive versus hyperactive/impulsive ADHD symptoms given evidence that they vary in their relations to stress and depression.

Results: Dependent stress mediated the association between total ADHD symptoms at baseline and later depressive symptoms; these effects were equivalent for inattentive versus hyperactive/impulsive ADHD symptoms.

Conclusion: These findings suggest stress generation as a mechanism for increased depression in individuals with ADHD symptoms

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J Atten Disord. 2021 Sep;25:1612-22.

EXAMINING LINK BETWEEN CHILDHOOD ADHD AND SEXUAL ASSAULT VICTIMIZATION.

Wymbs BT, Gidycz CA.

Objective: Adults with ADHD are often victims of psychological and physical violence by romantic partners, but less is known regarding whether ADHD is associated with sexual assault victimization.

Method: Adults with (n = 97) and without childhood histories of ADHD (n = 121) rated their experiences with sexual assault victimization and additional risk factors (i.e., alcohol abuse, illicit drug use, and experiencing child abuse).

Results: Adults with ADHD histories were more likely to report being victims of sexual assault, especially attempted rape or rape, than adults without ADHD histories. The rate of rape victimization was not greater for adults with ADHD histories and persistent symptoms or additional risk factors.
Conclusion: Research is needed to investigate potential mechanisms explaining the link between ADHD and sexual victimization. Clinicians seeking to prevent at-risk populations from becoming victims, or to provide services for victims, should consider screening adults for ADHD histories

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J Atten Disord. 2021 Nov;25:1908-18.
INFANT ATTENTIONAL BEHAVIORS ARE ASSOCIATED WITH ADHD SYMPTOMATOLOGY AND EXECUTIVE FUNCTION IN EARLY CHILDHOOD.
Stephens RL, Elsayed HE, Reznick JS, et al.
Objective: We explored associations between infant attentional behaviors as measured by the First Year Inventory (FYIv2.0) and dimensional ratings of ADHD symptomatology and executive function (EF) in early childhood.
Methods: This study included parents (N=229) who filled out the FYIv2.0 when their children were 12months of age. When children were approximately 54months (4.5years) of age, parents completed reports of children's ADHD symptomatology and EF abilities. Correlation and regression analyses were conducted among measures.
Results: We found significant associations among the variables of interest, both cross-sectionally and longitudinally, as well as gender differences. Notably, non-social sensory attention (NSA) was significantly related to 54-month ADHD symptom severity. All three 12-month attention variables were significantly related to 54-month EF.
Conclusion: Results suggest that infant attentional behaviors predict later ADHD-related behaviors in early childhood. Future research should explore associations using laboratory-based measures and could inform early intervention efforts

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J Atten Disord. 2021 Sep;25:1605-11.
SLUGGISH COGNITIVE TEMPO SYMPTOMS, BUT NOT ADHD OR INTERNALIZING SYMPTOMS, ARE UNIQUELY RELATED TO SELF-REPORTED MIND-WANDERING IN ADOLESCENTS WITH ADHD.
Fredrick JW, Becker SP.
Objective: The purpose of this study was to test the relation between sluggish cognitive tempo (SCT) symptoms and self-reported mind-wandering in a sample of adolescents with ADHD.
Method: Adolescents (N = 79; aged 13-17 years; 70% male) diagnosed with ADHD completed measures of SCT, ADHD, anxiety, and depression symptoms, in addition to mind-wandering. Parents also provided ratings of adolescents' ADHD symptoms.
Results: All adolescent-reported psychopathology dimensions, including ADHD, internalizing, and SCT, were significantly bivariately correlated with greater mind-wandering. However, in regression analysis that considered psychopathologies simultaneously, SCT was the only dimension uniquely associated with greater mind-wandering. This finding was unchanged when parent-reported ADHD symptoms were included in the model.
Conclusion: These findings are the first to show that SCT symptoms are uniquely related with self-reported mind-wandering in adolescents with ADHD and underscore the importance of considering co-occurring SCT symptoms when testing the interrelations between ADHD and mind-wandering. Replication is needed in larger samples and with other measures of mind-wandering

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J Atten Disord. 2021 Nov;25:1847-58.

DIET, PHYSICAL ACTIVITY, AND SCREEN TIME TO SLEEP BETTER: MULTIPLE MEDIATION ANALYSIS OF LIFESTYLE FACTORS IN SCHOOL-AGED CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hong GCC, Conduit R, Wong J, et al.

OBJECTIVE: This study examined the mediation roles of multiple lifestyle factors in school-aged children. Structural equation modeling (SEM) tested how lifestyle factors play mechanism roles one another in the impact of ADHD to seek theoretical and intervention insights.

METHOD: An online survey assessed children's lifestyle factors including diet, physical activity, screen time, sleep difficulties, and having ADHD diagnosis. A multi-country sample from English speaking nations included 309 caregivers. Multiple regression and SEM were planned to identify significant correlates and mediators of ADHD in explaining lifestyle differences.

RESULTS: Preliminary multiple regression showed only sleep quality was significantly different between children with and without ADHD. Significant triple mediation effects suggested diet, physical activity, and screen time mediated the ADHD impact on sleep quality.

CONCLUSION: Researchers and practitioners may incorporate the findings to develop intervention models for children with ADHD attending to the mediational roles of lifestyle factors to improve sleep quality

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J Atten Disord. 2021 Oct;25:1687-98.

MEDICATION DECISION MAKING AMONG AFRICAN AMERICAN CAREGIVERS OF CHILDREN WITH ADHD: A REVIEW OF THE LITERATURE.

Glasofer A, Dingley C, Reyes AT.

Background: Significant pharmacotherapy disparities exist among children from ethnic minorities with ADHD. Objective: The purpose of this review is to synthesize existing evidence on African American caregiver medication decision making (MDM) for children with ADHD.

Method: Databases queried for this review included the Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsychINFO, PubMed, and Education Resources Information Center (ERIC). Information regarding the unique culturally specific barriers and supports to MDM were examined through the relevant literature search.

Results: Fourteen articles were included in this review (seven observational studies, four qualitative studies, three mixed methods studies). Three main themes were identified which include (a) fundamental perspectives of ADHD, and cultural norms for child behavior; (b) the impact of fundamental perspectives on MDM in ADHD; and (c) ADHD diagnosis and treatment as forms of social control.

Conclusion: Evidence-based recommendations for clinicians are provided, along with direction for future research

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J Atten Disord. 2021 Oct;25:1743-53.

THE CONTRIBUTION OF THERAPEUTIC HORSEBACK RIDING TO THE IMPROVEMENT OF EXECUTIVE FUNCTIONS AND SELF-ESTEEM AMONG CHILDREN WITH ADHD.

Aviv TM, Katz YJ, Berant E.

Background: Attention deficit hyperactive disorder (ADHD) is associated with difficulties in executive functions (EFs), (assessed by questionnaires) and self-esteem.

Objective: To examine the contribution of therapeutic horseback riding to the EFs' improvement and self-esteem.

Method: In total, 123 Israeli children diagnosed with ADHD participated in the study. The study group participated in 20 weeks of therapeutic horseback riding sessions in addition to receiving medication, whereas the control group received only medication. The children and their mothers filled out questionnaires before treatment, at the end of treatment, and 12 weeks after the treatment ended. To examine changes in the children's EFs and self-esteem, a series of latent growth models (LGMs) were conducted.

Results: Therapeutic horseback riding contributed to the improvement of EFs and self-esteem. Improved self-esteem predicted subsequent improvement in EFs.

Conclusion: Therapeutic horseback riding is an effective therapeutic method to improve EFs and self-esteem among children with ADHD

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J Atten Disord. 2021 Sep;25:1529-33.

DISREGARDING IMPAIRMENT IN ADHD DIAGNOSIS INFLATES ITS PREVALENCE.

Fortes D, Figueiredo T, Lima G, et al.

Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-V) diagnostic criteria for attention-deficit hyperactivity disorder (ADHD) has reemphasized impairment although many studies have demonstrated that such approach may inflate prevalence rates. However, there is no consensus on how impairment should be measured and a myriad of approaches in different studies make comparisons difficult. Objective: To investigate whether impairment measured using a previous validate quantitative measure modifies prevalence rates in a sample of Brazilian children and adolescents. Method: Of 109 children (72 males, 37 females), mean age of 12.4 years, 68 were with ADHD (according to DSM criteria, except for impairment) and 41 were typically developing children. All were evaluated with semi-structured interviews and completed the Functional Impairment Scale (FIS). Results: Thirty-five percent of ADHD cases had impairment in one single domain or no impairment at all (among school performance, social life, family life, and self-perception) in the FIS. Conclusion: Disregarding impairment clearly inflates ADHD diagnosis

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J Atten Disord. 2021 Sep;25:1578-93.

THE VALIDITY OF TEACHER RATING SCALES FOR THE ASSESSMENT OF ADHD SYMPTOMS IN THE CLASSROOM: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Staff AI, Oosterlaan J, Van der Oord S, et al.

Objective: To assess attention-deficit/hyperactivity disorder (ADHD) symptoms in the classroom, most often teacher rating scales are used. However, clinical interviews and observations are recommended as gold standard assessment. This systematic review and meta-analysis evaluates the validity of teacher rating scales.

Method: Twenty-two studies (N = 3,947 children) assessing ADHD symptoms using teacher rating scale and either semi-structured clinical interview or structured classroom observation were meta-analyzed.

Results: Results showed convergent validity for rating scale scores, with the strongest correlations (r = .55-.64) for validation against interviews, and for hyperactive-impulsive behavior. Divergent validity was confirmed for teacher ratings validated against interviews, whereas validated against observations this was confirmed for inattention only.

Conclusion: Teacher rating scales appear a valid and time-efficient measure to assess classroom ADHD; although validated against semi-structured clinical interviews, there were only a few studies available. Low correlations between ratings and structured observations of inattention suggest that observations could add information above rating scales

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J Atten Disord. 2021 Nov;25:1871-80.

TEMPERAMENT TRAITS MARK LIABILITY FOR COEXISTING PSYCHIATRIC SYMPTOMS IN CHILDREN WITH ELEVATED ADHD SYMPTOMS.

Rutter TM, Arnett AB.

Objective: Among children with ADHD, coexisting psychiatric disorders are common and associated with greater impairment and symptom persistence. Given that temperament traits are easily measured, developmentally stable, and variable among youth with ADHD, temperament profiles may be clinically useful for predicting liability for coexisting psychiatric symptoms in this population.

Methods: Eighty-three children with ADHD symptoms participated. Caregivers rated their child's surgency, negative emotionality, and effortful control, as well as severity of internalizing and externalizing psychiatric symptoms. Hierarchical linear regressions were conducted to estimate associations between temperament traits and psychiatric symptoms, controlling for severity of ADHD.

Results: Temperament ratings explained significant variance in psychiatric symptoms above and beyond ADHD symptoms alone. Symptoms of each coexisting psychiatric disorder was associated with a distinct temperament and ADHD symptom profile.
Conclusion: Temperament ratings appear to have clinical utility for predicting coexisting psychiatric symptoms in children with elevated ADHD symptoms

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J Atten Disord. 2021 Nov;25:1881-94.
THE ROLE OF SLEEP IN THE RELATIONSHIP BETWEEN ADHD SYMPTOMS AND STOP SIGNAL TASK PERFORMANCE.
Mann B, Sciberras E, He J, et al.
Background: ADHD commonly occurs with sleep problems and secondary cognitive impairments such as inhibitory control. Sleep problems may explain attentional lapses and inhibition performance variability in children with ADHD. This study applied Bayesian analyses to examine the relationship between ADHD symptoms, sleep problems, and inhibition.
Methods: Participants included 73 children with ADHD and 73 non-ADHD controls, aged 10.5 to 13.5 years. The Stop Signal Task measured inhibition. Sleep problems were measured with the Adolescent Sleep Wake Scale and parent-report.
Results: ADHD symptoms are associated with sleep problems and reaction time variability, however, sleep problems accounted for more variance in inhibition performance than both hyperactive and inattentive symptoms.
Conclusion: Sleep problems account for inhibition performance over and above ADHD symptom severity in children with and without ADHD diagnoses. This suggests clinical utility in assessing sleep in children with manifestations of ADHD, and interventions targeting sleep problems concurrently with behavioral symptoms. This further adds to the discussion on overdiagnosis of ADHD due to behavioral presentations of underlying sleep disorders. Treatment for phenotypes of ADHD could be enhanced by targeting sleep problems, in addition to inhibition deficits and attentional lapses

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J Atten Disord. 2021 Nov;25:1919-30.
THE DIFFERENTIAL EFFECT OF ANXIETY AND ADHD SYMPTOMS ON INHIBITORY CONTROL AND SUSTAINED ATTENTION FOR THREAT STIMULI: A GO/NO-GO EYE-MOVEMENT STUDY.
Manoli A, Liversedge SP, Sonuga-Barke EJS, et al.
Objective: This study examined the synergistic effects of ADHD and anxiety symptoms on attention and inhibitory control depending on the emotional content of the stimuli.
Method: Fifty-four typically developing individuals (27 children/adolescents and 27 adults) completed an eye-movement based emotional Go/No-Go task, using centrally presented (happy, angry) faces and neutral/symbolic stimuli. Sustained attention was measured through saccade latencies and saccadic omission errors (Go trials), and inhibitory control through saccadic commission errors (No-Go trials). ADHD and anxiety were assessed dimensionally.
Results: Elevated ADHD symptoms were associated with more commission errors and slower saccade latencies for angry (vs. happy) faces. In contrast, angry faces were linked to faster saccade onsets when anxiety symptoms were high, and this effect prevailed when both anxiety and ADHD symptoms were high.
Conclusion: Social threat impacted performance in individuals with sub-clinical anxiety and ADHD differently. The effects of anxiety on threat processing prevailed when both symptoms were high

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J Atten Disord. 2021 Nov;25:1791-800.
EARLY CHILDHOOD SHIGELLOSIS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A POPULATION-BASED COHORT STUDY WITH A PROLONGED FOLLOW-UP.
Merzon E, Gutbir Y, Vinker S, et al.
BACKGROUND: Although the short-term neurological complications of Shigella spp. are well described, potential neuropsychiatric outcomes have not been studied yet. We investigated the association between early childhood shigellosis and subsequent ADHD.

METHODS: This is a retrospective population-based cohort. Using a large Health Maintenance Organization database, the prevalence of ADHD was investigated among children aged 5-18â€‰years who underwent stool culture prior to the age of 3â€‰years.
RESULTS: Of 52,761 children with a stool culture examined, 5,269 (9.98%) had Shigella-positive results. The rate of ADHD was 10.6% and 8.6% among children with Shigella-positive and Shigella-negative stool cultures, respectively (p < .001). Adjusted odds ratio for ADHD after controlling for gender and socioeconomic status was 1.21 (CI 1.13-1.29, p < .001). The younger the child was during Shigella gastroenteritis, the higher was the association with ADHD (p < .001).
CONCLUSION: Early childhood shigellosis is associated with an increased rate of long-term ADHD

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J Biomed Semantics. 2021 Apr;12:8.
PROJECT ROSETTA: A CHILDHOOD SOCIAL, EMOTIONAL, AND BEHAVIORAL DEVELOPMENTAL FEATURE MAPPING.
Maslowski A, Abbas H, Abrams K, et al.
BACKGROUND: A wide array of existing instruments are commonly used to assess childhood behavior and development for the evaluation of social, emotional and behavioral disorders such as Autism Spectrum Disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and anxiety. Many of these instruments either focus on one diagnostic category or encompass a broad set of childhood behaviors. We analyze a wide range of standardized behavioral instruments and identify a comprehensive, structured semantic hierarchical grouping of child behavioral observational features. We use the hierarchy to create Rosetta: a new set of behavioral assessment questions, designed to be minimal yet comprehensive in its coverage of clinically relevant behaviors. We maintain a full mapping from every functional feature in every covered instrument to a corresponding question in Rosetta.
RESULTS: In all, 209 Rosetta questions are shown to cover all the behavioral concepts targeted in the eight existing standardized instruments.
CONCLUSION: The resulting hierarchy can be used to create more concise instruments across various ages and conditions, as well as create more robust overlapping datasets for both clinical and research use

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J Child Adolesc Psychopharmacol. 2020 Nov;30:542-48.
TEMPORAL DISCOUNTING IMPULSIVITY AND ITS ASSOCIATION WITH CONDUCT DISORDER AND IRRITABILITY.
Blair RJR, Bashford-Largo J, Zhang R, et al.
Objectives: Temporal reward discounting impulsivity (TDI) reflects a propensity to choose smaller immediate rather than larger delayed rewards relative to age/IQ-matched peers. Previous work with adults has linked TDI to an increased risk for antisocial behavior but also psychopathology in general. However, little work has examined TDI in adolescents with conduct disorder (CD), or considered whether TDI might be associated dimensionally with traits associated with antisocial behavior, that is, impulsivity, irritability, and/or callous-unemotional traits. In this study TDI was investigated in a large adolescent group with varying levels of antisocial behavior.
Methods: Participants consisted of 195 adolescents (67 with CD, 77 in a psychiatric comparison group and 51 typically developing adolescents). Participants performed a temporal discounting task and individual differences were measured through the Connors rating scale for attention-deficit/hyperactivity disorder (impulsivity), Affective Reactivity Index (irritability), and Inventory of Callous-Unemotional traits.
Results: The adolescents with CD and those in the psychiatric comparison group showed significantly greater TDI than typically developing adolescents. However, these group differences were abolished when dimensional covariates were included. Irritability was significantly associated with TDI.
Conclusions: We conclude that TDI reflects a transdiagnostic form of dysfunction that particularly manifests in adolescents with increased irritability

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J Child Adolesc Psychopharmacol. 2021 Apr;31:205-13.

METHYLPHENIDATE TREATMENT ADHERENCE AND PERSISTENCE IN CHILDREN IN THE NETHERLANDS.

Cheung K, Dierckx B, El MH, et al.

Objectives: Numerous studies have examined determinants contributing to methylphenidate adherence and persistence, but these were mainly conducted in adults. These determinants are likely to be different in children as they usually rely on their parents to provide them with the care they need. The objective was to study child and family characteristics as determinants of methylphenidate adherence and persistence in children.

Methods: The study population consists of 307 children from the Generation R Study in the Netherlands, who had at least one dispensing record of methylphenidate until the age of 16 years. Adherence was defined as a medication possession ratio 0.80 up to 2 years after treatment initiation. Persistence was defined as the duration of treatment until a discontinuation period of 6 months. Family and child characteristics were tested as determinants of adherence with multivariable logistic regression analysis. Persistence was evaluated using a Kaplan-Meier analysis.

Results: Children of mothers with one child (adjusted odds ratio [OR]: 2.31, 95% confidence interval [CI]: 1.17-4.54) or of mothers with an average household income (compared to high) were more likely to be adherent (adjusted OR: 3.45, 95% CI: 1.43-8.31). Children who started treatment at the age of 12-16 years (compared to <12 years) (adjusted hazard ratio [HR]: 3.55, 95% CI: 2.54-4.98) and girls (adjusted HR: 1.44, 95% CI: 1.07-1.95) were more often nonpersistent.

Conclusion: Both child and family characteristics may play a role in methylphenidate treatment adherence. Furthermore, gender and the start age of treatment were found to be associated with nonpersistence. These findings may be important for health care professionals when initiating methylphenidate treatment in children

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J Child Adolesc Psychopharmacol. 2021 Apr;31:197-204.

FACTORS AFFECTING DELAYED INITIATION AND CONTINUATION OF MEDICATION USE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A NATIONWIDE STUDY.

Huang KL, Hsu JW, Tsai SJ, et al.

Objective: This study evaluated the predictors for delayed initiation and continuation of ADHD medication use in children and adolescents with ADHD in Taiwan.

Methods: This longitudinal cohort study enrolled 188,061 children and adolescents with ADHD between 2001 and 2011. Delayed initiation of ADHD medications was defined as the interval >365 days between diagnosis and first prescription, and continuation of ADHD medications was defined as â‰¥365 defined daily doses of ADHD medications.

Results: Of the included patients, 39.2% were never treated with ADHD medications. Delayed initiation and continuation of ADHD medication use were found in 11.9% and 19.9% of the ever-treated patients, respectively. Younger age at ADHD diagnosis, male sex, older mother's age at child's ADHD diagnosis, and higher family income were associated with more delayed initiation but were also associated with more continuation of ADHD medication use.

Conclusions: The initiation and continuation of ADHD medication use might be underlined by different mechanisms and warrant different strategies

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J Child Adolesc Psychopharmacol. 2021 Jun;31:390-92.

A PREPUBERTAL GIRL WITH DELUSIONS OF PREGNANCY.

Rush OE, Ferguson J, Coffey BJ.

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J Child Adolesc Psychopharmacol. 2021 Apr;31:187-96.

DIFFERENTIAL TREATMENT EFFECTS OF METHYLPHENIDATE AND ATOMOXETINE ON EXECUTIVE FUNCTIONS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wu CS, Shang CY, Lin HY, et al.

Objectives: This study aimed to compare the efficacy of methylphenidate and atomoxetine on improving executive functions among children with attention-deficit/hyperactivity disorder (ADHD).

Methods: This was an open-label, head-to-head, 3-month, randomized clinical trial with two-arm parallel-treatment groups: osmotic-release oral system methylphenidate (OROS-MPH; n=79) and atomoxetine once daily (n=78). Three major domains of executive functions were assessed, including response selection/inhibition, flexibility, and planning/working memory. The neuropsychological measures included the Conners' continuous performance test and the Cambridge Neuropsychological Test Automated Battery.

Results: We found that both treatment groups showed improvement in executive functions (p-value <0.05 for the major indices of each domain). In addition, OROS-MPH was associated with a greater magnitude of improvement in the response selection/inhibition; the slope for detectability improvement in the Conners' continuous performance test was 0.06 for atomoxetine and 0.15 for OROS-MPH (p-value <0.01); the slope in rapid visual information processing was 2.22 for atomoxetine and 3.45 for OROS-MPH (p-value <0.05).

Conclusion: Both OROS-MPH and atomoxetine improved various domains of executive functions in children with ADHD. There is greater improvement in response selection/inhibition among patients treated with OROS-MPH than those with atomoxetine. This trial was registered with ClinicalTrials.gov (no. NCT00916786)

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J Child Adolesc Psychopharmacol. 2021 Apr;31:164-78.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-WAY CROSSOVER CLINICAL TRIAL OF ORADUR-METHYLPHENIDATE FOR TREATING CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Huang YS, Yeh CB, Chen CH, et al.

Objective: Methylphenidate (MPH) is efficacious in reducing symptoms of attention-deficit/hyperactivity disorder (ADHD), but there are no data about the efficacy and safety of its new formulation (ORADUR(®)-MPH extended release, ORADUR-MPH) in patients with ADHD, which is the study objective.

Method: This was a Phase III, multicenter, randomized, double-blind, placebo-controlled, two-way crossover clinical trial. One hundred children and adolescents with a clinical diagnosis of ADHD (72.7% male) received at least one dose of ORADUR-MPH or a placebo during the 2-week treatment period of each phase. The primary efficacy measure was the Swanson, Nolan, and Pelham-IV-teacher (SNAP-IV-T) form. Secondary efficacy measures included the SNAP-IV-parent form, the Clinical Global Impression: ADHD-Severity score, the Conner's Teacher's Rating Scale score, and the investigator's rating for 18 Diagnostic and Statistical Manual of Mental Disorders, 5th edition ADHD symptoms. In addition, data related to vital signs, body weight, physical examination, laboratory testing, and adverse events (AEs) were also collected. All data were analyzed on an intent-to-treat basis.

Results: Without adjusting for differences in demographics and baseline measures, both treatment groups showed significant reductions in ADHD and oppositional defiant disorder symptoms after a 2-week treatment with greater effect sizes (Cohen's d) in the ORADUR-MPH group (Cohen's d ranging from -0.41 to -1.64; placebo, Cohen's d ranging from -0.26 to -1.18), except for oppositional symptoms, regardless of the informants. For the primary efficacy measure, ORADUR-MPH was significantly superior to the placebo, as evidenced by lower values for and greater reductions in the SNAP-IV-T scores at the endpoint (Cohen's d=-0.16, p=0.005) and from baseline to the endpoint (Cohen's d=-0.19, p=0.006), respectively. There were no serious AEs during the clinical study period. The most frequently observed AE was decreased appetite (49.1%). Most physical and laboratory test variables remained within the normal range.

Conclusions: Once-daily ORADUR-MPH is an effective, well-tolerable, and safe treatment for children and adolescents with ADHD. ClinicalTrials.gov number, NCT02450890

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J Child Adolesc Psychopharmacol. 2021 May;31:324-26.
LETTER TO THE EDITOR: DIFFERENCES IN RATE OF STIMULANT MEDICATION USE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BY WESTERN AND NON-WESTERN ORIGINS.
Veluri N, Patel RS.

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J Child Adolesc Psychopharmacol. 2021 Apr;31:227-32.
SURFACE ELECTROCARDIOGRAPHIC PARAMETERS OF CHILDREN AND ADOLESCENTS DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN AN AMBULATORY COMMUNITY PEDIATRIC CENTER: A FOCUS ON CARDIAC REPOLARIZATION ELECTROCARDIOGRAM INTERVALS.
Isart FA, Mason JW, Isart-Infante FJ, et al.
Objectives: Our research aims were to determine if repolarization measures (QTcF, QTcB, JTcF, and JTcB) in attention-deficit/hyperactivity disorder (ADHD) children and adolescents differ from normal subjects and determine if the JTc interval duration, as a purer repolarization measure than QTc, strengthens the differentiation between ADHD and normal children and adolescents.
Methods: This study included 418 subjects aged 5-18 years who were diagnosed with ADHD, and 1948 subjects in a historical normal control group. One-way analysis of variance (ANOVA) was performed to compare the independent groups on normal continuous outcomes. Means and standard deviations (SDs) were reported and interpreted for the ANOVA. Logistic regression analysis was performed to test the ability of four variables (QTcB, QTcF, JTcB, and JTcF) to predict an ADHD diagnosis, with age and gender as independent covariates. The log odds with standard errors for each variable were reported and interpreted for the logistic models.
Results: In the nominal logistic regressions with JTcF ≥322 or JTcB ≥335 (values 1 SD above the mean of the control group), age and sex were significant contributors to the models that showed that subjects with a JTcF ≥322 ms had a statistically and significantly higher probability to be diagnosed with ADHD in comparison with normal control subjects (odds ratio [OR]: 2.6, 95% confidence interval [95% CI] 2.02-3.33, $p < 0.0001$). Similarly, those subjects with a JTcB ≥335 ms were 2.7 times more likely to be diagnosed with ADHD than normal control subjects (OR: 2.7, 95% CI 2.1-3.45, $p < 0.0001$).
Conclusions: JTc provided a clearer separation of the groups than QTc. JTcB and JTcF 1 SD above the control group means are strong predictors of ADHD diagnosis and remain so even when strong demographic predictors of longer QTc (age and sex) are included in the regression models. Consideration should be given to recording a pretreatment electrocardiogram in all children and adolescents with ADHD, and to measuring and monitoring JTc in patients with ADHD, especially when considering the addition of QT prolonging drugs

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J Child Adolesc Psychopharmacol. 2021 May;31:288-93.
EFFECTS OF ANTIDEPRESSANT TREATMENT ON SYMPTOM MEASURES OF ATTENTION IN ADOLESCENTS WITH DEPRESSION: A PRELIMINARY OPEN-LABEL STUDY.
Choi CH, Lee J, Lee KH, et al.
Objective: The effects of selective serotonin reuptake inhibitor (SSRI) on deficits in attention and executive function in adolescents with major depressive disorder (MDD) are relatively unknown. We aimed to investigate changes in symptom measures of attention in adolescents with MDD treated with escitalopram.
Methods: The study included 82 MDD adolescents and 54 healthy controls aged from 12 to 17 years. Symptom measures of attention were assessed using the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) and Child Behavior Checklist attention problems scale at baseline and during week 8. Adolescents who showed at least 40% improvement in the Children's Depression Rating Scale-Revised (CDRS-R) scores from baseline to week 8 were referred to as "responders."
Results: No baseline differences were found between the responders (n=47) and nonresponders (n=35) in their age, sex, intelligence quotient, CDRS-R score, and attention measures. Linear mixed models showed significant group-by-time interaction effect in the ADHD-RS inattention subscale score, but not in the other attention measures.

Conclusion: Our results suggest that treating depressive symptoms with SSRI may lead to improvements in attention in MDD adolescents. Monitoring changes in symptom measures of attention can be useful when treating adolescents with MDD. ClinicalTrials.gov identifier: NCT03547219

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J Child Adolesc Psychopharmacol. 2021 Apr;31:214-26.

TRANSLATING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER RATING SCALE-5 AND WEISS FUNCTIONAL IMPAIRMENT RATING SCALE-PARENT EFFECTIVENESS SCORES INTO CLINICAL GLOBAL IMPRESSIONS CLINICAL SIGNIFICANCE LEVELS IN FOUR RANDOMIZED CLINICAL TRIALS OF SPN-812 (VILOXAZINE EXTENDED-RELEASE) IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Nasser A, Kosheleff AR, Hull JT, et al.

Objectives: Clinical trials in psychiatry frequently report results from lengthy, comprehensive assessments to characterize a subject emotionally, cognitively, and behaviorally before and after treatment. However, the potential treatment implications of these results and how they translate into clinical practice remain unclear. Conversely, the Clinical Global Impressions (CGI) scales are quick, intuitive assessments used to assess the functional impact of a treatment in clinically relevant terms. The objectives of the present analyses are to translate scores from comprehensive assessments of symptom severity and functional impairment into clinically meaningful CGI levels.

Methods: These post-hoc analyses use data integrated from four pivotal Phase 3 trials in attention-deficit/hyperactivity disorder (ADHD) in children and adolescents treated with the novel nonstimulant SPN-812 (Viloxazine Extended-Release). In this study, we evaluated the ADHD Rating Scale-5 (ADHD-RS-5) and Weiss Functional Impairment Rating Scale-Parent (WFIRS-P), assessments of symptom severity and functional impairment, respectively, by linking these scales with the CGI scales at baseline and end of study.

Results: For participants that improved, a one-level change on the CGI-Improvement (CGI-I) was associated with a 10-15-point change on the ADHD-RS-5, and a 0.2-0.5-point change on the WFIRS-P. On the CGI-I, ratings of much improved and very much improved were associated with a percent score decrease (i.e., improvement) of âˆ¼55% and 80% on the ADHD-RS-5 and âˆ¼40% and 70% on the WFIRS-P, respectively. Differences between children and adolescents were minor and are unlikely to be clinically meaningful.

Conclusion: These post-hoc analyses provide clinically meaningful benchmarks for the interpretation of scores on the ADHD-RS-5 and WFIRS-P in terms of CGI evaluations in subjects with ADHD. These results may be useful for physicians seeking to understand a treatment's potential impact on their ADHD patients or for researchers looking to define their study results within a clinically relevant context. Data are from clinical trials NCT03247530, NCT03247543, NCT03247517, and NCT03247556

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J Child Adolesc Psychopharmacol. 2021 Apr;31:147.

EDITORIAL TO THE JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY SPECIAL ISSUE ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER UPDATES.

Steingard R.

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J Child Adolesc Psychopharmacol. 2021 Apr;31:148-63.

POLYPHARMACY IN THE MANAGEMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A REVIEW AND UPDATE.

Baker M, Huefner JC, Bellonci C, et al.

Objective: Prescription of multiple medications concurrently for children and adolescents has increased in recent years. Examination of this practice has been undervalued relative to its incidence. This article reviews studies investigating effectiveness of medication combinations for youth with attention-deficit/hyperactivity disorder (ADHD).

Methods: A literature search identified studies that combined two or more prescribed medications for the treatment of ADHD. Included studies focused on youth; had study design of randomized controlled trial (RCT), nonrandomized trial, or case review (n>10); and included an outcome measure of treatment effectiveness.

Results: Thirty-nine pertinent studies were identified. All studies combined two medications, with the vast majority including a stimulant (n=37). The largest group (n=16) combined stimulant and alpha-agonist, finding greater efficacy than alpha-agonist alone but not stimulant alone in all cases. A few RCTs found benefit from the addition of risperidone or divalproex to stimulant for comorbid aggression. Four studies adding atomoxetine found mixed reports of benefit, including the only small RCT showing no benefit. RCTs with selective serotonin reuptake inhibitors found minimal evidence of benefit for mood or anxiety comorbidities.
Conclusion: The best studied combination is stimulant and alpha-agonist; addition of alpha-agonist to stimulant seems effective for residual symptoms of ADHD. Stimulant plus risperidone has the most evidence of efficacy for comorbid aggression or disruptive behavior. Limited support exists for the effectiveness of other medication combinations, including no trials studying three or more medications concurrently. Combinations frequently yielded more side effects, leaving monotherapy preferable if a sufficient treatment response can be achieved

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J Child Adolesc Psychopharmacol. 2021 Apr;31:179-86.

EFFECT OF DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE ON CAREGIVER STRAIN AND VALIDATION OF PSYCHOMETRIC PROPERTIES OF THE CAREGIVER STRAIN QUESTIONNAIRE: RESULTS FROM A PHASE 3 TRIAL IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lapez FA, Faraone SV, Newcorn JH, et al.

Objectives: Inadequately controlled symptoms and associated impaired functioning have a significant negative impact on caregivers of children with attention-deficit/hyperactivity disorder (ADHD). This study aimed to assess the impact of evening-dosed, delayed-release and extended-release methylphenidate (DR/ER-MPH) treatment on caregiver strain, measured by the Caregiver Strain Questionnaire (CGSQ), and present post hoc psychometric analyses assessing the reliability and validity of the CGSQ, its ability to detect change (responsiveness), and to derive responder definitions.
Methods: The CGSQ was an exploratory efficacy endpoint in a phase 3, 3-week, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration trial of DR/ER-MPH in children aged 6-12 years with ADHD (NCT02520388). Psychometric properties of the CGSQ evaluated post hoc included internal consistency using Cronbach's alpha; test/retest reliability using intraclass correlation coefficients (ICCs); construct validity (known groups and convergent/divergent validity); responsiveness to changes in assessments of ADHD severity (ADHD Rating Scale-IV [ADHD-RS-IV], Conners' Global Index-Parent [CGI-P], and Clinical Global Impression-Severity [CGI-S]/CGI-Improvement [CGI-I]); and meaningful change threshold (MCT) using receiver operating characteristic curves, which were used to compare response between DR/ER-MPH and placebo groups.
Results: Randomized DR/ER-MPH (54.5) and placebo (54.9) groups had similar mean CGSQ scores at screening. Caregivers of children on DR/ER-MPH reported significant reductions in CGSQ scores after 3 weeks of DR/ER-MPH treatment versus placebo (least-squares mean: 41.2 vs. 49.1; $p<0.001$). The CGSQ demonstrated strong internal consistency (Cronbach's alpha=.93) and good test/retest reliability (ICC=0.72). Known groups, convergent/divergent validity, and responsiveness were demonstrated from relationships between the CGSQ and the CGI-S, ADHD-RS-IV, and CGI-P. The mean anchor-based MCT for CGSQ total score was estimated as -9.0 (DR/ER-MPH vs. placebo: 53.2% vs. 29.9% p=0.003).
Conclusions: CGSQ scores significantly decreased after 3 weeks of DR/ER-MPH treatment versus placebo, and the CGSQ was found to be a valid and reliable measure of strain in caregivers of children with ADHD. Clinical trial registration identification number: NCT02520388

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J Child Adolesc Psychopharmacol. 2021 May;31:310-14.

MOOD AND PRONENESS TO BOREDOM ARE ASSOCIATED WITH POORER CONTINUOUS PERFORMANCE TEST RESULTS, WHICH MAY IMPROVE WITH METHYLPHENIDATE TREATMENT, IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Golubchik P, Schoen G, Weizman A.

Objectives: This study aimed to evaluate the relationship between baseline test of variables of attention (TOVA) performance, attention-deficit/hyperactivity disorder (ADHD) symptom severity, mood symptoms,

proneness to boredom in children with ADHD, and to assess the responses of the various scales to methylphenidate treatment.
Methods: Thirty-three children and adolescents with ADHD, aged 7-18 years, were assessed at baseline with TOVA and treated for 3 months thereafter with methylphenidate. The ADHD Rating Scale (ADHD-RS), Short Boredom Proneness Scale (SBPS), Children's Depression Inventory (CDI) scale, and CDI-academic and social subscale (CDI-AS) were administered to all participants at baseline and after 3 months of methylphenidate (MPH) treatment.
Results: The baseline TOVA reaction time (RT) and RT variability parameters correlated with baseline SBPS and CDI-AS scores as well as with baseline total CDI scores. Significant improvements were found in ADHD-RS, SBPS, and CDI-AS scores after MPH treatment. The alteration in ADHD-RS correlated with parallel changes in SBPS and CDI-AS scores.
Conclusions: Mood and proneness to boredom correlate with poor attention-span in children with ADHD. Improvement in ADHD levels after MPH treatment correlates with a parallel decrease in mood symptoms related to academic achievement and social functioning

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J Child Adolesc Psychopharmacol. 2021 Feb;31:73-78.

USE OF ANTIPSYCHOTICS: THE EXPERIENCES, VIEWS, AND MONITORING PRACTICES OF CHILD AND ADOLESCENT PSYCHIATRISTS IN TURKEY.

Ãakr B, Yaln SÅ, Kandemir H.

Objectives: The aim of this study is to evaluate the antipsychotics prescribed by child psychiatrists and their applications on the follow-up of these drugs.
Methods: The universe of this research included consultant physicians and child psychiatry residents working in the field. A questionnaire has been created that assesses the use of antipsychotics and follow-up processes of physicians. The survey involved 19 questions. Contents of the survey were sociodemographic data, short-term and long-term follow-up of antipsychotic drugs, side-effect intervention strategies, and diagnoses of the most commonly preferred antipsychotic medications. The survey was delivered via e-mail and sent as a message to the child and adolescent psychiatrists in Turkey.
Results: One hundred sixty-one physicians working in the field of child and adolescent psychiatry participated in the study. Aripiprazole (32.2%), risperidone (30.4%), and quetiapine (14.9%) were three most commonly prescribed antipsychotics. Disruptive behavior-related disorders (28.9%), behavior problems related to autism spectrum disorder (20.7%), behavior problems related to intellectual disability (14.5%), and attention-deficit/hyperactivity disorder (12.4%) were the most common diagnoses requiring antipsychotics medications. Before starting antipsychotic treatment, the most commonly evaluated parameters were body mass index (BMI) (47.2%), waist circumference (10.5%), blood pressure (28.5%), lipid profile (37%), and blood glucose level (41.6%). When the evaluations made at least in a year after starting antipsychotic drug therapy were examined, 80.2% of physicians reported blood glucose, 79.6% lipid profile, 65.7% BMI, 59.1% blood pressure, and 26.6% waist circumference measurement almost always done.
Conclusions: The results showed that the adherence to recommendations in guidelines for the screening of antipsychotic-related side effects was low. This study suggests that interventions should be made about antipsychotic monitoring training to physicians

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J Child Psychol Psychiatry. 2021 Apr;62:449-57.

INVESTIGATING ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER TRAITS IN THE GENERAL POPULATION: WHAT HAPPENS IN ADULT LIFE?

Riglin L, Leppert B, Langley K, et al.

BACKGROUND: Attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are generally considered early-onset disorders so most research has therefore tended to focus on children. Differences between ADHD/ASD in adult life and childhood have been noted, but few population-based studies have examined them in adulthood. Furthermore, the interpretation of findings is hampered by changes in measure and from parent report to self-report.

METHOD: We examined continuous/trait measures of parent- and self-rated ADHD and ASD in adulthood (age 25 years) in a UK prospective longitudinal sample ALPSAC (the Avon Longitudinal Study of Parents and Children), using many of the same measures that parents reported on in childhood (N=6,064). Our aim was to investigate these traits in this population for mean-level sex differences, overlaps with other cognitive, learning and communication problems and their associations with polygenic risk scores (PRS) for neuropsychiatric disorders (ADHD, ASD, schizophrenia, depression and anxiety).
RESULTS: ADHD and ASD traits in adulthood, as in childhood, showed associations with childhood cognitive, learning and communication problems and adult communication/language measures, although less so for self-ratings than parent-ratings. Males had higher ADHD and ASD trait levels, but this was not as marked as in childhood. In adulthood, ADHD (both parent- and self-rated) and ASD (parent-rated) symptoms showed associations with ADHD PRS; self-reported ADHD also showed association with depression PRS, whereas self-reported ASD did not show strong PRS associations.
CONCLUSIONS: Our findings suggest that in young adults, ADHD and ASD symptoms have similar characteristics as they do in childhood. Associations with other cognitive, learning and communication problems, and ADHD PRS were somewhat less pronounced for self-reported adult ADHD and ASD symptoms, suggesting that even at age 25, parent reports, where available, could be clinically useful

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J Child Psychol Psychiatry. 2021 Jun;62:680-700.

PRACTITIONER REVIEW: PHARMACOLOGICAL TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN AND YOUTH WITH AUTISM SPECTRUM DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Rodrigues R, Lai MC, Beswick A, et al.

BACKGROUND: Clinically significant attention-deficit/hyperactivity disorder (ADHD) symptoms are common and impairing in children and youth with autism spectrum disorder(ASD). The aim of this systematic review and meta-analysis was to (a) evaluate the efficacy and safety of pharmacotherapy for the treatment of ADHD symptoms in ASD and (b) distil findings for clinical translation.
METHODS: We searched electronic databases and clinical trial registries (1992 onwards). We selected randomized controlled trials conducted in participants <25 years of age, diagnosed with ASD that evaluated ADHD outcomes (hyperactivity/impulsivity and inattention) following treatment with stimulants (methylphenidate or amphetamines), atomoxetine, alpha-2 adrenergic receptor agonists, antipsychotics, tricyclic antidepressants, bupropion, modafinil, venlafaxine, or a combination, in comparison with placebo, any of the listed medications, or behavioral therapies. Data were pooled using a random-effects model.
RESULTS: Twenty-five studies (4 methylphenidate, 4 atomoxetine, 1 guanfacine, 14 antipsychotic, 1 venlafaxine, and 1 tianeptine) were included. Methylphenidate reduced hyperactivity (parent-rated: standardized mean difference [SMD] = -.63, 95%CI = -.95,-.30; teacher-rated: SMD = -.81, 95%CI = -1.43,-.19) and inattention (parent-rated: SMD = -.36, 95%CI = -.64,-.07; teacher-rated: SMD = -.30, 95%CI = -.49,-.11). Atomoxetine reduced inattention (parent-rated: SMD = -.54, 95%CI = -.98,-.09; teacher/investigator-rated: SMD = -0.38, 95%CI = -0.75, -0.01) and parent-rated hyperactivity (parent-rated: SMD = -.49, 95%CI = -.76,-.23; teacher-rated: SMD = -.43, 95%CI = -.92, .06). Indirect evidence for significant reductions in hyperactivity with second-generation antipsychotics was also found. Quality of evidence for all interventions was low/very low. Methylphenidate was associated with a nonsignificant elevated risk of dropout due to adverse events.
CONCLUSIONS: Direct pooled evidence supports the efficacy and tolerability of methylphenidate or atomoxetine for treatment of ADHD symptoms in children and youth with ASD. The current review highlights the efficacy of standard ADHD pharmacotherapy for treatment of ADHD symptoms in children and youth with ASD. Consideration of the benefits weighed against the limitations of safety/efficacy data and lack of data evaluating long-term continuation is undertaken to help guide clinical decision-making regarding treatment of co-occurring ADHD symptoms in children and youth with ASD

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J Child Psychol Psychiatry. 2021 Sep;62:1079-89.

THE PREDICTIVE CAPACITY OF PSYCHIATRIC AND PSYCHOLOGICAL POLYGENIC RISK SCORES FOR DISTINGUISHING CASES IN A CHILD AND ADOLESCENT PSYCHIATRIC SAMPLE FROM CONTROLS.

Jansen AG, Jansen PR, Savage JE, et al.

BACKGROUND: Psychiatric traits are heritable, highly comorbid and genetically correlated, suggesting that genetic effects that are shared across disorders are at play. The aim of the present study is to quantify the predictive capacity of common genetic variation of a variety of traits, as captured by their PRS, to predict case-control status in a child and adolescent psychiatric sample including controls to reveal which traits contribute to the shared genetic risk across disorders.

METHOD: Polygenic risk scores (PRS) of 14 traits were used as predictor phenotypes to predict case-control status in a clinical sample. Clinical cases (N = 1,402), age 1-21, diagnostic categories: Autism spectrum disorders (N = 492), Attention-deficit/ hyperactivity disorders (N = 471), Anxiety (N = 293), disruptive behaviors (N = 101), eating disorders (N = 97), OCD (N = 43), Tic disorder (N = 50), Disorder of infancy, childhood or adolescence NOS (N = 65), depression (N =64), motor, learning and communication disorders (N = 59), Anorexia Nervosa (N = 48), somatoform disorders (N = 47), Trauma/stress (N = 39) and controls (N = 1,448, age 17-84) of European ancestry. First, these 14 PRS were tested in univariate regression analyses. The traits that significantly predicted case-control status were included in a multivariable regression model to investigate the gain in explained variance when leveraging the genetic effects of multiple traits simultaneously.

RESULTS: In the univariate analyses, we observed significant associations between clinical status and the PRS of educational attainment (EA), smoking initiation (SI), intelligence, neuroticism, alcohol dependence, ADHD, major depression and anti-social behavior. EA (p-value: 3.53E-20, explained variance: 3.99%, OR: 0.66), and SI (p-value: 4.77E-10, explained variance: 1.91%, OR: 1.33) were the most predictive traits. In the multivariable analysis with these eight significant traits, EA and SI, remained significant predictors. The explained variance of the PRS in the model with these eight traits combined was 5.9%.

CONCLUSION: Our study provides more insights into the genetic signal that is shared between childhood and adolescent psychiatric disorders. As such, our findings might guide future studies on psychiatric comorbidity and offer insights into shared etiology between psychiatric disorders. The increase in explained variance when leveraging the genetic signal of different predictor traits supports a multivariable approach to optimize precision accuracy for general psychopathology

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J Child Psychol Psychiatry. 2021 Apr;62:372-81.

RESEARCH REVIEW: A META-ANALYSIS OF THE INTERNATIONAL PREVALENCE AND COMORBIDITY OF MENTAL DISORDERS IN CHILDREN BETWEEN 1 AND 7 YEARS.

Vasileva M, Graf RK, Reinelt T, et al.

BACKGROUND: Children younger than 7 years can develop mental disorders that might manifest differently than in older children or adolescents. However, little is known about the prevalence of mental disorders at this early age.

METHODS: We systematically searched the literature in the databases Web of Science, PsycINFO, PSYNDEX, MEDLINE, and Embase to identify epidemiological studies of community samples published between 2006 and 2020. A series of meta-analyses was conducted to estimate the pooled worldwide prevalence of mental disorders in general, specific mental disorders, and comorbidity in young children.

RESULTS: A total of ten epidemiological studies reporting data on N=18,282 children (12-83Â months old) from eight countries met the inclusion criteria. The pooled prevalence of mental disorders in general was 20.1%, 95% CI [15.7, 25.4]. Most common disorders were oppositional defiant disorder (4.9%, 95% CI [2.5, 9.5]) and attention-deficit hyperactivity disorder (4.3%, 95% CI [2.5, 7.2]). The prevalence of any anxiety disorders was 8.5%, 95% CI [5.2, 13.5], and of any depressive disorders was 1.1%, 95% CI [0.8, 1.6]. Comorbidity was estimated at 6.4%, 95% CI [1.3, 54.0].

CONCLUSIONS: The literature search reveals that the epidemiology of mental disorders in children younger than 7 years is still a neglected area of research. The findings also indicate that there are a significant number of young children suffering from mental disorders who need appropriate age-adapted treatment

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J Clin Child Adolesc Psychol. 2021 Jul;50:464-77.

MODERATORS OF TREATMENT FOR PEDIATRIC BIPOLAR SPECTRUM DISORDERS.

Roley-Roberts ME, Fristad MA.

Objective: We review the current limited research on pediatric bipolar spectrum disorder (BPSD) treatment moderators.

Method: Four pharmacotherapy and nine psychotherapy moderator studies in youth with pediatric BPSD is summarized.

Results: Two pharmacotherapy studies suggest that younger children and those with more aggression fare worse. Regarding preferential outcomes, one study found that older youth respond better to lithium than younger youth; all youth, regardless of age, respond similarly to valproate. One study found non-obese youth and those with comorbid attention deficit hyper-activity disorder respond better to risperidone than lithium. Results are mixed for psychosis and disruptive behavior disorders on risperidone compared to divalproex. Tentatively, youth with generalized anxiety are more likely to respond to valproate while youth with panic preferentially respond to lithium. Psychotherapy findings from two studies suggest that sex, age, race, baseline mania, and past-month suicidal ideation/non-suicidal self-injury do not moderate outcomes. Although not replicated, higher baseline inflammatory markers are associated with greater decreases in depressive symptoms; baseline higher self-esteem and comorbid attention deficit hyperactivity disorder are associated with steeper decreases in (hypo)manic symptoms.

Conclusions: Findings are mixed on the role of baseline mood severity, other comorbid disorders, parental depression, family income, and expressed emotion in moderating treatment outcomes. Replication of these possible moderators is needed for both pharmacotherapy and psychotherapy interventions before conclusive results can be determined. Examination of larger samples of youth with BPSD and longer duration follow-up are needed to clarify meaningful treatment moderators

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J Clin Child Adolesc Psychol. 2021 Mar;50:267-80.

SLUGGISH COGNITIVE TEMPO AND ADHD SYMPTOMS IN A NATIONALLY REPRESENTATIVE SAMPLE OF U.S. CHILDREN: DIFFERENTIATION USING CATEGORICAL AND DIMENSIONAL APPROACHES.

Burns GL, Becker SP.

A nationally representative sample of U.S. children was used to determine the empirical and clinical differentiation of sluggish cognitive tempo (SCT) and attention-deficit/hyperactivity disorder (ADHD) symptoms using both categorical and dimensional approaches. Mothers of children (N= 2,056, M± SD(age)= 8.49 ± 2.15 years, 49.3% girls) completed measures of SCT, ADHD, oppositional defiant disorder (ODD), anxiety, depression, sleep difficulties, daily life executive functioning, conflicted shyness, friendship difficulties, and social and academic impairment. Scores greater than the top 5% on SCT and ADHD measures were used to create SCT-only (n = 53, 2.58%), ADHD-only (n = 93, 4.52%), SCT+ADHD (n = 49, 2.38%), and comparison (n = 1,861, 90.52%) groups. Fifty-two percent of the SCT group did not qualify for the ADHD group, whereas 65% of the ADHD group did not qualify for the SCT group. The SCT-only group had higher levels of anxiety, depression, conflicted shyness, and sleep difficulties than the ADHD-only group. In contrast, the ADHD-only group had greater executive functioning deficits and higher ODD than the SCT-only group. SCT-only and ADHD-only groups showed similar levels of friendship, social, and academic impairment. Similar findings emerged when using structural regression analyses to determine the unique clinical correlates of SCT and ADHD dimensions. This is only the second study to examine the distinction of clinically-elevated SCT from ADHD in a national sample of children and extends previous findings to a broader array of functional outcomes. Normative information on the SCT scale also provides a validated rating scale to advance research and clinical care

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J Clin Psychiatry. 2021 Jun;82.

SYMPTOMATIC AND FUNCTIONAL RESPONSE AND REMISSION FROM THE OPEN-LABEL TREATMENT-OPTIMIZATION PHASE OF A STUDY WITH DR/ER-MPH IN CHILDREN WITH ADHD.

Childress AC, Cutler AJ, Po MD, et al.

Objective: Delayed-release and extended-release methylphenidate (DR/ER-MPH), the first stimulant predicted to be absorbed primarily in the colon, demonstrated significant improvements in attention-deficit/hyperactivity disorder (ADHD) symptoms and functional impairment from awakening until evening versus placebo in clinical trials. The clinical significance of these improvements was explored post hoc by examining response and remission thresholds as well as safety in the context of dose optimization.

Methods: Data from the open-label, treatment-optimization phase of a phase 3 study of DR/ER-MPH in children (aged 6-12 years) with ADHD, as diagnosed by DSM-5 criteria and enrolled between July 2015 and March 2016, were analyzed. Thresholds for response (anchored to Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and remission were applied to ADHD Rating Scale-IV (ADHD-RS-IV), Before School Functioning Questionnaire (BSFQ), and Parent Rating of Evening and Morning Behavior, Revised, Morning Subscale (PREMB-R AM) and Evening Subscale (PREMB-R PM) scores. Rates of response, remission, and treatment-emergent adverse events by starting dose were examined.

Results: Mean DR/ER-MPH dose increased from 29.7 mg/d at baseline (51% on 20 mg/d; 49% on 40 mg/d) to 66.2 mg/d at week 6. At week 6, most participants achieved response/remission thresholds (response/remission: ADHD-RS-IV: 97%/89%; BSFQ: 98%/94%; PREMB-R AM: 94%/98%; PREMB-R PM: 91%/84%). More participants starting on a 40-mg versus 20-mg dose achieved thresholds at week 1 (P<.02). Weekly treatment-emergent adverse event rates over the open-label period were similar between starting doses.

Conclusions: When DR/ER-MPH dosing was optimized for ADHD symptom control throughout the day, the majority of participants achieved thresholds indicating all-day control of ADHD symptoms and functional impairment to the level of their non-ADHD peers. Trial Registration: Data used in this post hoc analysis came from the study with ClinicalTrials.gov identifier: NCT02493777

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J Clin Psychiatry. 2021 Jul;82.

POSTPARTUM DEPRESSION AND PSYCHOSIS AND SUBSEQUENT SEVERE MENTAL ILLNESSES IN MOTHERS AND NEURODEVELOPMENTAL DISORDERS IN CHILDREN: A NATIONWIDE STUDY.

Chen MH, Pan TL, Bai YM, et al.

Background: The association between postpartum depression and postpartum psychosis and subsequent maternal and offspring mental disorders in Western countries has been established; however, whether the relationship can be generalized to the Asian population is unknown.

Methods: Using the Taiwan National Health Insurance Research Database, this study enrolled 933,745 mother-infant pairs who delivered their first child and had no history of severe mental illness before childbirth from 2001 to 2010. Postpartum depression and postpartum psychosis were assessed in 3 periods between childbirth and 3, 6, or 12 months after childbirth. Subsequent maternal schizophrenia (ICD-9-CM code: 295), bipolar disorder (ICD-9-CM code: 296 except 296.2x, 296.3x, 296.9x, and 296.82), and depressive disorder (ICD-9-CM codes: 296.2x, 296.3x, 300.4, and 311) and offspring autism spectrum disorder (ASD; ICD-9-CM code: 299) and attention-deficit/hyperactivity disorder (ADHD; ICD-9-CM code: 314) were identified during the follow-up period to the end of 2011.

Results: Both postpartum depression and postpartum psychosis were found to be related to increased risks of schizophrenia, bipolar disorder, and depressive disorder in mothers, with hazard ratios (HRs) ranging between 8.80 (95% CI, 7.95-9.74) and 63.96 (95% CI, 50.39-81.18). Children exposed to maternal postpartum depression and psychosis were more likely to develop ADHD. Only postpartum depression was related to the likelihood of offspring ASD.

Conclusions: Per these findings, we clinicians and health care providers should closely monitor the mental health condition of postpartum women and their children

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S35-S57.

SOCIETY FOR DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS CLINICAL PRACTICE GUIDELINE FOR THE ASSESSMENT AND TREATMENT OF CHILDREN AND ADOLESCENTS WITH COMPLEX ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Barbaresi WJ, Campbell L, Diekroger EA, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder and is associated with an array of coexisting conditions that complicate diagnostic assessment and treatment. ADHD and its coexisting conditions may impact function across multiple settings (home, school, peers, community), placing the affected child or adolescent at risk for adverse health and psychosocial outcomes in adulthood. Current practice guidelines focus on the treatment of ADHD in the primary care setting. The Society for Developmental and Behavioral Pediatrics has developed this practice guideline to facilitate integrated, interprofessional assessment and treatment of children and adolescents with "complex ADHD" defined by age (<4 years or presentation at age >12 years), presence of coexisting conditions, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S99-S104.

CHRONIC CARE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: CLINICAL MANAGEMENT FROM CHILDHOOD THROUGH ADOLESCENCE.

Moss CM, Metzger KB, Carey ME, et al.

OBJECTIVE: Impairments generally persist when children diagnosed with attention-deficit/hyperactivity disorder (ADHD) mature into adolescence. To examine changes in ADHD care during the transition from childhood to adolescence, we conducted a retrospective, longitudinal cohort study of patients diagnosed with ADHD before the age of 10 years to assess changes from preadolescence through adolescence in (1) frequency by which primary care providers offer ADHD care to patients, (2) range of concerns assessed during patient encounters, and (3) treatments implemented or recommended.

METHODS: We identified patients from 3 practices included in a large primary care network who (1) were born between 1996 and 1997, (2) were diagnosed with ADHD before the age of 10 years, and (3) received primary care continuously from age 9 through late adolescence. Clinical care was compared among patients in preadolescence (age 9-11), early adolescence (age 12-14), and late adolescence (age 15-18).

RESULTS: Children diagnosed with ADHD before the age of 10 years were less likely to have a documented visit for ADHD during late adolescence (41% of patients) compared with preadolescence (63%, $p < 0.001$). Evidence of monitoring for depression, suicide, and substance abuse increased from preadolescence to adolescence ($p < 0.001$) and occurred in about 90% of adolescent patients. However, monitoring for risky sexual activity occurred in only about 50% of adolescents. Discussions of medication diversion and driver readiness were essentially not documented.

CONCLUSION: The findings raise concerns about how primary care providers manage adolescents with a history of ADHD. Improving monitoring of risky sexual behavior and driver readiness and providing patient education about medication diversion are needed

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J Dev Behav Pediatr. 2020 Sep;41:565-70.

EFFICACY OF GUANFACINE EXTENDED RELEASE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID OPPOSITIONAL DEFIANT DISORDER.

Newcorn JH, Huss M, Connor DF, et al.

OBJECTIVE: To assess the efficacy of the non-stimulant guanfacine extended release (GXR) on attention-deficit/hyperactivity disorder (ADHD) symptoms in children and adolescents, with and without comorbid oppositional defiant disorder (ODD).

METHODS: Data were derived from 4 phase 3, randomized, placebo-controlled trials of dose-optimized GXR monotherapy, in which at least 10% of participants had a diagnosis of comorbid ODD. SPD503-312 and SPD503-316 were 10- to 13-week studies of GXR (1-7 mg/d). SPD503-314 and SPD503-307 were 8-week studies of GXR (1-4 mg/d). Efficacy was assessed using the ADHD Rating Scale IV (ADHD-RS-IV) total scores.

RESULTS: In total, 1,084 participants were included (SPD503-312 and SPD503-316, n = 537; SPD503-314, n = 333; and SPD503-307, n = 214). GXR was associated with significant improvements in ADHD core symptoms at endpoint in participants with and without ODD ($p < 0.01$ in all studies). Placebo-adjusted least-squares mean (95% confidence interval) changes from baseline to endpoint in the ADHD-RS-IV total scores in participants with and without ODD were -8.6 (-14.4, -2.8) and -7.3 (-9.5, -5.0) in the pooled data from SPD503-312 and SPD503-316, -12.6 (-19.6, -5.7) and -8.7 (-11.8, -5.5) in SPD503-314, and -12.7 (-17.3, -8.1) and -11.8 (-19.3, -4.4) in SPD503-307, respectively. The corresponding effect sizes were 0.688 and 0.598 in SPD503-312 and SPD503-316, 0.876 and 0.729 in SPD503-314, and 0.962 and 0.842 in SPD503-307.
CONCLUSION: The findings demonstrate the efficacy of GXR for treating ADHD in children and adolescents with comorbid ODD

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S105-S110.
DEVELOPING THE EVIDENCE-GRADING TOOLS AND PROCESS FOR THE COMPLEX ATTENTION-DEFICIT/HYPERACTIVITY DISORDER GUIDELINE.
Chan E, Froehlich TE, Barbaresi WJ, et al.
Clinical practice guidelines (CPGs) rely on a robust assessment of the quality of evidence supporting guideline recommendations. For the Society for Developmental and Behavioral Pediatrics (SDBP) CPG for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit Hyperactivity Disorder (ADHD), the nature of the evidence and resource constraints led the guideline panel to develop an innovative, yet rigorous, approach to evidence grading. This study will (1) describe the challenges of evidence grading for the SDBP Complex ADHD Guideline; (2) discuss the rationale, process, and tools developed to conduct evidence grading; and (3) report on the experiences and readiness of the volunteer reviewers with diverse background in research methodology to conduct evidence grading. This evidence review process may serve as an example of approaches that can be used by other groups tasked with evaluating the evidence in support of new CPGs

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S88-S98.
COMBINED TREATMENT FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: BRIEF HISTORY, THE MULTIMODAL TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER STUDY, AND THE PAST 20 YEARS OF RESEARCH.
Pelham WE, Jr., Altszuler AR.
Decades of research support 3 interventions for youth with attention-deficit/hyperactivity disorder (ADHD): behavioral intervention, stimulant medication, and their combination. However, professional organizations have long disagreed regarding the best approach for implementing evidence-based interventions for ADHD in practice. The accompanying Society of Developmental and Behavioral Pediatrics guidelines for complex ADHD provide a framework for initiating treatment with behavioral intervention and adding stimulant medication as necessary, resulting in combined/multimodal treatment for many, if not most, children. In this special article, we review the extant literature on combined treatment, with special emphasis on the past 15 years of research that have led to the recommendation for this approach. Specifically, we review the literature on dosing and sequencing of multimodal treatment for youth with ADHD and the impact of multimodal interventions on areas of functional impairment. The extant research provides clear support for a psychosocial-first approach in treating youth with complex ADHD

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S58-S74.
THE SOCIETY FOR DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS CLINICAL PRACTICE GUIDELINE FOR THE ASSESSMENT AND TREATMENT OF CHILDREN AND ADOLESCENTS WITH COMPLEX ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PROCESS OF CARE ALGORITHMS.
Barbaresi WJ, Campbell L, Diekroger EA, et al.

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J Dev Behav Pediatr. 2020 Oct;41:587-95.

BEHAVIORAL HEALTH SCREENING: VALIDATION OF A STRENGTH-BASED APPROACH.

Mautone JA, Pendergast LL, Cassano M, et al.

OBJECTIVE: To evaluate the validity of the Behavioral Health Checklist (BHCL) strength-based factor scores and the extent to which this factor has a buffering effect on the relationship between behavioral health symptom severity and children's social problems.

METHOD: The parents of 1,392 children aged 4 to 12 completed the BHCL and Child Behavior Checklist (CBCL) during sick and well-child visits to urban and suburban primary care practices affiliated with a large children's hospital.

RESULTS: Findings support a single, strength-based factor on the BHCL, and the structure was largely invariant across race, sex, and socioeconomic status. Increased psychopathology symptoms (internalizing, externalizing, and attention-deficit hyperactivity disorder) and lower levels of strengths predicted increased social problems ($p < 0.001$). Moreover, the interaction terms were statistically significant in all analyses, suggesting that higher levels of strengths may buffer the deleterious impact of psychopathology symptoms on social problems. Post hoc analyses indicated that the buffering influence of strengths on the relationship between psychopathology symptoms and social problems was clinically meaningful except in the older sample for the relationship between externalizing and social problems.

CONCLUSION: The findings support the validity of a strength-based factor of the BHCL and indicate that this factor has a buffering effect on the association between the degree of child mental health symptoms and level of social impairment. This factor, in combination with the problem-focused factors of the BHCL, provides a balanced approach to screening children's mental health functioning

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J Dev Behav Pediatr. 2020 Feb;41 Suppl 2S:S77-S87.

PSYCHOSOCIAL INTERVENTIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SYSTEMATIC REVIEW WITH EVIDENCE AND GAP MAPS.

Schatz NK, Aloe AM, Fabiano GA, et al.

OBJECTIVE: To inform the scope of future systematic reviews, meta-analyses, and treatment outcome studies, this review aims to describe the extent of the evidence for psychosocial interventions for children and adolescents with attention-deficit/hyperactivity disorder, with particular attention to specific types of interventions, targets of outcome assessment, and risk of bias.

METHOD: A comprehensive search of relevant databases (i.e., Medline, PsychInfo, Education Resources Information Center, and ProQuest Dissertation Database) was conducted. Detailed information related to treatment type, outcome assessment, study design, and risk of bias was extracted by trained coders. Evidence and gap maps were created to summarize evidence within types of treatments and targets of outcome assessment. Indicators of risk of bias were assessed for selected combinations of treatments and outcome assessment.

RESULTS: We identified 185 eligible individual studies and 3817 effect sizes. Behavioral parent training and cognitive training (COG) were the most commonly studied stand-alone interventions. Treatment versus control comparisons for stand-alone interventions (s = 70) were less common than for complex interventions involving combinations of psychosocial interventions (s = 100). Combinations of behavioral and child training (e.g., COG, organizational training) interventions were the most frequently studied.

CONCLUSION: There is a considerable variability within this literature regarding combinations of treatments across outcome assessment targets. To address gaps in existing evidence, more primary studies assessing direct comparisons of isolated and combined treatment effects of specific types of psychosocial treatments relative to control and other treatments are needed. Future meta-analyses should take into account the complexity and breadth of available evidence

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J Dev Behav Pediatr. 2021 May;42:257-63.
ASSOCIATIONS BETWEEN PARTICIPATION IN AFTER-SCHOOL ACTIVITIES, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SEVERITY, AND SCHOOL FUNCTIONING.
Lax Y, Brown SN, Silver M, et al.
OBJECTIVE: To examine the association between after-school activity (ASA) participation, attention-deficit/hyperactivity disorder (ADHD) severity, and school functioning among children with ADHD.
METHODS: A cross-sectional study was conducted using data from the 2016 National Survey of Children's Health on ADHD severity, ASAs and 2 domains of school functioning among children with ADHD: missed days from school and calls home from school.
RESULTS: Of 4,049 children with ADHD (weighted N = 5,010,662), 71.8% participated in at least 1 ASA. In multivariable regression analyses, ASA participation was associated with lower odds of moderate-to-severe ADHD [adjusted odds ratio (aOR): 0.62, 95% confidence interval (CI), 0.46-0.85] and lower odds of missed school days (aOR 0.55, 95% CI, 0.41-0.74). We did not find significant associations with calls home from school (aOR 0.79, 95% CI, 0.59-1.07).
CONCLUSION: After-school activity participation is associated with decreased ADHD severity and reduced school absenteeism. Efforts to optimize ADHD outcomes should consider engaging children and adolescents in ASAs

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J Dev Behav Pediatr. 2021 Feb;42:83-90.
DEVELOPMENTAL-BEHAVIORAL PEDIATRICS 13 YEARS AFTER THE FIRST BOARD CERTIFICATION: EVOLVING SUBSPECIALTY.
Roizen NJ, Ruch-Ross HS, Bauer NS, et al.
OBJECTIVE: To examine and define the evolving subspecialty of developmental-behavioral pediatrics (DBP) by analyzing workforce surveys presubspecialty and postsubspecialty certification.
METHODS: In 2015, an electronic workforce survey was sent to the members of the American Academy of Pediatrics Section on DBP and Council on Children with Disabilities and the Society for DBP. Answers from the 1998 survey for respondents with subspecialty fellowship training were compared.
RESULTS: Compared with the 1998 group of 265 DBPs, the 368 DBPs in the 2015 group were older, more female, and more diverse. In both groups, â‰¥80% evaluated and treated autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and developmental delays, but significantly ($p < 0.001$) fewer cared for children with physical disabilities (e.g., cerebral palsy [58% to 41%], multihandicapped [53% to 39%], neonatal follow-up [47% to 31%], and spina bifida [26% to 13%]) and other disorders (e.g., failure to thrive and obesity/eating disorders [27% to 15%]). Time for new patient and return visits remained the same (1.5 hours and 0.7 hours). Pediatric generalists and family practice physicians initiated most referrals; fewer 2015 DBPs ($p < 0.001$) reported school districts (83% to 70%) and more reported pediatric subspecialty (57% to 77%; $p < 0.001$) referrals. Acknowledgment of the need for more community DBP specialists increased from 66% to 80% ($p < 0.001$).
CONCLUSION: Survey data indicated that the workforce is aging and changing. ADHD, ASD, and developmental delays are solidifying as the defining clinical focus of DBP. Current trends can identify training needs, facilitate recruitment, and advocate for system change to support the DBP workforce to respond to the great need

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J Dev Behav Pediatr. 2021 Jan;42:9-15.
BREASTFEEDING IS ASSOCIATED WITH A REDUCED RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG PRESCHOOL CHILDREN.
Soled D, Keim SA, Rapoport E, et al.
BACKGROUND: Breastfeeding has been associated with a lower risk of attention-deficit/hyperactivity disorder (ADHD). However, most studies examining this association have focused on small samples outside the United States or were likely subject to substantial residual confounding. Our objectives were to investigate, in a nationally representative sample of preschool children in the United States, the associations

between ADHD and both age of breastfeeding cessation and age of formula introduction, as well as associations between ADHD and exclusive breastfeeding duration.
METHODS: Analysis of data from children aged 3 to 5 years in the 2011/12 National Survey of Children's Health (n = 12,793). Logistic regressions were used to model current medical diagnosis of preschool ADHD as a function of breastfeeding duration, breastfeeding exclusivity, and the timing of formula introduction with adjustment for 12 potential confounders using propensity scores, including sex, age, race, household income, prematurity, insurance, and medical home.
RESULTS: After adjustment for potential confounders, exclusive breastfeeding for at least 6 months was associated with substantially reduced odds of ADHD (adjusted prevalence odds ratio [aPOR] = 0.38; 95% confidence interval [CI], 0.15-0.99). Breastfeeding duration was also associated with ADHD, with 8% reduced odds of ADHD for each additional month of breastfeeding (aPOR = 0.92; 95% CI, 0.86-0.99). The results for exclusive breastfeeding duration were similar, but the confidence interval included the null (aPOR = 0.92; 95% CI, 0.85-1.00). The age of formula introduction was not associated with ADHD (aPOR = 0.92; 95% CI, 0.81-1.05).
CONCLUSION: In a nationally representative sample of preschool children, breastfeeding was associated with a lower prevalence of ADHD. These findings provide evidence in support of the neurodevelopmental benefits of breastfeeding

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J Dev Behav Pediatr. 2021 Aug;42:457-62.
EXPLORING LINKS BETWEEN PRENATAL ADVERSITY AND ADOLESCENT PSYCHIATRIC RISK IN A CANADIAN POPULATION-BASED SAMPLE.
Faltyn M, Savoy C, Krzeczkowski JE, et al.
OBJECTIVE: Adverse prenatal and postnatal exposures may have long-lasting effects on health and development. However, it remains unclear whether being exposed to a greater number of prenatal adversities affects mental health risk. The current study examined whether exposure to maternal health problems prenatally is associated with an increasing risk of psychiatric morbidity in adolescents.
METHODS: Using data from the 2014 Ontario Child Health Study (OCHS), we examined associations between a count of 7 prenatal risk factors (maternal hypertension, diabetes mellitus, bleeding during pregnancy, influenza, urinary tract infection, thyroid disease, and depression/anxiety) and adolescent psychiatric morbidity. Adolescents (N = 2219) aged 12 to 17 years were assessed using the Mini-International Neuropsychiatric Interview for Children and Adolescents.
RESULTS: Exposure to each additional prenatal adversity was correlated with increased odds of attention-deficit/hyperactivity disorder (odds ratio [OR] = 1.29, 95% confidence interval [CI] = 1.03-1.60), generalized anxiety disorder (OR = 1.27, 95% CI = 1.05-1.55), and social anxiety disorder (OR = 1.35, 95% CI = 1.01-1.80) after adjustment for confounding variables.
CONCLUSION: Exposure to prenatal adversity in the form of maternal health problems was correlated with an increased risk of attention deficit hyperactivity disorder and anxiety disorders in adolescence. Future studies should further investigate the effects of antenatal environmental exposures on these associations to determine the potential value of close monitoring of those exposed to prenatal risks

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J Dev Behav Pediatr. 2021 May;42:340-42.
ASSESSMENT AND TREATMENT OF A YOUNG ADULT WITH CONGENITAL HEART DISEASE AND ADHD.
Hammerness PG, Cassidy AR, Potts H, et al.
CASE: Phillip is a young man born with hypoplastic left heart syndrome referred to your practice for a range of mental health concerns. He underwent palliation to an extracardiac Fontan in infancy and experienced multiple complications over the next decade including valvular regurgitation and arrhythmias necessitating a pacemaker. Phillip continued to have systolic heart failure with New York Heart Association class II symptoms, managed with 4 medications and anticoagulation. Despite this complex history, Phillip had intact cognitive abilities, achieved typical milestones, and performed well academically in secondary school. His first year of college proved to be more challenging, and Phillip presented to the outpatient psychiatry service with an acute depressive episode. His family history included depression, without known attention-

deficit/hyperactivity disorder (ADHD). Treatment, including a selective serotonin reuptake inhibitor, cognitive behavioral therapy, and family support, led to near resolution of his symptoms of depression. In subsequent appointments, Phillip described a long history of inattention and disorganization with onset in childhood. This contributed to the decision to leave college, despite remission of symptoms of depression. Phillip was unable to study for any extended period without "perfect conditions," described as the absence of potential distractions except for background music. Despite attempts to maintain "perfect conditions," Phillip was often off task and "hyperfocusing" on irrelevant topics. Phillip struggled with planning and time management and would misplace items daily. Moreover, although the importance of self-care was well understood, Phillip often forgot to take his cardiac medication or to exercise, and he admitted to inconsistent sleep habits because of losing track of time. Based on a comprehensive psychiatric evaluation including retrospective report from a parent, Phillip was diagnosed with ADHD, coexisting with major depressive disorder, in remission. Significant ADHD symptoms were documented by interview, self-report, and administration of an abbreviated neuropsychological battery. Considering concerns regarding use of stimulants in a patient with congenital heart disease, including death, stroke, and myocardial infarction,1,2 how would you assess the risks-benefits of use of stimulants with Phillip? REFERENCES: 1. Wilens TE, Prince JB, Spencer TJ, et al. Stimulants and sudden death: what is a physician to do? Pediatrics. 2006;118:1215-1219.2. Zito JM, Burcu M. Stimulants and pediatric cardiovascular risk. J Child Adolesc Psychopharmacol. 2017;27:538-545

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J Dev Behav Pediatr. 2021 Sep;42:540-52.

ADOLESCENTS TREATED FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PEDIATRIC PRIMARY CARE: CHARACTERIZING RISK FOR STIMULANT DIVERSION.

Molina BSG, Joseph HM, Kipp HL, et al.

OBJECTIVE: To describe the clinical and psychosocial characteristics, and their hypothesized interrelations, as it pertains to risk for stimulant diversion (sharing, selling, or trading) for adolescents in pediatric primary care treatment for attention-deficit/hyperactivity disorder.

METHODS: Baseline data for 341 adolescents in a cluster-randomized controlled trial of stimulant diversion prevention in pediatric primary care (NCT_03080259) were used to (1) characterize diversion and newly measured risk factors, (2) examine their associations with age and sex, and (3) test whether associations among risk factors were consistent with model-implied predictions. Data were collected through multi-informant electronic surveys from adolescents and parents.

RESULTS: Diversion was rare (1%) in this sample (Mage = 15, SD = 1.5, 74% male participants). Older age was associated with being approached to divert ($r = 0.25$, $p < 0.001$) and higher risk on variables pertinent to stimulant treatment, such as treatment disclosure ($r = 0.12$, $p < 0.05$), tolerance for stimulant misuse and diversion ($r = 0.17$, $p < 0.05$), and peer norms favorable to stimulant misuse and diversion (r values = 0.15-0.34, $p < 0.001$). Sex differences were minimal. Variables from our conceptual model and specific to stimulants (e.g., perceived likelihood of negative consequences from diversion and schoolmate stimulant misuse/diversion) were related in multivariable regressions to hypothesized immediate precursors of diversion (e.g., diversion intentions).

CONCLUSION: Although diversion was rare for these primary care-treated adolescents, risk levels appear to be higher for older adolescents. Prevention may be most effective by capitalizing on current psychosocial strengths and discussing stimulant-specific attitudes, behaviors, and social norms before vulnerability to diversion increases in the final years of high school and into college

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J Dev Behav Pediatr. 2021 Jun;42:415-27.

LONGITUDINAL PSYCHIATRIC AND DEVELOPMENTAL OUTCOMES IN 22Q11.2 DELETION SYNDROME: A SYSTEMATIC REVIEW.

Jhawar N, Brown MJ, Cutler-Landsman D, et al.

OBJECTIVE: 22q11.2 deletion syndrome (22q11DS) is a common genetic deletion syndrome associated with psychiatric disorders and developmental delays. A significant amount of 22q11DS research literature is published annually; here, we focus exclusively on longitudinal data that have been published in the past 5

years regarding psychiatric disorders and/or cognitive and social development. After a review, areas for future research consideration and clinical recommendations are presented.
METHODS: Articles were reviewed and organized in adherence with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting systematic reviews. The literature search identified 852 studies, and 22 studies met inclusion criteria.
RESULTS: Longitudinal study findings indicate that developmental considerations for youth with 22q11DS should focus on the primacy and enduring nature of social and executive functioning deficits, attention-deficit/hyperactivity disorder, anxiety, and negative symptoms of psychosis.
CONCLUSION: From the diathesis of physiological conditions and genetic variance, 22q11DS and its associated phenotype of persistent cognitive deficits, comorbid psychiatric disorders, and social impairments likely conspire to increase the risk for stress in adolescence. The diathesis-stress framework, along with chronic stress, increases psychosis risk in individuals with 22q11DS. The existing literature has a heavy focus on the impact of the deletion on individual skills and attributes, such as cognition, but lacks information on the impact of the environment. Future 22q11DS research should consider specific aspects of social functioning, including interactions with parenting styles and family communication, as well as high demands in educational settings, as possible risk factors for psychosis

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J Dev Behav Pediatr. 2021 Jan;42:61-65.
USE OF STIMULANTS IN PATIENTS WITH COMORBID ANOREXIA NERVOSA AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A STRUCTURED INPATIENT SETTING.
Shear M, Deliberto T, Kerrigan S, et al.
OBJECTIVE: Clinicians may be concerned about using psychostimulant medications in patients in whom weight gain is desired because of their potential side effects of appetite suppression and weight loss. This report depicts the successful treatment of 2 adolescent patients with anorexia nervosa (AN) and attention-deficit/hyperactivity disorder (ADHD) in an inpatient eating disorders unit.
METHOD: A report of 2 clinical cases (ages 19 and 20 years) was used to describe the management of comorbid AN and ADHD. Tolerance to stimulants, meal completion, and ability to restore weight were assessed over the course of hospitalization.
RESULTS: Behaviorally focused refeeding combined with psychostimulants notably improved symptoms of AN and comorbid ADHD without adverse effects.
CONCLUSION: Psychostimulant medications may be used successfully in patients with AN and ADHD in the context of structured behavioral treatment designed for weight restoration

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J Dev Behav Pediatr. 2021 Feb;42:122-27.
NETWORK-SPECIFIC CORTICOTHALAMIC DYSCONNECTION IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Hua MH, Chen YL, Chen MH, et al.
BACKGROUND: Functional connectivity (FC) is believed to be abnormal in attention-deficit hyperactivity disorder (ADHD). Most studies have focused on frontostriatal systems, and the role of the thalamic network in ADHD remains unclear. The current study used FC magnetic resonance imaging (fcMRI) to explore corticothalamic network properties and correlated network dysconnection with ADHD symptom severity.
METHODS: Eighteen adolescents with ADHD and 16 healthy controls aged 12 to 17 years underwent resting functional MRI scans, clinical evaluations, and 2 parent rating scales, namely the Swanson, Nolan, and Pelham IV scale and the Child Behavior Checklist. Six a priori cortical regions of interest were used to derive 6 networks: the dorsal default mode network, frontoparietal network, cingulo-opercular network (CON), primary sensorimotor network (SM1), primary auditory network, and primary visual network (V1). The corticothalamic connectivity for each network was calculated for each participant and then compared between the groups. We also compared the 2 scales with the network connectivity.
RESULTS: The corticothalamic connectivity within the CON was significantly reduced ($p < 0.05$) among adolescents with ADHD compared with the controls. The corticothalamic dysconnection within the CON, SM1, and V1 networks negatively correlated with ADHD symptom severity.

CONCLUSION: This network analysis indicates that corticothalamic dysconnection in ADHD involves the CON, SM1, and V1 networks and relates to symptom severity. The findings provide evidence of dysfunctional thalamus-related networks in ADHD

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J Dev Behav Pediatr. 2021 Jun;42:343-54.

UNIQUE ASSOCIATIONS BETWEEN SPECIFIC ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND RELATED FUNCTIONAL IMPAIRMENTS.

Zoromski AK, Epstein JN, Ciesielski HA.

OBJECTIVE: The purpose of this study was to explore the unique relationships between specific attention-deficit hyperactivity disorder (ADHD) symptoms and functional impairment in school-age children using parent and teacher ratings.

METHODS: Parents and teachers rated ADHD symptoms and comorbidities (internalizing and oppositional behaviors) as well as impairments (academic, relationship, and classroom behavior) for 8689 children using the Vanderbilt ADHD Diagnostic Rating Scales. Stepwise regression was used to determine which of the 18 ADHD symptom items were most associated with specific domains of impairment with relevant demographic and clinical characteristics used as covariates (e.g., sex, comorbidities, medication status, and age).

RESULTS: "Careless mistakes" and "avoids tasks" significantly predicted academic impairment across content areas and across parent- and teacher-rating models. ADHD symptoms accounted for limited variance in impairment in the family and peer relationship domains or in organized activities when oppositional symptoms were entered as a covariate. Regarding teacher-rated classroom behavior, the strongest predictor of impairment was "talks too much."

CONCLUSION: The findings indicate that the symptoms that were most predictive of impairment varied by domain of impairment

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J Dev Behav Pediatr. 2021 Aug;42:481-84.

PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TELEPHONE MEDICATION MANAGEMENT AT DEVELOPMENTAL-BEHAVIORAL PEDIATRIC NETWORK SITES.

Harstad E, Shults J, Barbaresi W, et al.

OBJECTIVE: To understand developmental-behavioral pediatricians' (DBPs') use of clinic versus telephone encounters for preschool attention-deficit/hyperactivity disorder (ADHD) medication management. Understanding use of telephone encounters for pharmacologic management of ADHD in preschoolers may inform care for children with ADHD.

METHODS: DBP investigators within Developmental Behavioral Pediatrics Research Network abstracted data from medical records of 503 children aged younger than 72 months treated for ADHD with medication by a DBP clinician between January 1, 2013, and July 1, 2017, across 7 sites. We abstracted data about medication treatment episodes (defined as start and end/change of a specific type, dose, and frequency of ADHD medication) and encounter type (clinic vs telephone). We present descriptive statistics related to encounter types and Ï‡2 analyses to compare frequencies across reasons for the end of treatment episode and across sites.

RESULTS: The study included 503 participants with a total of 1734 treatment episodes. The initial medication was started via a clinic encounter 85.9% of the time and via telephone encounters 14.1% of the time. When evaluating reasons for end of treatment episode, decreases in dose/frequency of medication were less common for clinic versus telephone encounters (27% vs 73%; $p < 0.001$) and adding an additional medication was more common at clinic versus telephone encounters (64% vs 36% $p < 0.001$). Sites varied significantly in frequency of telephone encounters, ranging from 16.9% to 68.9% (mean 45.7%).

CONCLUSION: Telephone encounters were used for pharmacologic management of ADHD in preschoolers to varying degrees across 7 DBP sites. These findings suggest that telephone management serves an important role in ADHD care

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J Dev Behav Pediatr. 2021 Jan;42:1-8.

SLEEP VARIABLES AS PREDICTORS OF TREATMENT EFFECTIVENESS AND SIDE EFFECTS OF STIMULANT MEDICATION IN NEWLY DIAGNOSED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Davidson F, Rigney G, Rusak B, et al.

OBJECTIVE: There is a growing body of research on the impact of stimulant medication on sleep in children with attention-deficit/hyperactivity disorder (ADHD). Negative sleep side effects are a common reason for nonadherence or for discontinuing a course of treatment. However, there is no published evidence as to whether pretreatment sleep can predict responses to treatment and the emergence of side effects.

METHOD: In this study, baseline sleep variables were used to predict therapeutic effect (i.e., reduction of ADHD symptoms) and side effects (both sleep and global side effects) in a sample of newly diagnosed, medication-naive children (n = 50).

RESULTS: The results of hierarchical regression analysis showed that parent-reported shorter sleep duration before medication treatment significantly predicted better response to treatment, independent of pretreatment ADHD symptoms. Baseline sleep features did not significantly predict global (nonsleep) side effects but did predict increased sleep side effects during treatment.

CONCLUSION: These results indicate that baseline sleep variables may be helpful in predicting therapeutic response to medication and sleep disturbance as a side effect of stimulant medication

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J Dev Behav Pediatr. 2021 Aug;42:433-41.

PREVALENCE AND CORRELATES OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN A DIVERSE, TREATMENT-SEEKING PEDIATRIC OVERWEIGHT/OBESITY SAMPLE.

Merrill BM, Morrow AS, Sarver D, et al.

OBJECTIVE: Attention-deficit hyperactivity disorder (ADHD) and obesity are highly prevalent, impairing, and costly conditions, affecting about 10% of children each. Research indicates heightened prevalence of childhood obesity among youth with ADHD. However, more research is needed, examining comorbid ADHD among youth with overweight/obesity (OV/OB) from diverse demographic backgrounds and effects on medically relevant behaviors. The aim of the current study was to examine the prevalence of ADHD in a racially diverse sample of youth in a weight management clinic. Furthermore, we examined the effects of race, rurality, and ADHD on weight status and health behaviors in this under-researched population.

METHOD: Participants included 1003 patients (Mage = 12.55; 58% female; 67% Black/African American; MBMI Z-Score = 2.54; 98.6% with obesity) in a pediatric weight management clinic serving a rural and urban/suburban area in the southern United States. Parent-reported demographics, ADHD diagnosis, and child health behaviors were recorded.

RESULT: In total, 17.6% (n = 177) of the sample had an ADHD diagnosis. ADHD status interacted with race to predict standardized body mass index (BMIz), and rurality predicted higher BMIz. Children with comorbid ADHD had significantly more meals per day and fewer active days compared with children with OV/OB without ADHD.

CONCLUSION: ADHD prevalence was higher in this diverse sample of children seeking obesity treatment (17.6%) compared with the prevalence nationally (9%-10%) and in other obesity samples. Comorbid ADHD was related to higher weight status among racial minority youth and increased engagement in unhealthy lifestyle behaviors often targeted in weight management treatment. It is critical to screen for ADHD in pediatric specialty clinics and assess healthy lifestyle behaviors

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J Int Neuropsychol Soc. 2021 Aug;27:686-96.

SEVERITY OF ONGOING POST-CONCUSSIVE SYMPTOMS AS A PREDICTOR OF COGNITIVE PERFORMANCE FOLLOWING A PEDIATRIC MILD TRAUMATIC BRAIN INJURY.

Sicard V, Hergert DC, Pabbathi RS, et al.

OBJECTIVE: This study aimed to examine the predictors of cognitive performance in patients with pediatric mild traumatic brain injury (pmTBI) and to determine whether group differences in cognitive performance on a computerized test battery could be observed between pmTBI patients and healthy controls (HC) in the sub-acute (SA) and the early chronic (EC) phases of injury.

METHOD: 203 pmTBI patients recruited from emergency settings and 159 age- and sex-matched HC aged 8-18 rated their ongoing post-concussive symptoms (PCS) on the Post-Concussion Symptom Inventory and completed the Cogstate brief battery in the SA (1-11 days) phase of injury. A subset (156 pmTBI patients; 144 HC) completed testing in the EC (~4 months) phase.
RESULTS: Within the SA phase, a group difference was only observed for the visual learning task (One-Card Learning), with pmTBI patients being less accurate relative to HC. Follow-up analyses indicated higher ongoing PCS and higher 5P clinical risk scores were significant predictors of lower One-Card Learning accuracy within SA phase, while premorbid variables (estimates of intellectual functioning, parental education, and presence of learning disabilities or attention-deficit/hyperactivity disorder) were not.
CONCLUSIONS: The absence of group differences at EC phase is supportive of cognitive recovery by 4 months post-injury. While the severity of ongoing PCS and the 5P score were better overall predictors of cognitive performance on the Cogstate at SA relative to premorbid variables, the full regression model explained only 4.1% of the variance, highlighting the need for future work on predictors of cognitive outcomes

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J Interpers Violence. 2021 Sep;36:NP9738-NP9756.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND COMMUNITY VIOLENCE EXPOSURE IN RUSSIAN ADOLESCENTS.
Stickley A, Koposov R, Koyanagi A, et al.
A large body of research has shown that exposure to community violence is common for many children across the world. However, less is known about exposure in particular subgroups such as those children with developmental disorders. To address this research gap, the aim of this study was to examine community violence exposure (CVE) in adolescents with attention-deficit/hyperactivity disorder (ADHD) symptoms and the role of gender in this association. Data were analyzed from 2,782 adolescents aged 13 to 17 years from Arkhangelsk, Russia that were collected during the Social and Health Assessment (SAHA). ADHD status was assessed with the hyperactivity/inattention scale of the Strengths and Difficulties Questionnaire (SDQ). Information was obtained on past-year witnessing and violence victimization in the community. Results showed that CVE was more prevalent in children with ADHD symptoms. Specifically, 75.1% of children with ADHD symptoms had been exposed to any violence versus 62.3% in the non-ADHD group (Ї‡(2) = 18.65, p < .001). Multivariate analyses of covariance (MANCOVAs) revealed that CVE was significantly higher for adolescents with ADHD symptoms for both witnessing and victimization, while exposure was significantly higher for ADHD boys compared with girls. The findings of this study suggest that CVE may be elevated in adolescents with higher ADHD symptoms. Given that CVE has been associated with a variety of negative social and psychological outcomes in typically developing children, an important task for future research is to determine what factors are associated with CVE in adolescents with ADHD symptoms including those relating to such phenomena as comorbid psychopathology, the family, and peer relations, so that interventions can be designed and implemented to reduce CVE and its detrimental effects in this population

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J Interpers Violence. 2021 Sep;36:NP8992-NP9014.
BULLYING INVOLVEMENT IN ADOLESCENCE: IMPLICATIONS FOR SLEEP, MENTAL HEALTH, AND ACADEMIC OUTCOMES.
Hysing M, Askeland KG, La Greca AM, et al.
Adolescents' involvement in bullying is associated with both sleep and mental health problems, but the nature of this association remains unclear; further, its association with academic outcomes has received little attention. Thus, the aims of the current study were to (a) determine whether involvement in bullying as a victim, bully, or bully-victim was associated with greater sleep and mental health problems and (b) explore the potential mediating effect of sleep and mental health problems on the association between bullying and academic outcomes. A large 2012 population-based study in Hordaland County, Norway, surveyed 10,220 adolescents (16-19 years; 54% girls) about bullying involvement using the revised version of the Olweus Bully/Victim Questionnaire, detailed sleep assessment, and mental health questionnaires. Academic outcomes were obtained from official administrative registries. 1.7% of the adolescents (n = 156) reported being victims of bullying, 1.0% (n = 92) reported being a bully, and 0.5% (n = 50) reported being a bully-

victim. All categories of bullying involvement had higher rates of mental health problems compared with adolescents not involved in bullying. Victims reported more symptoms of anxiety and depression, whereas bullies reported higher rates of conduct problems. Adolescents in all bullying categories also reported significantly shorter sleep duration and higher prevalence of insomnia as well as lower grade point average (GPA) compared with adolescents not involved; however, school absence was not associated with bullying involvement. Bullying involvement and GPA showed complete mediation for bullies and bully-victims and partial mediation for victims through sleep duration, conduct problems, and symptoms of depression and attention deficit hyperactivity disorder (ADHD). Bullying is strongly associated with mental health and sleep problems, in addition to lower academic performance. Findings support the importance of addressing bullying involvement during this important developmental period

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J Med Internet Res. 2021 Aug;23:e29328.

CLASSIFICATION OF CHILDREN WITH AUTISM AND TYPICAL DEVELOPMENT USING EYE-TRACKING DATA FROM FACE-TO-FACE CONVERSATIONS: MACHINE LEARNING MODEL DEVELOPMENT AND PERFORMANCE EVALUATION.

Zhao Z, Tang H, Zhang X, et al.

BACKGROUND: Previous studies have shown promising results in identifying individuals with autism spectrum disorder (ASD) by applying machine learning (ML) to eye-tracking data collected while participants viewed varying images (ie, pictures, videos, and web pages). Although gaze behavior is known to differ between face-to-face interaction and image-viewing tasks, no study has investigated whether eye-tracking data from face-to-face conversations can also accurately identify individuals with ASD.

OBJECTIVE: The objective of this study was to examine whether eye-tracking data from face-to-face conversations could classify children with ASD and typical development (TD). We further investigated whether combining features on visual fixation and length of conversation would achieve better classification performance.

METHODS: Eye tracking was performed on children with ASD and TD while they were engaged in face-to-face conversations (including 4 conversational sessions) with an interviewer. By implementing forward feature selection, four ML classifiers were used to determine the maximum classification accuracy and the corresponding features: support vector machine (SVM), linear discriminant analysis, decision tree, and random forest.

RESULTS: A maximum classification accuracy of 92.31% was achieved with the SVM classifier by combining features on both visual fixation and session length. The classification accuracy of combined features was higher than that obtained using visual fixation features (maximum classification accuracy 84.62%) or session length (maximum classification accuracy 84.62%) alone.

CONCLUSIONS: Eye-tracking data from face-to-face conversations could accurately classify children with ASD and TD, suggesting that ASD might be objectively screened in everyday social interactions. However, these results will need to be validated with a larger sample of individuals with ASD (varying in severity and balanced sex ratio) using data collected from different modalities (eg, eye tracking, kinematic, electroencephalogram, and neuroimaging). In addition, individuals with other clinical conditions (eg, developmental delay and attention deficit hyperactivity disorder) should be included in similar ML studies for detecting ASD

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J Med Invest. 2021;68:53-58.

USEFULNESS OF NEAR-INFRARED SPECTROSCOPY (NIRS) FOR EVALUATING DRUG EFFECTS AND IMPROVEMENTS IN MEDICATION ADHERENCE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Kawai C, Mori K, Tanioka T, et al.

The symptoms of attention deficit hyperactivity disorder (ADHD) are inattention, hyperactivity, and impulsiveness. Physicians often prescribe methylphenidate (MPH) for children with ADHD for long periods of time. The purpose of the present study was to investigate the usefulness of near-infrared spectroscopy (NIRS) for evaluating drug effects and improvements in medication adherence in children with ADHD. Subjects were 10 male children diagnosed with ADHD……average age, 9.3 years, and 10 boys with typical development…average age 9.5 years. Children with intellectual disability, autism, and obvious depressive

symptoms were excluded. The present study revealed that in the ADHD group, oxy-Hb concentrations in the left and right lateral prefrontal cortex significantly increased during the execution of the Stroop color-word test in both channels when taking MPH. This method was considered to be useful for assessing drug effects on ADHD because NIRS is an objective indicator for evaluating ADHD executive dysfunction and visualizes the activation of frontal lobe function by MPH. A pediatric neurologist explained the results of NIRS while presenting images to the ADHD group, and medication adherence and the drug-taking ratio both markedly improved. Therefore, this therapeutic explanation is an effective strategy for improving medication compliance and adherence among patients. J. Med. Invest. 68 : 53--58, February, 2021

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J Mol Neurosci. 2021 Mar;71:607-12.

A Novel CREBBP in-Frame Deletion Variant in a Chinese Girl with Atypical Rubinstein-Taybi Syndrome Phenotypes.

Wang Q, Xu W, Liu Y, et al.

Loss-of-function variants in CREBBP or EP300 result in Rubinstein-Taybi syndrome (RSTS). The previously reported cluster of variants in the last part of exon 30 and the beginning of exon 31 of CREBBP, overlapping with the ZNF2 (zinc finger, ZZ-type; residues 1701 to 1744) and ZNF3 (zinc finger, TAZ-type; residues 1764 to 1853) domains, is associated with atypical RSTS. The main features include developmental delay, short stature, microcephaly, distinctive facial features, autistic behavior, feeding difficulties, recurrent upper airway infections, and hearing impairment. Here, we report a 2-year-7-month-old Chinese girl presenting mild cognitive impairments, developmental delay, short stature, recurrent upper airway infections, and facial dysmorphism that resembled the phenotypes of previously reported atypical RSTS patients. The characteristic facial and limb dysmorphism for RSTS was absent in our patient. In addition, our patient exhibited novel phenotypes including attention deficit hyperactivity disorder (ADHD), sleep problem, and abnormal walking posture. Whole-exome sequencing (WES) identified a novel de novo in-frame deletion variant in the beginning of exon 30 of CREBBP (NM_004380:c.4897_4899delTTC, p.Phe1633del) in the HAT domain where no pathogenic variants have been previously reported to be responsible for atypical RSTS. Our case allows us to more accurately define the borders of the CREBBP coding sequence resulting in atypical RSTS, which are extended to the beginning of exon 30 (residue 1633) at the 5' end of CREBBP in the HAT domain, and reveals novel phenotypes observed in our atypical Chinese RSTS patient

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J Neural Transm (Vienna). 2021 Aug;128:1239-48.

Atypical resting-state gamma band trajectory in adult attention deficit/hyperactivity disorder.

Tombor L, Kakuszi B, Papp S, et al.

Decreased gamma activity has been reported both in children and adults with attention deficit/hyperactivity disorder (ADHD). However, while ADHD is a lifelong neurodevelopmental disorder, our insight into the associations of spontaneous gamma band activity with age is limited, especially in adults. Therefore, we conducted an explorative study to investigate trajectories of resting gamma activity in adult ADHD patients (N=42) versus matched healthy controls (N=59). We investigated the relationship of resting gamma activity (30-48Â Hz) with age in four right hemispheric electrode clusters where diminished gamma power in ADHD had previously been demonstrated by our group. We found significant non-linear association between resting gamma power and age in the lower frequency gamma(1) range (30-39Â Hz) in ADHD as compared to controls in all investigated locations. Resting gamma(1) increased with age and was significantly lower in ADHD than in control subjects from early adulthood. We found no significant association between gamma activity and age in the gamma(2) range (39-48Â Hz). Alterations of gamma band activity might reflect altered cortical network functioning in adult ADHD relative to controls. Our results reveal that abnormal gamma power is present at all ages, highlighting the lifelong nature of ADHD. Nonetheless, longitudinal studies are needed to confirm our results

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J Neural Transm (Vienna). 2021 Jul;128:1099-108.

ASSESSMENT AND TREATMENT OF SUBSTANCE USE IN ADULTS WITH ADHD: A PSYCHOLOGICAL APPROACH.

Young S, Woodhouse E.

Over half of young people and adults diagnosed with Attention Deficit Hyperactivity Disorder [ADHD] also have substance use disorder [SUD]. Their use of substances may arise from an attempt to self-medicate and/or to cope with their difficulties. This manuscript reviews key research in the literature and identifies that traditional SUD psychological interventions are an effective treatment for those presenting with a dual diagnosis of ADHD and SUD. However, typically, this is only available to those presenting to specialist SUD services for treatment of harmful use and/or dependency. This misses an opportunity to intervene much earlier, before drug use escalates to these levels. The manuscript aims to provide practical guidance for healthcare practitioners, by detailing a psychological framework for earlier assessment and intervention of problematic drug use in young people and adults with ADHD. Specific techniques are outlined drawing on psychoeducation, motivational interviewing and cognitive behavioural therapy in a phased approach to address factors that motivate initial use of substances and those that maintain use

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J Neural Transm (Vienna). 2021 Jul;128:1009-19.

ADHD AND OFFENDING.

Young S, Cocallis K.

OBJECTIVES: International studies have reported disproportionately higher rates of Attention Deficit Hyperactivity Disorder (ADHD) among youth and adult offenders across police custody, prison, probation and forensic mental health settings, estimated to fall at around 25%. This review aimed to investigate the presentation and vulnerabilities of this subpopulation of people with ADHD compared to those with ADHD in the general population and consider how this may impact on the approach to assessment and treatment in this population.

METHODOLOGY: A selective review of the extant literature was conducted to investigate how offenders with ADHD may present differently from their non-ADHD peers in their clinical presentation, criminogenic behaviour and psychological vulnerabilities.

RESULTS: Nearly all (around 96%) offenders with ADHD have additional comorbid problems, including mood, anxiety, conduct, substance use and personality disorders. Compared with offenders without ADHD, they become involved in the criminal justice system (CJS) at a younger age, have higher rates of recidivism, are more likely to make a false confession, engage in behavioural disturbances in custody, have health risk behaviours and a lower quality of life. Assessing and treating ADHD in this subpopulation may be more complex due to their presentation.

CONCLUSIONS: Offenders with ADHD are disadvantaged within the system by their ADHD symptoms being unrecognised and/or misunderstood; their diagnosis of ADHD may be missed or misdiagnosed. This is at cost to the individual, from both a health and rehabilitative perspective, as well as more broadly to society

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J Neural Transm (Vienna). 2021 Jul;128:993-1008.

PUBLIC PERCEPTIONS OF ADULT ADHD: INDICATIONS OF STIGMA?

Godfrey E, Fuermaier ABM, Tucha L, et al.

Stigmatization represents a major barrier to treatment seeking across mental disorders. Despite this, stigma research on individual mental disorders remains in its infancy. Attention-deficit hyperactivity disorder (ADHD) in adults also represents an under-researched area-being far less studied than its child counterpart. This study examined the current state of public perceptions towards adult ADHD. A simulation group consisting of 105 participants performed the Weiss Functional Impairment Rating Scale (WFIRS) and Conners' Adult ADHD Rating Scales (CAARS) as though they had ADHD. These scores were compared to a group consisting of 98 individuals with adult ADHD and a group of 117 healthy individuals both groups being instructed to complete the WFIRS and CAARS to the best of their abilities. Simulators were found to overestimate impairments in adult ADHD (to a large effect) in the domains of hyperactivity, DSM-IV hyperactivity-impulsivity, DSM-IV total, work, school, (to a medium effect) in family and social, and (to a negligible-small effect) in inattention, impulsivity, DSM-IV inattention, and life skills when compared to the

ADHD group, and in all domains (to a large effect) when compared to the control group. Current and retrospective ADHD symptoms were found to be associated with more accurate perceptions in a number of domains. Evidence for the presence of perceptions considered to be stigmatizing was found, with largest effects present in the domains of hyperactivity, impulsivity, impairments at work, school, and engagement in risky behaviour

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J Neuropsychiatry Clin Neurosci. 2021;33:90-97.

COGNITIVE, GRAPHOMOTOR, AND PSYCHOSOCIAL CHALLENGES IN PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS (PANDAS).

Colvin MK, Erwin S, Alluri PR, et al .

OBJECTIVES: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) is characterized by the sudden onset of obsessive-compulsive disorder (OCD) and other neurobehavioral symptoms following group A streptococcal infection. The cardinal neuropsychiatric symptoms are believed to reflect an aberrant autoimmune or inflammatory response that may selectively disrupt basal ganglia function. The investigators examined whether neuropsychological skills associated with frontostriatal networks (executive functions and motor skills) are affected in patients with PANDAS following resolution of acute symptoms and the degree to which there are persistent social, emotional, and academic difficulties.

METHODS: Twenty-seven patients ages 6-14 years (mean age=9.63 years [SD=1.78]; male, N=22) completed neuropsychological testing as part of routine clinical care. Performances on measures of intellectual ability, executive function, motor skills, and academic skills are reported, as well as parent-reported emotional, behavioral, and social skills.

RESULTS: On neuropsychological measures, patients exhibited average intellectual functioning with relative and mild difficulties in skills supporting cognitive efficiency, including attentional regulation, inhibitory control, and processing speed. Dexterity was normal but graphomotor skills were reduced. Core reading, math, and writing skills were within expectations, but reading and math fluency were reduced, and the majority of patients received special education services or accommodations. Parents reported high levels of concern about anxiety, depression, inattention, hyperactivity, and social skills.

CONCLUSIONS: These findings indicated relative difficulties with aspects of executive and motor functions. Although evaluations were performed following the resolution of acute symptoms, ongoing and significant academic difficulties and emotional, behavioral, and social concerns were targets for clinical intervention and support

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J Pediatr Health Care. 2021 Jan;35:32-41.

PREVALENCE OF MENTAL HEALTH AND NEURODEVELOPMENTAL CONDITIONS IN U.S. CHILDREN WITH TOBACCO SMOKE EXPOSURE.

Mahabee-Gittens EM, Yolton K, Merianos AL.

INTRODUCTION: This study investigated the prevalence and correlates of current mental health and neurodevelopmental conditions among U.S. school-age children with tobacco smoke exposure (TSE).

METHOD: Data from the 2016-17 National Survey of Children's Health were analyzed. Multivariable logistic regression analyses among 6-11-year-olds (n=21,539) and among subsamples aged 6-8 years (n=10,100) and 9-11 years (n=11,439) were conducted.

RESULTS: Among 6-11-year-olds who lived with a smoker with no home TSE, the top mental health/neurodevelopmental conditions were other mental health conditions (22.1%), behavioral/conduct problems (21.7%), attention deficit disorder or attention deficit hyperactivity disorder (20.5%), depression (21.7%), and learning disability (19.3%). Children who lived with a smoker, with or without home TSE, were at increased odds of having anxiety problems, depression, attention deficit disorder or attention deficit hyperactivity disorder, behavioral/conduct problems, other mental health conditions, or learning disabilities. Many associations were more notable in younger children with home TSE.

DISCUSSION: TSE is associated with mental health and neurodevelopmental conditions. Interventions to decrease TSE are needed to protect children

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J Pediatr Psychol. 2021 Aug;46:835-43.

ACCIDENTAL INJURIES IN PRESCHOOLERS: ARE WE MISSING AN OPPORTUNITY FOR EARLY ASSESSMENT AND INTERVENTION?

Allan CC, DeShazer M, Staggs VS, et al.

OBJECTIVE: Children with attention-deficit/hyperactivity disorder (ADHD) are at risk for accidental injuries, but little is known about age-related changes in early childhood. We predicted that ADHD would be associated with greater frequency and volume of accidental injuries. We explored associations between ADHD and injury types and examined age-related changes within the preschool period.

METHODS: Retrospective chart review data of 21,520 preschool children with accidental injury visits within a large pediatric hospital network were examined. We compared children with ADHD (n=524) and without ADHD (n=20,996) on number of injury visits by age, total number of injury visits, injury volume, and injury type.

RESULTS: Children with ADHD averaged fewer injury visits at age 3 and 90% more visits at age 6. Children with ADHD had injury visits in more years during the 3-6 age. There were no differences in injury volumes. Among patients with an injury visit at age 3, children with ADHD had 6 times the probability of a subsequent visit at age 6. At age 3, children with ADHD were estimated to have 50% fewer injury visits than children without ADHD, but by age 6, children with ADHD had an estimated 74% more injury visits than children without ADHD. Risk for several injury types for children with ADHD exceeded that for patients without ADHD by at least 50%.

CONCLUSIONS: Early identification and treatment of preschool ADHD following accidental injury may prevent subsequent injuries. Clinical implications and future directions are discussed with emphasis on the maintenance of parental monitoring into the older preschool years

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J Pediatr Psychol. 2021 Oct;46:1249-57.

TEACHER VERSUS PARENT INFORMANT MEASUREMENT INVARIANCE OF THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE.

Murray AL, Speyer LG, Hall HA, et al.

BACKGROUND AND OBJECTIVES: Obtaining a multi-informant perspective is important when assessing mental health issues in childhood and adolescence. Obtaining ratings from both parents and teachers also facilitates the evaluation of similarities and contrasts in the nature and severity of symptoms across home and school contexts. However, these informants may differ in their interpretations of observed behaviors, raising questions about the validity of comparing parents' and teachers' ratings.

METHODS: We evaluated the cross-informant measurement invariance of one of the most widely used measures of child and adolescent mental health: The Strengths and Difficulties Questionnaire (SDQ). Using data from the UK-population representative Millennium Cohort Study, we evaluated configural, metric, and scalar measurement invariance across parents and teachers when children were aged 7 (N=10,221) and 11 (N=10,543).

RESULTS: Scalar measurement invariance held at both ages. Parents reported higher levels of symptoms in all domains measured at both ages as well as higher prosociality.

CONCLUSIONS: For a UK sample, valid comparisons of parent and teacher SDQ ratings at ages 7 and 11 appear to be possible, facilitating the evaluation of contextual differences in child mental health problems. Further, parents report more problem and prosocial behavior in their children than teachers attribute to them

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J Pediatr Rehabil Med. 2021;14:19-29.

Prevalence of elimination disorders and comorbid psychiatric disorders in Iranian children and adolescents.

Mohammadi MR, Hojjat SK, Ahmadi N, et al.

PURPOSE: Currently, there is a paucity of studies on the prevalence of Elimination Disorders among Iranian children and adolescents. Due to the ongoing need to monitor the health status of these children and adolescents, the present study aims to investigate the prevalence of Elimination Disorders and comorbid disorders in Iranian children and adolescents.

METHODS: In this cross-sectional study, 29,781 children and adolescents age 6 to 18 years old were selected and studied from all the provinces in Iran. The sampling was carried out by employing a multistage cluster sampling method, and several clinical psychologists using semi-structured interviews collected the data. Furthermore, clinical psychologists collected demographic information (including information about gender, age, place of residence, education level, and parental education level). The collected data were analyzed using SPSS version 20.

RESULTS: Generally, the prevalence of Elimination Disorders was found to be 5.4% covering both enuresis (p= 5.4, 95% CI = 5.1-5.7) and encopresis (p= 0.13, 95% CI = 0.09-0.2). The total prevalence of comorbid disorders was 38%, and among the comorbid disorders, Attention Deficit Hyperactivity Disorder (ADHD) (p= 11, 95% CI = 9.5-12.7) and Separation Anxiety (p= 10.6, 95% CI = 9.1-12.2) were the most prevalent.

CONCLUSION: The prevalence of Elimination Disorders in Iranian children and adolescents is moderate compared to similar studies elsewhere. As for comorbid disorders, ADHD and Separation Anxiety were found to be the most prevalent disorders. Since Elimination Disorders coexist with psychiatric disorders in children, further studies of these comorbidities may give better insight into the treatment and prognosis of Elimination Disorders

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J Pediatr Urol. 2021 Aug;17:514.

POSTERIOR URETHRAL VALVES AND THE RISK OF NEURODEVELOPMENTAL DISORDERS IN TWO FINNISH COHORTS.

Pakkasjrvi N, et al.

BACKGROUND: The Posterior Urethral Valve (PUV) is a persistent membrane of the urethra, which causes obstruction in the urogenital tract in boys. To our knowledge, no comprehensive reports have been published on whether PUV is associated to neurodevelopmental disorders. Here, we analyzed a cohort of PUV patients for neurodevelopmental disorders and verified findings in an older cohort.

METHODS: In a register based study, we reviewed the hospital registries for patients treated for PUV during 1992-2013 to identify those with neurodevelopmental disorders. Primary outcome measure was any neurodevelopmental diagnosis. Secondary outcome measures were specific disorders: ASD; ADHD, intellectual disability, learning disabilities. Birth weight and gestational age were recorded, serum creatinine levels at specific timepoints were noted. We then investigated these variables to see any correlations to neurodevelopmental disorders. We replicated the strategy for verification in an older cohort of PUV-patients, who had been treated in our institute during 1970-1991.

RESULTS: We identified 87 patients treated for PUV of which thirteen (15%) had a verified diagnosis of a neurodevelopmental disorder. 2.3% of PUV patients fulfilled criteria of mild intellectual disability (F70.0/F79.0), 9% had ADHD/ADD-spectrum diagnoses (F90.0/F90.9) and 2.3% had learning disabilities (F83/F81.3). 5.7% of patients presented with difficulties in social interactions (F93.89, F94.8). Five patients presented with more than one neurodevelopmental diagnosis. We confirmed these findings in the older cohort of patients, where a verified neurodevelopmental diagnosis was detected in 14% of patients. We identified no statistically significant associations to gestational age, birth weight or creatinine levels of PUV-patients with neurodevelopmental diagnoses as compared to the PUV-patients not diagnosed for neurodevelopmental disorders. Intellectual disability/mental retardation was more prevalent in our material and this association was statistically significant.

DISCUSSION: We show, that the prevalence of intellectual disability among PUV patients exceeds the cumulative prevalence in Finland in both cohorts analyzed here. 15% of PUV-patients presented with a diagnosis of a neurodevelopmental disorder. To our knowledge, this is the first study attempting to outline neurodevelopmental disorders among boys with PUV. This study has limitations. It is register based and only diagnoses made at an institute within our hospital district are considered. The PUV-patients may

be under closer surveillance than age-matched healthy children, which may lead to an overrepresentation of cases. The patient number is small and the small subsets of patients within each cohort hamper any further statistical analysis. The neurodevelopmental impacts of pediatric general anesthesia remain elusive and may have corollaries which must be kept in mind when interpretating our results. Patients with PUV require close follow-up in a multi-disciplinary manner, not forgetting neurodevelopmental aspects. Attention to intellectual disability is mandatory. Any suspicion of a developmental delay in a patient with PUV warrants further investigation and corresponding interventions

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J Pers Disord. 2021 Jun;35:48-55.

SYMPTOMATIC DISORDERS IN ADULTS AND ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER.

Zanarini MC, Athanasiadi A, Temes CM, et al.

Symptomatic disorders often co-occur with borderline personality disorder (BPD). This study's purpose was to compare the rates of comorbidity reported by adult and adolescent inpatients with BPD, including complex comorbidity (i.e., a combination of disorders of affect and impulsivity). One hundred four adolescents (aged 13-17) and 290 adults (aged 18-35) with BPD were interviewed using an age-appropriate semistructured interview for the assessment of symptomatic disorders. Lifetime rates of mood disorders and ADHD were quite similar for the two study groups. However, rates of anxiety disorders, including PTSD, substance use disorders, eating disorders, and complex comorbidity were significantly higher among adults than adolescents. Taken together, the results of this study suggest that broadly defined disorders of both affect and impulsivity are more common among adults than adolescents with BPD. They also suggest that a pattern of complex comorbidity is even more distinguishing for these two groups of borderline patients

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J Sch Psychol. 2020 Jun;80:15-36.

COMPARISON OF ACCOMMODATIONS AND INTERVENTIONS FOR YOUTH WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.

Harrison JR, Evans SW, Baran A, et al.

School psychologists have a variety of evidence-based interventions from which to choose when recommending classroom-based strategies for students with attention deficit hyperactivity disorder (ADHD); however, strategies frequently found on individualized education plans are accommodations designed to remove barriers to learning, which have limited empirical evidence. As such, the purpose of the current study was to compare the efficacy of three interventions (i.e., organization training, self-management, note-taking instruction) and three accommodations (i.e., organization support, extended time, copy of teacher notes) to address difficulties with organization and maintaining attention during a science lesson and associated independent practice. The study included 64 middle school students with ADHD randomized to either an intervention or an accommodation condition. The intervention group was further divided into two subgroups, consisting of (a) students who were willing to follow intervention procedures and (b) students who were not willing to follow the procedures (behavioral indicators of social validity). Results indicated that adolescents with ADHD in the intervention group were statistically significantly more likely to organize and maintain binder organization and to take complete and accurate notes than those in the accommodation group. In addition, exploratory analyses indicated that adolescents who demonstrated willingness to follow intervention procedures were more likely to be academically engaged during instruction and independent work and to complete independent work accurately than those who resisted the procedures

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J Sch Psychol. 2021 Feb;84:19-31.

INTERVENTION RESPONSE AMONG PRESCHOOLERS WITH ADHD: THE ROLE OF EMOTION UNDERSTANDING.

Hare MM, Garcia AM, Hart KC, et al.

Emotion recognition/understanding (ERU), which is the ability to correctly identify emotional states in others as well as one's self, plays a key role in children's social-emotional development and is often targeted in early intervention programs. Yet the extent to which young children's ERU predicts their intervention response remains unclear. The current study examined the extent to which initial levels of ERU and changes in ERU

predicted intervention response to a multimodal early intervention program (Summer Treatment Program for Pre-Kindergarteners; STP-PreK). Participants included 230 young children (M(age)=4.90, 80.0% male) with attention-deficit/hyperactivity disorder (ADHD) who participated in the 8-week STP-PreK. Children's ERU was measured via a standardized behavioral task. Similarly, standardized measures of academic achievement (Woodcock-Johnson-IV), executive functioning (Head-Toes-Knees-Shoulders-Task), and social-emotional functioning (Challenging Situation Task) were obtained pre- and post-intervention. Parents and teachers also reported on children's behavioral functioning pre- and post-intervention. Children with better initial ERU made greater improvements in academic, executive functioning (EF), and social-emotional domains, along with decreases in inattention symptom severity. However, pre-intervention levels of ERU were not associated with improvements in parent/teacher report of hyperactivity, oppositional defiant disorder, and overall behavioral impairment. Lastly, changes in ERU only predicted improvement in EF, but not any other school readiness outcomes. We provide preliminary evidence that initial levels of ERU predict intervention response across school readiness domains in a sample of preschoolers with ADHD

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J Sch Psychol. 2021 Aug;87:48-63.

SCHOOL-BASED INTERVENTION FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EFFECTS ON ACADEMIC FUNCTIONING.

Dupaul GJ, Evans SW, Owens JS, et al.

Multi-component training interventions such as the Challenging Horizons Program (CHP) improve organization skills and academic functioning of middle school students with attention-deficit/hyperactivity disorder (ADHD); however, few studies have investigated treatment for high school students. We explored the extent to which CHP adapted for high school would improve proximal (e.g., organization skills, homework performance) and distal (e.g., report card grades) academic outcomes through 6-month follow-up relative to a community care (CC) condition. Participants included 186 adolescents who were randomly assigned to CHP (n=92; 80% male; M age=15.0; SD=0.8) or CC (n=94; 78% male; M age=15.1; SD=0.9) with CHP delivered over one school year. Parent, teacher, and self-report ratings of organization skills and academic performance, report card grades, and achievement tests were collected across multiple occasions. Intent-to-treat analyses using hierarchical linear modeling revealed significant improvements of small to medium magnitude (d range=0.32 to 0.58) for parent-rated organization skills, homework performance, and academic functioning at 6-month follow-up. CHP effect on grades was small, but associated with a less steep decline than that found for CC. No statistically significant effects on teacher or self-report ratings were obtained. CHP appears efficacious for ameliorating organization skills and homework performance deficits exhibited by high school students with ADHD and can protect against decline in report card grades experienced by these students. CHP may require supplementation with academic skills instruction for some students and may need implementation beyond one school year to produce durable effects

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J Sch Psychol. 2021 Jun;86:133-50.

A SCHOOL-BASED PARENTING PROGRAM FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IMPACT ON PATERNAL CAREGIVERS.

Fabiano GA, Schatz NK, Lupas K, et al.

Engaging male caregivers within school settings is a major need within the educational field. Paternal engagement may be particularly important for children with attention-deficit/hyperactivity disorder (ADHD). Children with ADHD have increased risk for a number of poor educational outcomes, which may be attenuated by the benefits of positive male caregiver involvement. The Coaching Our Acting Out Children: Heightening Essential Skills (COACHES) program has been illustrated to be an effective approach for engaging, retaining, and improving the parenting of male caregivers of children with ADHD in clinical settings. The present study reports on the efficacy of the COACHES in Schools program, an adaptation intended for deployment in elementary school settings. Sixty-one male caregivers were randomly assigned to COACHES in Schools or a waitlist control. Results indicated that male caregivers in COACHES in Schools used significantly more praise and less negative talk in a parent-child activity relative to male caregivers in the waitlist control at post-treatment and one-month follow-up. Distal outcomes related to child behavior at home

and at school were not significantly different. Implications of the results for future studies and continued efforts to engage male caregivers within school settings are discussed

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J Speech Lang Hear Res. 2021 Sep;64:3564-70.

REVISITING THE INFLUENCES OF BILINGUALISM AND DEVELOPMENTAL LANGUAGE DISORDER ON CHILDREN'S NONVERBAL PROCESSING SPEED.

Ebert KD.

Purpose This study examined the influences of bilingualism and developmental language disorder (DLD) on nonverbal processing speed. DLD is associated with slower processing speed, but the extent to which slowing extends to bilingual populations is not established. The possible presence of bilingual cognitive effects could also lead to faster processing speed among bilingual children. Method Participants included 108 children of ages 6-8 years, including 56 Spanish-English bilinguals (29 with DLD and 27 with typical development) and 52 English-only monolinguals (25 with DLD and 27 with typical development). Language testing (in both languages for bilingual children) was combined with parent and school report to classify children as having DLD or typical language development. Children with attention-deficit/hyperactivity disorder were excluded from the sample. Reaction time from a choice visual detection task was used to index nonverbal processing speed. Results Children with DLD demonstrated slower processing speed than their typically developing peers, whereas bilingual children demonstrated faster processing speed than monolinguals. The effects of DLD and bilingualism did not interact. Conclusions This study replicates prior findings of slowed processing speed among children with DLD in both monolingual and bilingual children. Evidence of faster processing speed among bilingual children contributes to the complex literature surrounding the circumstances of bilingual cognitive effects. Supplemental Material https://doi.org/10.23641/asha.15138747

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J Am Med Assoc. 2021;325:2067-75.

α2 - ADRENERGIC AGONISTS OR STIMULANTS FOR PRESCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Harstad E, Shults J, Barbaresi W, et al.

Importance: Attention-deficit/hyperactivity disorder (ADHD) is diagnosed in approximately 2.4% of preschool-age children. Stimulants are recommended as first-line medication treatment. However, up to 25% of preschool-age children with ADHD are treated with α2-adrenergic agonist medications, despite minimal evidence about their efficacy or adverse effects in this age range.

Objective: To determine the frequency of reported improvement in ADHD symptoms and adverse effects associated with α2-adrenergic agonists and stimulant medication for initial ADHD medication treatment in preschool-age children.

Design, setting, and participants: Retrospective electronic health record review. Data were obtained from health records of children seen at 7 outpatient developmental-behavioral pediatric practices in the Developmental Behavioral Pediatrics Research Network in the US. Data were abstracted for 497 consecutive children who were younger than 72 months when treatment with an α2-adrenergic agonist or stimulant medication was initiated by a developmental-behavioral pediatrician for ADHD and were treated between January 1, 2013, and July 1, 2017. Follow-up was complete on February 27, 2019.

Exposures: α2-Adrenergic agonist vs stimulant medication as initial ADHD medication treatment.

Main outcomes and measures: Reported improvement in ADHD symptoms and adverse effects.

Results: Data were abstracted from electronic health records of 497 preschool-age children with ADHD receiving α2-adrenergic agonists or stimulants. Median child age was 62 months at ADHD medication initiation, and 409 children (82%) were males. For initial ADHD medication treatment, α2-adrenergic agonists were prescribed to 175 children (35%; median length of α2-adrenergic agonist use, 136 days) and stimulants were prescribed to 322 children (65%; median length of stimulant use, 133 days). Improvement was reported in 66% (95% CI, 57.5%-73.9%) of children who initiated α2-adrenergic agonists and 78% (95% CI, 72.4%-83.4%) of children who initiated stimulants. Only daytime sleepiness was more common for those receiving α2-adrenergic agonists vs stimulants (38% vs 3%); several adverse effects were reported more commonly

for those receiving stimulants vs α2-adrenergic agonists, including moodiness/irritability (50% vs 29%), appetite suppression (38% vs 7%), and difficulty sleeping (21% vs 11%).
Conclusions and relevance: In this retrospective review of health records of preschool-age children with ADHD treated in developmental-behavioral pediatric practices, improvement was noted in the majority of children who received α2-adrenergic agonists or stimulants, with differing adverse effect profiles between medication classes. Further research, including from randomized clinical trials, is needed to assess comparative effectiveness of α2-adrenergic agonists vs stimulants

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JMIR Mhealth Uhealth. 2021 Oct;9:e20638.
A Mobile Sensing App to Monitor Youth Mental Health: Observational Pilot Study.
MacLeod L, Suruliraj B, Gall D, et al.
BACKGROUND: Internalizing disorders are the most common psychiatric problems observed among youth in Canada. Sadly, youth with internalizing disorders often avoid seeking clinical help and rarely receive adequate treatment. Current methods of assessing internalizing disorders usually rely on subjective symptom ratings, but internalizing symptoms are frequently underreported, which creates a barrier to the accurate assessment of these symptoms in youth. Therefore, novel assessment tools that use objective data need to be developed to meet the highest standards of reliability, feasibility, scalability, and affordability. Mobile sensing technologies, which unobtrusively record aspects of youth behaviors in their daily lives with the potential to make inferences about their mental health states, offer a possible method of addressing this assessment barrier.
OBJECTIVE: This study aims to explore whether passively collected smartphone sensor data can be used to predict internalizing symptoms among youth in Canada.
METHODS: In this study, the youth participants (N=122) completed self-report assessments of symptoms of anxiety, depression, and attention-deficit hyperactivity disorder. Next, the participants installed an app, which passively collected data about their mobility, screen time, sleep, and social interactions over 2 weeks. Then, we tested whether these passive sensor data could be used to predict internalizing symptoms among these youth participants. RESULTS: More severe depressive symptoms correlated with more time spent stationary (r=0.293; P=.003), less mobility (r=0.271; P=.006), higher light intensity during the night (r=0.227; P=.02), and fewer outgoing calls (r=-0.244; P=.03). In contrast, more severe anxiety symptoms correlated with less time spent stationary (r=-0.249; P=.01) and greater mobility (r=0.234; P=.02). In addition, youths with higher anxiety scores spent more time on the screen (r=0.203; P=.049). Finally, adding passively collected smartphone sensor data to the prediction models of internalizing symptoms significantly improved their fit.
CONCLUSIONS: Passively collected smartphone sensor data provide a useful way to monitor internalizing symptoms among youth. Although the results replicated findings from adult populations, to ensure clinical utility, they still need to be replicated in larger samples of youth. The work also highlights intervention opportunities via mobile technology to reduce the burden of internalizing symptoms early on

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J Affective Disord. 2022;296:175-82.
The effects of persistent sleep disturbances during early childhood over adolescent ADHD, and the mediating effect of attention-related executive functions: Data from the 2004 Pelotas Birth Cohort.
Carpena MX, Matijasevich A, Loret de Mola C, et al.
Objective: Investigate effects of persistent sleep disturbances during early childhood over ADHD during the adolescence, and the potential attention-related executive functions mediating this effect.
Methods: We used data from the 2004 Pelotas Birth Cohort. Children's Sleep disturbances were reported by their mothers at 12, 24, and 48 months of age, whereas the Test-of-Everyday-Attention-for-Children (TEA-Ch) and the Development and Well Being Assessment (DAWBA) were applied at 11 years of age to evaluate attention-related executive functions and ADHD, respectively. Persistent sleep problems were defined as reporting have two or more points of difficulty to sleep, nightmares, restless sleeps, and/or <10h/24h sleep duration. Logistic regression and mediation models were used, adjusting for maternal and child sociodemographic, behavior and health related variables.

Results: The highest prevalence of adolescent ADHD (15.4%) was on the group who reported having nightmares at 2,4 and 6 years. In adjusted models, we observed an odd of ADHD in the adolescence 2.26 higher in those who reported persistent nightmares (CI95% 1.33, 4.01) compared to those reported transitory or no nightmares. Persistent difficulty to sleep (OR=1.74 CI95% 1.13, 2.66) and restless sleep (OR=1.80, CI95% 1.23, 2.64) during childhood also increased ADHD odds at 11 years. No indirect effect through attention related executive functions was found using mediating models.
Discussion: Persistent early sleep disturbances may increase odds of ADHD among adolescents and could be consider as early marker of such disorder, specially nightmares problems. These effects were not mediated by attention-related executive functions. Nevertheless, we had 75% of cohort inception response

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J Altern Complement Med. 2021;27:477-88.
EQUINE-ASSISTED SERVICES FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.
Helmer A, Wechsler T, Gilboa Y.
Objective: This systematic review evaluated equine-assisted activities and therapies (EAATs), formerly referred to as equine-assisted services (EAS), in children and youth (ages 6-18 years) with attention-deficit/hyperactivity disorder (ADHD), according to the International Classification of Functioning, Disability, and Health.
Methods: Electronic database searches were conducted of studies from inception through December 2020.
Results: A total of 12 articles were included: 8 noncontrolled prospective studies and 4 randomized-controlled trials (RCTs). Furthermore, seven of moderate methodological quality studies and five of moderate high methodological quality studies were included. Evidence was found for the effectiveness of various forms of EAS, including equine-assisted physical therapy (EAPT) and therapeutic riding (TR). Improvements in body functions and structures (n = 10) were found in the domains of mental and neuromusculoskeletal functions, as well as functions of the cardiovascular system using EAPT (n = 6). Limited evidence was found regarding the positive effect on activity and participation (n = 4) following TR interventions. Quality of life (QoL) was improved in both TR and EAPT (n = 4).
Conclusion: There seems to be preliminary evidence that EAS may be beneficial in promoting the physiological functions of body systems for children with ADHD. The influence on participation and QoL still requires further evidence. More generally, further controlled studies, including bigger sample sizes, are needed to understand the specific effects of different EAS on the core symptoms and consequence of ADHD

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J Autism Dev Disord. 2021 Oct;51:3610-23.
DNA METHYLATION OF THE OXYTOCIN RECEPTOR ACROSS NEURODEVELOPMENTAL DISORDERS.
Siu MT, Goodman SJ, Yellan I, et al.
Many neurodevelopmental disorders (NDDs) share common learning and behavioural impairments, as well as features such as dysregulation of the oxytocin hormone. Here, we examined DNA methylation (DNAm) in the 1st intron of the oxytocin receptor gene, OXTR, in patients with autism spectrum (ASD), attention deficit and hyperactivity (ADHD) and obsessive compulsive (OCD) disorders. DNAm of OXTR was assessed for cohorts of ASD (blood), ADHD (saliva), OCD (saliva), which uncovered sex-specific DNAm differences compared to neurotypical, tissue-matched controls. Individuals with ASD or ADHD exhibiting extreme DNAm values had lower IQ and more social problems, respectively, than those with DNAm within normative ranges. This suggests that OXTR DNAm patterns are altered across NDDs and may be correlated with common clinical outcomes.

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J Child Psychol Psychiatry. 2021 Oct;62:1202-19.
ANALYSIS OF STRUCTURAL BRAIN ASYMMETRIES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN 39 DATASETS.
Postema MC, Hoogman M, Ambrosino S, et al.
Objective: Some studies have suggested alterations of structural brain asymmetry in attention-deficit/hyperactivity disorder (ADHD), but findings have been contradictory and based on small samples.

Here, we performed the largest ever analysis of brain left-right asymmetry in ADHD, using 39 datasets of the ENIGMA consortium.
Methods: We analyzed asymmetry of subcortical and cerebral cortical structures in up to 1,933 people with ADHD and 1,829 unaffected controls. Asymmetry Indexes (AIs) were calculated per participant for each bilaterally paired measure, and linear mixed effects modeling was applied separately in children, adolescents, adults, and the total sample, to test exhaustively for potential associations of ADHD with structural brain asymmetries.
Results: There was no evidence for altered caudate nucleus asymmetry in ADHD, in contrast to prior literature. In children, there was less rightward asymmetry of the total hemispheric surface area compared to controls ($t = 2.1$, $p = .04$). Lower rightward asymmetry of medial orbitofrontal cortex surface area in ADHD ($t = 2.7$, $p = .01$) was similar to a recent finding for autism spectrum disorder. There were also some differences in cortical thickness asymmetry across age groups. In adults with ADHD, globus pallidus asymmetry was altered compared to those without ADHD. However, all effects were small (Cohen's d from -0.18 to 0.18) and would not survive study-wide correction for multiple testing.
Conclusion: Prior studies of altered structural brain asymmetry in ADHD were likely underpowered to detect the small effects reported here. Altered structural asymmetry is unlikely to provide a useful biomarker for ADHD, but may provide neurobiological insights into the trait

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Journal of Clinical Medicine. 2021;10.

THE INFLUENCE OF STATE AND TRAIT ANXIETY ON THE ACHIEVEMENT OF A VIRTUAL REALITY CONTINUOUS PERFORMANCE TEST IN CHILDREN AND ADOLESCENTS WITH ADHD SYMPTOMS.

Areces D, et al.

The three types of presentations of ADHD often co-occur with other disorders, anxiety being one of the most prevalent. For this reason and because there are few studies that have examined the influence of anxiety on attentional activities, this study aims to determine how internalizing difficulties (anxiety levels) can influence performance in a virtual reality continuous performance test. The study used a non-probabilistic clinical sample comprising 68 boys (66%) and 35 girls (34%) aged between 6 and 16 ($M = 12.24$; $SD = 2.45$) who had been referred to clinical services for the evaluation of ADHD symptoms. Once informed consent was given, the children were administered the STAI-C scale and a virtual reality continuous performance test by expert researchers. Hierarchical regression models showed that only state anxiety demonstrated significant explanatory power over attentional variables. These findings confirm how important it is for children to feel relaxed when they undergo psychological evaluation tests, as otherwise the individualΓÇÖs intervention design would be based on biased data. Similarly, the findings also suggested an effect of IQ in the interpretation of continuous performance scores

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Journal of Clinical Medicine. 2021;10.

TREATMENT OF ADOLESCENTS WITH CONCURRENT SUBSTANCE USE DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Hûzgen H, Spijkerman R, Noack M, et al.

Childhood attention-deficit/hyperactivity disorder (ADHD) is a risk factor for the development of substance abuse and substance use disorders (SUD) in adolescence and (early) adulthood. ADHD and SUD also frequently co-occur in treatment-seeking adolescents, which complicates diagnosis and treatment, and is associated with poor treatment outcomes. In this study, we provide a systematic review of controlled studies on the effectiveness of pharmacological, psychosocial, and complementary treatments of ADHD in adolescents with and without comorbid SUD. In addition, we review the longitudinal association between pharmacotherapy for childhood ADHD and the development of SUD in adolescence and early adulthood. We conducted a systematic review of the research literature published since 2000 using Medline, PsycINFO, and the Cochrane Database of Systematic Reviews databases to select randomized clinical trials, observational studies, and meta-analyses. The quality of the evidence from each study was rated using the SIGN grading system. Based on the limited evidence available, strong clinical recommendations are not justified, but provisionally, we conclude that stimulant treatment in children with ADHD may prevent the

development of SUD in adolescence or young adulthood, that high-dose stimulant treatment could be an effective treatment for adolescents with ADHD and SUD comorbidity, that cognitive behavior therapy might have a small beneficial effect in these patients, and that alternative treatments are probably not effective. More studies are needed to draw definitive conclusions that will allow for strong clinical recommendations

J Indian Assoc Child Adolesc Ment Health. 2021;17:30-43.

PSYCHIATRIC MORBIDITY IN THE PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Nagpal S, Kumar D, Kumar M, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders of childhood and adolescence. Due to chronic and pervasive natures, parents find difficulties in dealing with the behavioral problems of such children. A number of studies have shown that parents of ADHD children display substantial psychiatric morbidity in the form of depression, anxiety, and substance abuse. Aim: To examine psychiatric morbidity in parents of children with ADHD.

Methods: Thirty parents (one parent either mother or father for each ADHD child was selected) were screened for psychological distress by applying GHQ-12. Those parents who had score of ГёÑ2 on GHQ-12 and/or history of substance use were subjected to SCAN-based interview which evaluated psychiatric morbidity in them.

Results: The results of this study suggest that 46.67% of parents of children with ADHD had the presence of a psychiatric diagnosis in which the most common psychiatric diagnosis was depressive disorder (26.67%) which is several times higher than the general population. One-fourth of the parents of children with ADHD (26%) had substance use disorders.

Conclusion: In our study, nearly half of the parents had psychiatric morbidities, mainly depressive and anxiety disorders, and nearly a quarter of the parents had substance use disorders

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J Am Acad Child Adolesc Psychiatry. 2021;60:S155.

5.16 THE ROLE OF ALPHA-2 ADRENERGIC (α2A) AGONISTS IN ADHD TREATMENT IN PRESCHOOL CHILDREN: BENEFITS, TRENDS, AND DEMOGRAPHICS FROM THE CURRENT LITERATURE EVIDENCE.

Javed S, Usmani S, Abouelnasr A, et al.

Objectives The objective of this presentation is to highlight the role and trends of the use of adrenergic alpha-2A (α2A) receptor agonists alone or in combination with other medications to treat ADHD in preschool-aged children.

Methods Using 4 electronic databases, we did a literature search in May 2021 for studies describing the use of α2A agonists as ADHD treatment, which yielded 73 studies. We included studies that were: 1) observational; 2) enrolled children aged 2 to 6 years; and 3) treated with α2A agonists alone or in combination with stimulants. Seven studies were included in the final review.

Results Both stimulants and nonstimulants were prescribed for ADHD treatment, with α2A agonists being increasingly prescribed in very young children, including preschoolers. The use of α2A agonists alone increased from 10% to 23%, more prominently between 2015 and 2017. Both α2A agonists and stimulants (eg, methylphenidate) were well tolerated, effectively reduced symptoms, and improved function in preschool-aged children. Choice of treatment was determined by insurance type, affordability, availability, comorbidities, race/ethnicity, age, and prescriber type. Blacks/Hispanics had lesser odds of receiving α2A agonists vs no medication. Clonidine was the most prescribed medication (44.64%), followed by risperidone (28.7%), methylphenidate (10.7%), and atomoxetine (10.7%). Both α2A agonists and stimulants were prescribed 6 times more to children with impulse control disorder, while the odds were twofold for children with comorbid ODD. Clonidine was effective and well tolerated in preschool-aged children with autism spectrum disorder and ADHD. Primary care physicians accounted for 50% of total prescriptions, while prescriptions from psychiatrists reduced from 36% to 27% between 2012 and 2017. More side effects were reported with stimulants, including irritability (50% vs 29%), decreased appetite (38% vs 7%), and sleeping difficulties (21% vs 11%). However, daytime sleepiness was more common in patients on α2A agonists (38% vs 3%).

Conclusions The promising efficacy and safety results of α2A agonists in preschoolers' ADHD management are based on limited studies and data. The lack of well-designed studies warrants randomized controlled

trials, which will improve prescribing guidelines using these agents, assess comparative efficacy vs stimulants, and determine their safety and long-term outcome on the developing brain.

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J Am Acad Child Adolesc Psychiatry. 2021;60:S155.

5.17 PSYCHOMETRIC PROPERTIES OF THE ADHD STIGMA QUESTIONNAIRE-REVISED AMONG PARENTS OF CHILDREN IN PRIMARY CARE.

Sikov J, Ji C, Baul T, et al.

Objectives: Children with ADHD and their families may face stigma as a result of ADHD symptoms, label, or treatment. The ADHD Stigma Questionnaire (ASQ) is an existing measurement tool that has been validated with adolescents. However, it does not include items capturing medication or courtesy stigma (ie, stigma toward parents due to a child's ADHD). In this study, we worked with an expert panel to add 8 new medication and courtesy stigma items to the ASQ and conducted a psychometric evaluation of the revised version (ASQ-R) completed by parents.

Methods: A total of 159 English-speaking parents of children between ages 0 and 17 years were recruited from pediatric clinics at an urban safety-net hospital between September 2018 and May 2021 to complete the ASQ-R and a demographic questionnaire. We conducted an exploratory factor analysis on the ASQ-R and calculated average scores to assess the level of ADHD stigma perceived by parents.

Results: The ASQ-R supports a new 4-factor model including the following 4 factors: 1) concern for public attitudes; 2) disclosure concerns; 3) medication stigma; and 4) parenting inadequacy. Factors reflecting concern for public attitudes and disclosure concerns are similar to the original factors. The newly added items delineated 2 newly defined factors, and 8 items (7 old, 1 new) were dropped from the final questionnaire due to failure to load or redundancy.

Conclusions: The ASQ-R can help to evaluate ADHD stigma perceived by parents of children with ADHD with its 4 factors. More data should evaluate its performance with other populations. ADOL, ADHD, PAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S155.

5.18 UNDERSTANDING AND IMPROVING ADHD SYMPTOM RECALL: AN INVESTIGATION OF TEMPERAMENT AND CHILDHOOD SYMPTOM RECALL OVER TIME.

Taylor L, Rohacek A, Orantes D, et al.

Objectives: Symptom onset before age 12 years is needed for an ADHD diagnosis. The current study aimed to examine symptom recall and avenues to improve this recall. This was accomplished through comparing retrospective recall of ADHD symptoms to actual past report of symptoms and examining retrospective report of temperament in relation to childhood ADHD symptoms. It is hypothesized that: 1) retrospective recall of ADHD symptoms will be significantly lower than actual past report; 2) higher levels of current symptoms will be associated with higher levels of retrospectively recalled symptoms; and 3) retrospective reports of temperament traits will be associated with childhood ADHD symptoms.

Methods: Data were collected from 50 parents and 40 children (Time 2 age M = 13.63 years) who had previously completed a measure of ADHD symptoms (Time 1 age M = 10.72 years). Parents and children completed a retrospective recall of previous child ADHD symptoms, measures of current child ADHD symptoms, and a retrospective report of child temperament.

Results: Time 1 childhood ADHD symptoms were higher than Time 2 retrospective recall for both parent (attention F1,47 = 5.98, p = 0.02, +2 = 0.11; hyperactivity F1,47 = 3.71, p = 0.06, +2 = 0.07) and child report (attention F1,38 = 41.01, p < 0.001, +À2 = 0.52); hyperactivity (F1,38 = 7.76, p = 0.01, +2 = 0.17). Current ADHD symptoms were the strongest predictor of childhood symptoms for parent and self-report of attention problems (t = 5.29, +¦ = 0.66, p Γëñ 0.001; t = 4.07, +¦ = 0.50, p Γëñ 0.001) and parent-reported hyperactivity (t = 5.70, +¦ = 0.68, p Γëñ 0.001). Reward dependence was associated with parent report of children's childhood attention problems (t = 1.73, +¦ = 0.27, p = 0.09) and hyperactivity (t = 2.03, +¦ = 0.31, p = 0.05), as well as self-reported childhood hyperactivity (t = 1.20, +¦ = 0.22, p = 0.24). Novelty-seeking was associated with parent report of children's childhood attention problems (t = 1.28, +¦ = 0.23, p = 0.20) and self-reported childhood attention problems (t = 2.12, +¦ = 0.43, p = 0.04) and hyperactivity (t = 1.10, +¦ = 0.22, p = 0.28).

Conclusions: Parent and children underreport previous symptoms of ADHD. Assuming these findings can be replicated in a larger, more diverse sample, assessing child temperament, specifically related to motivational processes and reward seeking, may aid ADHD diagnostic processes. ADHD, ND, DIAG

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J Am Acad Child Adolesc Psychiatry. 2021;60:S156.

5.19 A LITERATURE REVIEW: RACIAL AND ETHNIC DISPARITIES IN THE DIAGNOSIS AND TREATMENT OF ADHD.

Gosal R, Rizwan B, Kronsberg H.

Objectives: ADHD is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. ADHD has a prevalence rate of approximately 5% in children and responds well to therapeutic interventions. If untreated, ADHD can cause impairment in academic and social functioning. This review aims to study the current literature to identify disparities in diagnoses and treatment among non-Hispanic White and ethnic and racial minority patients.

Methods: A literature review was conducted among studies from the last 10 years from PubMed and PsycINFO. The search terms used in PsycINFO were treat/intervention or diagnosis/assess or clinical decision and ADHD and racial bias/racial or ethnic differences. The search terms used in PubMed were ADHD, ADHD and racial disparity, and ADHD, treatment and racial disparities. Combined, 36 studies were imported for screening from 2 sources with 9 duplicates, leaving 27 studies. Of these, 5 were considered irrelevant by authors. A full-text review was done for 22 studies.

Results: Nearly all studies showed that ethnic and racial minority children, mainly African Americans and Latinx, were less likely to be diagnosed with ADHD when compared to the non-Hispanic White youth. These disparities remained even after various environmental and sociocultural confounding factors were statistically controlled for by logistic regression. Furthermore, minority children were also less likely to receive care and were at risk of early discontinuation of treatment. Two recent studies have shown increasing rates of diagnosis and treatment of ADHD in Black children; however, the disparity remains.

Conclusions: Although ethnic and racial minority children exhibit the same severity of ADHD symptoms when compared to non-Hispanic White youth, they are less likely to be diagnosed with ADHD and have decreased odds of receiving appropriate psychopharmacologic and other treatment modalities. Barriers to care included minority status, less parental education, and lack of insurance, which decreased the chances of getting a comprehensive evaluation and which also decreased the odds of identifying comorbidities associated with ADHD. When ethnic minority children receive less comprehensive evaluations, there may be more opportunities for unconscious bias to impact diagnosis and treatment. ADHD, DEI, PPC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S50.

33.4 MANAGEMENT OF ADHD IN INDIVIDUALS WITH COMORBID AUTISM SPECTRUM DISORDER.

Henriksson LH.

Objectives: Despite frequent comorbidity between ADHD and autism spectrum disorder (ASD), there is a shortage of controlled studies on how this comorbidity affects the outcome of ADHD treatment. More knowledge on how comorbidity affects treatment outcome is essential to better apply personalized medicine in clinical practice. The objective of this presentation is to discuss the management of ADHD in individuals with comorbid ASD.

Methods: Here we summarize results from previous studies on the effects and side-effects in individuals with ADHD and comorbid ASD. Next, data from a recent register-based study on prescriptions of ADHD drugs for individuals with ADHD (n = 34,374) and ADHD with comorbid ASD (n = 5012), will be presented. Finally, data from a sample of approximately 500 children with ADHD from an ongoing clinical prospective cohort study (Adhering to Dietary Approaches for Personal Taste [ADAPT]) will represent a direct comparison of ADHD treatment effect and side-effects in children with a high level of ASD symptoms, compared to children below the cutoff for ASD.

Results: Differences in prescription patterns between individuals with ADHD vs ADHD with comorbid ASD will be presented. In the clinical cohort, treatment effectiveness and tolerability between these 2 groups will be discussed.

Conclusions: Data and opinions on the effects and side-effects of ADHD drug treatment in individuals with comorbid ASD are divergent. Until present, evidence on the plausible differences in treatment effects in this population is lacking. However, slight differences in prescription patterns can be observed. ADHD, ASD, TREAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S264.

4.1 RELATIONSHIP BETWEEN ADHD AND PTSD: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Biederman J.

Objectives: PTSD is a disorder that occurs after a traumatic experience. Although exposure to trauma is common, few individuals exposed to trauma develop PTSD, suggesting that these individuals have predisposing risk factors. ADHD is one such possible risk factor. The goal of this study was to examine the relationship between ADHD and PTSD by conducting a systematic review and meta-analysis of the literature on the association between ADHD and PTSD. We hypothesized that the literature would show a robust and bidirectional association between ADHD and PTSD.

Methods: We reviewed literature through PubMed and PsycINFO in the year 2014 utilizing the search (posttraumatic stress disorder OR PTSD) AND (ADHD OR attention deficit hyperactivity disorder OR ADD OR attention deficit disorder OR hyperkinetic syndrome OR minimal brain dysfunction). We included original human research in English that operationalized diagnoses of ADHD and PTSD, evaluated the relationship between the disorders, and included controls. We extracted sample size, age, diagnostic methods, design, referral status, control type, and number of subjects with and without ADHD and PTSD alone and combined. We computed meta-analyses for studies examining ADHD in PTSD and PTSD in ADHD using a random-effects model and meta-analytic regression. We assessed for heterogeneity and publication bias and adjusted for intrastudy clustering.

Results: We identified 402 articles; 29 met the criteria for inclusion (14 with adult subjects and 15 with child subjects). The relative risk (RR) for PTSD in individuals with ADHD was 2.9 ($p < 0.0005$). In samples using only normal controls, the RR was 3.7 ($p = 0.001$), and in samples using trauma-exposed controls, the RR was 1.6 ($p = 0.003$). The RR for ADHD in individuals with PTSD was 1.7 ($p < 0.0005$), and in samples using trauma-exposed controls, the RR was 2.1 ($p < 0.0005$). All 6 studies examining the temporality of each disorder found earlier ADHD onset than PTSD. All 6 studies examining the correlation between ADHD and PTSD symptoms found a positive and significant correlation.

Conclusions: Results indicate a bidirectional association between ADHD and PTSD, suggesting clinical implications and highlighting the need for neurobiological research examining the mechanisms underlying this connection. ADHD, PTSD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S231.

42.1 SLUGGISH COGNITIVE TEMPO IN CHILDREN WITH READING DISORDER: IS IT JUST ADHD? FINDINGS FROM A LONGITUDINAL COHORT STUDY.

Hossain B, Bent S, Parenteau C, et al.

Objectives: Sluggish cognitive tempo (SCT), characterized by lethargy, daydreaming, drowsiness, and mental confusion, is considered a phenotype of ADHD-Inattentive subtype, but recent studies suggest it to be a distinct construct. SCT has been shown to predict anxiety, depression, and academic difficulties. However, these qualities have not been examined in children with reading disorder (RD), who have poorer mental health and face significant academic challenges. We therefore investigated whether SCT was associated with anxiety, depression, and academic performance (AP) in children with RD and whether ADHD moderated these relationships.

Methods: This 18-month longitudinal cohort study included 144 participants from 3 RD schools. All evaluations were completed by parents and/or teachers every 3 months. SCT and ADHD symptoms were evaluated by the Kiddie-SCT (K-SCT) Rating Scale and ADHD Rating ScaleΓÇô5, respectively. Outcome measures included anxiety (8-item Spence ChildrenΓÇÖs Anxiety Scale), depression (Short Mood and Feelings Questionnaire [SMFQ]), and teacher ratings of AP (standardized to z scores). Multivariate linear regression models (adjusting for age and sex) assessed the associations at baseline. Repeated measures

analysis using mixed models assessed the relationship between change in SCT and change in outcomes within an individual over time. An interaction term (of SCT with ADHD) was added to each model to determine if ADHD affects the relationship between SCT and the outcome variables.
Results: There were statistically significant associations between teacher-rated SCT and teacher-rated anxiety and AP at baseline and over time, but no evidence of effect modification by ADHD. After adjusting for age and sex and testing for interaction with ADHD, increases in SCT were associated with increased anxiety (+¦ = 0.1; 95% CI, 0.04-0.2; p < 0.001) and reduced AP (+¦ = 0.03; 95% CI, 0.05 to 0.01; p < 0.001) over time within an individual, but the interaction effects of ADHD were not significant (p = 0.1 and 0.4 for anxiety and AP, respectively). SCT was not associated with depression over time.
Conclusions: SCT can predict anxiety and AP in children with RD, and these relationships are not moderated by ADHD symptoms. This suggests that SCT's effects are not affected by ADHD and that further characterizing SCT may identify useful treatment targets. SLD, AD, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S234.
43.7 Sex-Based Differences in Clinical Profiles and Cannabis Abstinence in Adolescents Receiving Combination Treatment for ADHD and Comorbid Cannabis Use Disorder.
Rizwan B, Pink A, Park G, et al.
Objectives: Recent studies indicate sex-based differences in clinical presentation and treatment response for both ADHD and cannabis use disorders (CUDs). Given the high rate of comorbidity of ADHD and CUD, the present study sought to investigate whether sex differences are present in adolescents (ages 13-18 years) with co-occurring ADHD and CUD.
Methods: This post hoc analysis examined sex-based differences in baseline clinical profiles, cannabis abstinence, and ADHD and substance use disorder (SUD) treatment outcomes in 271 adolescents (19% female, mean age = 16.5 years) meeting DSM-IV criteria for ADHD and comorbid CUD. The sample represents a subset of participants from a 16-week multisite randomized controlled trial of osmotic-release methylphenidate (OROS-MPH) + CBT vs placebo + CBT for the treatment of ADHD and nontobacco SUD (CTN-0028).
Results: Compared to males, females with ADHD and CUD had lower self-reported ADHD symptoms and higher global functioning measured via Children's Global Assessment Scale (CGAS) scores at baseline. Both males and females showed significant reductions in days of cannabis use and ADHD symptoms following treatment. There was no evidence of differential improvement in ADHD and nontobacco/noncannabis substance use outcomes with treatment, with persistent sex differences in ADHD symptoms and CGAS scores. Female participants showed greater reductions in cannabis use compared to males, but these differences did not reach statistical significance (eg, reduction in days of cannabis use: 12.0 vs 9.4 days; p = 0.07; end-of-treatment cannabis abstinence: 35% vs 25%; p = 0.13).
Conclusions: Sex-based differences in the severity of ADHD symptoms and global functioning are present in adolescents with ADHD and comorbid CUD and largely persist during OROS-MPH + CBT treatment. Identifying overlapping and distinct mechanisms of behavioral change in males and females with co-occurring ADHD and CUD may guide sex-specific and sex-shared intervention development. ADOL, ADHD, SUD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S154-S155.
5.15 Influential Factors in ADHD Diagnosis and Treatment in Black and White Youth.
Montgomery C, Antshel K, London A.
Objectives: To help resolve inconsistencies in the literature, this study aimed to: 1) examine race-related disparities between Black and White youth in ADHD diagnosis, severity, parenting support, and treatment; and 2) assess the role of insurance type.
Methods: Using the 2017-2019 National Survey of ChildrenΓÇÖs Health (NSCH), which is a nationally representative and cross-sectional survey of parents, racial disparities were considered in ADHD diagnosis and treatment type. Health insurance type, severity, and use of informal social supports were considered as potential mediators of the relationship between race and ADHD treatment. Race was examined as a moderator of the influence of severity and type of support on treatment type.

Results: ADHD prevalence rates were comparable between Black (13.2%) and White (12.0%) youth aged 6 to 17 years (Mage = 11.52). In multivariate models that included demographic characteristics, race remained nonsignificant. However, the association between race and lifetime ADHD diagnosis became significant when the insurance type was added, indicating a suppression effect of insurance type. Once insurance type is controlled, Black youth are less likely to ever be diagnosed with ADHD ($p < 0.05$). Among those with a current ADHD diagnosis, a significant bivariate association emerged between race and severity ($p = 0.002$); Black youth were significantly more likely to have both moderate and severe parent-reported ADHD symptoms. However, after controlling for demographic and socioeconomic variables, no significant race-related difference in ADHD severity remained. With respect to treatment: 1) neither race nor informal support was associated with treatment type, but severity predicted all treatment types; 2) parents who reported place-of-worship support were more likely to access medical treatment only; and 3) race moderated the influence of severity and type of support in models controlling for demographic and socioeconomic variables, including insurance type.
Conclusions: Race-related disparities in lifetime ADHD diagnosis do not emerge until insurance type is considered. Then, Black youth are less likely to ever be diagnosed, yet they have more severe ADHD symptoms. This finding suggests social/race-related influences on diagnosis that are not explained by socioeconomic factors. ADHD, DIAG, TREAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S292.

23.1 WE CARE TO PRE CARE: WELL-CHILD CARE, EVALUATION, COMMUNITY RESEURCES, ADVOCACY, REFERRAL, AND EDUCATIONAL FOR PRESCHOOLERS WITH EARLY ADHD SYMPTOMS IN THE PRIMARY CARE SETTING.

Spencer A.

Objectives: ADHD disproportionately affects socioeconomically disadvantaged children but for unclear reasons. We examined the association between specific social determinants of health (SDH) and ADHD symptoms in preschool-age children and adapted a validated social needs intervention, WE CARE (Well-child care, Evaluation, Community resources, Advocacy, Referral, Education), for preschoolers with early ADHD symptoms in the primary care setting. Methods: We conducted exploratory factor analysis (EFA) and exploratory structural equation modeling (ESEM) with a sample of 7565 children aged 3 to 5 years from the 2016 National Survey of Children's Health, to examine the association between ADHD symptoms and SDH. We also conducted in-depth interviews with diverse parents of children aged 3 to 5 years at risk for ADHD, recruited from our safety-net hospital setting, about the relationship between their child's symptoms and unmet social needs.
Results: EFA indicated a 1-factor structure for ADHD symptoms, and 3 factors for SDH (socioeconomic status, access to basic needs, and caregiver well-being). Independently, all 3 SDH were significantly associated with higher ADHD symptoms. However, in the ESEM model, only worse caregiver well-being (+¦ = 0.39; $p < 0.01$) was significantly associated with ADHD symptoms, and fully mediated the relationship between SDH and ADHD symptoms. In our qualitative data, parents described a bidirectional association between their child's symptoms and their own mental health, physical health, and employment prospects. They also reported that trouble accessing early childhood education, activities, and behavioral health services increased impairment related to their child's behavior.
Conclusions: Thus, we adapted WE CARE to create PRE CARE (PREschooler evaluation, Community resources, Advocacy, Referral, Education), a primary care-based intervention to address SDH in preschoolers at risk for ADHD. To supplement needs already addressed in WE CARE (child care, education, employment, food security, household heat, and housing), we added caregiver health care (mental and physical), child health care (mental and physical), and child education and enrichment programs. ADHD, CON, DEI

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J Am Acad Child Adolesc Psychiatry. 2021;60:S204.

28.4 RELATIONSHIP BETWEEN SLUGGISH COGNITIVE TEMPO, IQ AND ACADEMIC ACHIEVEMENT TEST SCORES, AND ACADEMIC IMPAIRMENT IN AUTISM SPECTRUM DISORDER, ADHD, AND ELEMENTARY SCHOOL SAMPLES.

Kallus R, Mayes S, Bangert L, et al.

Objectives: Sluggish cognitive tempo (SCT) symptoms include spacey, staring, daydreaming, in own world, slow thinking and responding, sluggish, underactive, and drowsy. SCT has strong convergent and divergent validity. This study investigates correlations between SCT and IQ and academic functioning and determines if SCT is a significant independent predictor of academic functioning.

Methods: The sample comprised 1443 children (6-16 years old); among those, there were 218 with autism spectrum disorder (ASD), 489 with ADHD-Combined, 187 with ADHD-Inattentive, and 549 elementary school students. All children had an IQ ΓëÑ80. Children were rated by their mothers on the Pediatric Behavior Scale (PBS), and children with ASD/ADHD were also rated by teachers. The PBS assesses SCT, ADHD, ODD and conduct disorders, anxiety, depression, somatic complaints, and cognitive and learning problems. Children in the ASD/ADHD sample were administered the Wechsler Intelligence Scale for Children (WISC) and Wechsler Individual Achievement Test (WIAT). Children in the elementary school sample were administered the Wechsler Abbreviated Scale of Intelligence, Digit Span, Coding, and Wide Range Achievement Test.

Results: Correlations between SCT and IQ (verbal, nonverbal, working memory, and processing speed) and reading, math, and written expression achievement scores were all negative, with a pattern of decreasing scores with increasing SCT. Correlations were small (r = 0.01 to 0.15) and nonsignificant, except for processing speed and timed math, but the explained variance for these was only 2%. In regression analysis, SCT was not a significant predictor of achievement scores or academic impairment ratings. The strongest predictors were IQ for achievement scores and mother and teacher ratings of cognitive impairment for mother and teacher academic impairment ratings, respectively (explained variance = 23%-63%; p < 0.0001). Mother and teacher inattention ratings predicted mother and teacher academic impairment ratings, respectively. Ratings of SCT, impulsivity, hyperactivity, anxiety, depression, and ODD and conduct disorder were nonsignificant.

Conclusions: SCT was not an independent predictor of achievement scores or mother and teacher academic impairment ratings when other variables were controlled. Inattention is more strongly related to academic functioning than is SCT. ADHD, ASD, COG

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J Am Acad Child Adolesc Psychiatry. 2021;60:S205.

28.5 CO-OCCURRENCE OF ADHD, DISRUPTIVE BEHAVIOR DISORDERS, ANXIETY, AND DEPRESSION IN SCHOOL-AGED YOUTH: PROJECT TO LEARN ABOUT YOUTH-MENTAL HEALTH.

Dimitrov L, Lipton C, Danielson M, et al.

Objectives: The objective of this presentation is to understand the prevalence of co-occurring mental disorders as determined by a DSM-IV criteriaΓÇôbased approach to disorder ascertainment among a K-12 sample of children, drawn from a single school district in each of 4 states: Colorado, Florida, Ohio, and South Carolina.

Methods: This study used data from the Project to Learn About Youth ΓÇô Mental Health (PLAY-MH), which utilized a 2-stage design. First, teachers completed screening tools to classify a child as high vs low risk for externalizing, internalizing, or tic disorders. Parents of children who were selected into stage 2 participated in one-on-one interviews, including the Diagnostic Interview Schedule for Children, version IV (DISC-IV) to identify those who met criteria for one or more disorders. Analyses were restricted to 305 children with at least 1 disorder and used SAS v9.4 survey procedures (SAS Institute, Inc.; Cary, NC) to account for the complex sample design and produce weighted percentages and 95% CI; comparisons with nonoverlapping CIs are described as being different.

Results: Co-occurring disorders were present in over half of children with each disorder examined (51.7%, CI 40.0-63.3 for disruptive behavior disorders; 54.5%, CI 41.4-67.6 for ADHD; 58.4%, CI 43.9-72.8 for anxiety disorders; 90.3%, CI 80.3-100 for depressive disorders). Among children with an anxiety disorder, boys were more likely than girls to have a disruptive behavior disorder, children aged 5 to 11 years were more likely than children older than 12 years to have ADHD, and non-Hispanic White children were more likely than Hispanic children or children of another race/ethnicity (not including Black) to have a disruptive behavior disorder. Among children with a disruptive behavior disorder, non-Hispanic White children were more likely

than Hispanic children or children of another race/ethnicity (not including Black) to also have an anxiety disorder.
Conclusions: Mental disorder co-occurrence in the PLAY-MH sample is prevalent, particularly among children with a depressive disorder, with unique patterns of co-occurrence by disorder type and clinical and demographic characteristics. These results can be used in conjunction with other modes of mental disorder surveillance to inform mental health screening, treatment, and educational services. EPI, CM, DEMF

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J Am Acad Child Adolesc Psychiatry. 2021;60:S210.
29.7 HELICOPTER PARENTING IN ADOLESCENTS WITH ADHD: EXAMINATION OF SCALE FACTOR STRUCTURE AND ASSOCIATIONS WITH OTHER INDICES OF PARENTING.
Botkin T, Wiggs K, Kipp H, et al.
Objectives: Prior work has documented helicopter parenting (HP) as a distinct form of parental control of young adults, but less is known about HP in adolescence or in relation to ADHD. This study examined the factor structure of HP in adolescents with ADHD.
Methods: Parents (n = 341; 91% female) and adolescents (n = 333; ages 13-18 years; 25% female) completed a survey as part of a study on physician training in stimulant diversion prevention. A validated HP measure was modified for adolescents. Other measures assessed parenting style and knowledge of their adolescents activities. We conducted principal component analysis (PCA) for both informants HP reports, forcing convergent solutions. We examined associations between factors and informants demographics and other parenting measures.
Results: Our PCA yielded a 2-factor solution: an intervention factor characterized by parents problem solving and decision making for their children and a parental monitoring and short-term planning (MSP) factor. For both reporters, parents exhibited less MSP HP when their child was older ($r = 0.21$; $r = 0.15$; $p < 0.001$). Parents reported higher levels of intervention HP when they or their adolescent belonged to a marginalized race/ethnicity ($t89.8 = 2.73$; $p < 0.01$), or when their adolescent was male ($t157 = 2.79$; $p < 0.01$). Parents reported more of both HP types if they were single ($t99.6 = 2.63$; $t93.8 = 2.01$; $p < 0.05$). For both reporters, higher levels of intervention ($r = 0.25$; $r = 0.13$; $p < 0.05$) and MSP HP ($r = 0.19$; $r = 0.12$; $p < 0.01$) were associated with more knowledge of adolescents activities, and higher intervention HP was associated with higher levels of positive parenting ($r = 0.20$; $r = 0.17$; $p < 0.01$). For adolescent reports, higher intervention HP was associated with higher parental warmth ($r = 0.18$, $p < 0.01$).
Conclusions: The present study expanded work documenting unique features of HP in a younger sample with ADHD. Whereas the original HP measure loaded onto 1 factor, we observed that HP can function in 2 conceptually distinct ways, differing by adolescent age. This is supported by our finding that the 2 factors differentially related to other variables but performed similarly across reporters. More research is needed to determine whether these HP factors are functional or overreaching for adolescents with ADHD. ADHD, ADOL, PAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S153.
5.11 POLYGENIC RISK FOR ADHD INDEXES BEHAVIOR RATINGS OF EXECUTIVE FUNCTIONS IN CHILD PSYCHIATRY OUTPATIENTS.
Capawana M, Vuijk P, Pollastri A, et al.
Objectives: The first significant genome-wide association study (GWAS) of ADHD has made it possible to quantify common genetic variation underlying the condition in individuals. Determining the clinical utility of such polygenic risk scores (PRS) awaits a better understanding of the phenotypes that these scores index in clinical samples. Parent rating scales of executive function (EF) associate with functional difficulties and capture behaviors beyond the DSM ADHD criteria. Thus, the extent to which EF rating scales relate to ADHD PRS has implications for clinical translation.
Methods: Subjects were 365 youth (11.4 -¦ 3.1 years; 35.3% girls) referred for neuropsychiatric evaluation, enrolled in the Longitudinal Study of Genetic Influences on Cognition and genotyped with the Illumina PsychChip. ADHD PRS was derived from the largest published ADHD GWAS. Parents rated EF using the Behavior Rating Inventory of Executive Function (BRIEF), which reflects behavioral and emotional regulation

(BER) and metacognition (MC). Linear regression models related ADHD PRS to these constructs alone, after accounting for polygenic variation (PV) for cognitive ability (COG), and after controlling for ADHD diagnoses. Finally, using structural equation modeling (SEM), we examined the extent to which ADHD PRS and BRIEF associations were mediated by ADHD diagnoses. Analyses controlled for age, sex, medication, and the first 5 principal ancestry components. Benjamini-Hochberg False Discovery Rate (FDR) 0.05 was used to correct for multiple testing.
Results: ADHD PRS was significantly associated with BER and MC. Controlling for COG PV resulted in a smaller but significant association of ADHD PRS with BER (R2 = 2.40%; t = 3.22; p = 0.0014), but the association with MC was not significant. Controlling for ADHD only yielded a significant association with BER (R2 = 2.41%; t = 3.27; p = 0.0012). SEM indicated a partial mediation effect for the model for BER, with a significant indirect effect of ADHD PRS via ADHD (b = 0.02; z = 2.13; p = 0.0335) and a direct effect (b = 0.16; z = 3.32; p = 0.0009). In contrast, the association between ADHD PRS and MC was fully mediated by ADHD status.
Conclusions: ADHD PRS influence behavioral and emotional regulation indirectly via ADHD as well as directly, suggesting that the risk score captures variation relevant to functional outcome beyond the traditional ADHD diagnosis. COG, GS, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S153-S154.

5.12 Relationship Between Polypharmacy and Clinical Functioning in Patients With ADHD: A Retrospective Analysis of Real-World Data.

Valko M, Renteria M, Kollins S.

Objectives: Polypharmacy is common in the treatment of ADHD, but little is known about its relation to clinical functioning. The primary objective of this analysis was to use a large real-world data (RWD) source derived from electronic health records to examine this relationship in patients with ADHD across the life span. Notably, this RWD source includes information regarding both medications and clinical functioning, measured with a clinician-rated Clinical Global Impression-Severity (CGI-S) score.
Methods: The NeuroBluΓäó database includes deidentified data from more than 550,000 unique patients over 20 years, including CGI-S scores. Data were from US sites using a common electronic health record system. All patients with an ICD diagnosis of ADHD were included. Additional inclusion criteria included: ΓëÑ3 clinical visits within a 12-month period, CGI-S recorded at initial visit, and prescription medication information. Cohorts were defined by the maximum number of simultaneous medications prescribed in a 12-month time frame and included patients prescribed 0, 1, 2, 3, 4, and 5 or more medications at a single time point. Mean and median CGI-S scores at initial ADHD diagnosis were compared across cohorts. Cohorts were further stratified for children (aged 0-12 years), adolescents (aged 13-17 years), and adults (aged 18 years and older).
Results: Of 53,744 patients with ADHD, 31,824 met the eligibility criteria; 59% were White, and 58% were male. The proportion of patients included in each of the polypharmacy cohorts was as follows: 0 (6%); 1 (21%); 2 (24%); 3 (19%); 4 (13%); and 5+ (18%). Patients on 0-4 medications had a median CGI of 4, and those with 5+ medications had a median CGI of 5. Although there was a statistically significant difference across cohorts with respect to mean CGI-S score, the clinical significance of this difference was small. Pairwise comparisons indicated that there were no differences in CGI-S scores between patients receiving 0, 1, or 2 medications and only a nominal difference between those receiving 0 and 3 medications. Results were similar when examined across age groups.
Conclusions: Polypharmacy practices in patients with ADHD may not be meaningfully associated with clinical functioning. Findings highlight the need for additional research with RWD sources to better understand these prescribing practices. ADHD, PPC, IMP

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J Am Acad Child Adolesc Psychiatry. 2021;60:S154.

5.13 THE EXPERIENCE OF CHILDREN AND ADOLESCENTS WITH ADHD AND THEIR CAREGIVERS DURING THE COVID-19 PANDEMIC: THE UNCOVER STUDY.

Thorley EM, Burke M, Raveendran S, et al.

Objectives: The challenges of the COVID-19 pandemic on patients (pts) with mental health disorders are complex and not fully understood. This study surveyed parents/guardians of pediatric pts with ADHD in the United States to better understand the impact of the pandemic on their disorder and quality of life.

Methods: A 39-question cross-sectional survey was conducted (March 10, 2021 to April 2, 2021) via the PatientsLikeMe (PLM) health tracking platform within an online social network. Participants were US-resident PLM members who were caregivers of dependents aged 6 to 18 years with ADHD. Data related to the impact on treatment, medical care access, symptoms, and ADHD management goals are reported.

Results: The cohort comprised 37 adult caregivers. Twenty children were currently taking prescription medication (Rx) for ADHD (treated-pts), and 16 were not (untreated-pts). An 11% decrease in Rx use status was reported during the pandemic. In treated-pts, 25% had 1 switch in ADHD Rx type and 40% had an Rx dosage change. Compared to before the pandemic, 37% of the caregivers of treated-pts reported difficulty in adhering to ADHD Rx use as prescribed. Of the 79% of caregivers of treated-pts who reported a pandemic-related negative impact on their daily ADHD Rx routine, 67% reported interference in their structured routine and 53% reported changes in their virtual learning environment as the main reasons. Regarding telehealth and medical care access, 38% of caregivers reported having 1 telehealth visit (24% treated-pts vs 15% untreated-pts); 27% of caregivers reported not wanting to use telehealth. On a 4-point scale (none, minor, moderate, major), caregivers of untreated-pts reported a major impact of the pandemic on ADHD-related medical care (12%, vs treated-pts, 0%; p = 0.04). Caregivers of treated-pts were more likely to agree that ADHD symptoms were well managed during the pandemic (21%, vs untreated-pts, 6%). Regardless of treatment status, 53% of dependents had an ADHD management goal; of those, all reported a negative impact of the pandemic on their goal.

Conclusions: Compared with the prepandemic period, children/adolescents with ADHD experienced a higher disease burden that translated into a negative impact on their lives and that of their caregivers. The effect of the COVID-19 pandemic appears to have been more pronounced in pts not treated with ADHD medications during this period. ADHD, SAC, R

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J Am Acad Child Adolesc Psychiatry. 2021;60:S154.

5.14 EFFICACY OF COMPUTER GAMEΓÇôBASED EXECUTIVE FUNCTIONING/ATTENTION TRAINING IN CHILDREN AND ADOLESCENTS WITH ADHD: A SYSTEMATIC REVIEW.

Deng Y, Pannu A, Khalid-Khan S.

Objectives: ADHD is common among children and adolescents, affecting 5% to 7% of the population worldwide. The core symptoms of ADHD are inattentiveness, hyperactivity, and impulsivity. Recent studies discovered that ADHD patients have impairment in executive functioning associated with goal setting and planning, which are essential for school performance and social functioning. Although medications effectively reduce ADHD core symptoms, due to stigma, side effects, and medication cost, medication adherence is low in this population. This systematic review focused on determining the effectiveness of computer games-based training programs as a treatment modality for children and adolescents with ADHD.

Methods: We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, searching 5 databases from inception to 2021 for relevant studies. From 563 original studies on computerized executive functions/attention intervention on pediatric patients aged 6 to 17 years old with ADHD, 28 studies met the inclusion of systematic review. Two researchers independently reviewed each study, and the results were analyzed using Review Manager 5.4.

Results: A total of 1980 participants were recruited in 28 studies. Of the 28 studies, 22 are randomized controlled trials, 1 is a case study, and 5 are nonΓÇôrandomized controlled trial cohort studies. Fifteen of 28 studies reported improved ADHD symptoms after intervention, but only 5 studies reported the significant difference between the intervention group and the control group. Less than 50% of included studies provided details of allocation concealment, and were blinded, which increased the risks of biases.

Conclusions: There is some ADHD symptom improvement observed after the interventions. A meta-analysis should be conducted to examine the effect size of training effectiveness. ADHD, P, COMP

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J Am Acad Child Adolesc Psychiatry. 2021;60:S87.

COMMON PSYCHIATRIC COMORBIDITIES IN AUTISM SPECTRUM DISORDER: ADHD, ANXIETY, DEPRESSION, AND CATATONIA.

Thom RP, McDougle CJ, McCracken JT.

Objectives: Children and adolescents with autism spectrum disorder (ASD) are at elevated risk of developing common mental illness comorbidities including ADHD, anxiety disorders, MDD, and catatonia. The objective of this Clinical Perspectives is to describe the salient features of these mental health comorbidities, improving attendees ability to accurately recognize, diagnose, and treat comorbid mental health disorders in ASD.
Methods: Each of the 4 presenters will discuss one of the following mental illness comorbidities: ADHD, anxiety disorders, MDD, and catatonia. Each presentation will include a description of the common clinical presentations in ASD and review the evidence base and gaps in knowledge for informed approaches to diagnosis and treatment. This will be followed by a clinical expert discussion of real-life approaches to diagnosis and treatment using case-based presentations.
Results: Attendees will have a better knowledge of common mental illness comorbidities associated with ASD and helpful treatment approaches.
Conclusions: Comorbid mental health disorders are highly prevalent among youth with ASD. Early, accurate identification and treatment of mental illness comorbidity in children with ASD can promote healthy development by facilitating participation in educational, recreational, and social activities. However, there are several significant challenges in diagnosis and treatment, including the childΓÇÖs decreased ability to communicate symptoms, the need for modified psychotherapies, the lack of high-quality treatment trials, atypical responses to medications, and the lack of provider experience. The overall goal of this Clinical Perspectives is to highlight the clinical presentation of common mental illness comorbidities and helpful treatment approaches to assist the general child and adolescent psychiatrist when caring for these patients. ASD, PPC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S272.

9.1 THE COURSE OF ADHD DURING PREGNANCY.

Baker AS.

Objectives: Approximately 1 in 30 women has ADHD, and it is a disorder linked to poorer general and mental health. Approximately 30% of people elect to maintain their regimen into adulthood, and a growing number of women enter their reproductive years treated with medication for ADHD. Women with ADHD experience difficulties with parenting during early childhood often related to impulsivity, inattention, and hyperactivity. Preliminary prospective data from the first studies on the course of ADHD during pregnancy and the postpartum period will be discussed, highlighting functional impairment, ADHD symptom severity, and associated comorbidities as outcomes of relevance to optimal maternal health and functioning.
Methods: Pregnant women aged 18-45 years were prospectively followed through pregnancy and up to 6 months postpartum using structured clinical interviews. ADHD symptoms were evaluated at each time point using the Adult ADHD Investigator Rating Scale (AISRS). Additionally, anxiety, depression, stress, and functional impairment were monitored throughout the perinatal period.
Results: A total of 28 women with ADHD were followed, and a total of 22 were eligible for analysis. There was a significant increase in average total ADHD symptom score across the entire sample, regardless of medication status (effect size = 5.13; CI, 0.60-9.7; p = 0.027). Further, women who returned to work during the postpartum period had a significant increase in total functional impairment score (effect size = 1.26; CI, 0.042-2.48; p = 0.043) as compared to those who were not working.
Conclusions: The transition to motherhood is significant for all women, characterized by many and often novel demands in domains of attention, focus, multitasking, and executive functioning. Women with ADHD are a particularly vulnerable population who experience mood symptom roughening antepartum and a significant increase in their ADHD symptoms across the postpartum period. There is a large evidence base

on associations between perinatal mental disorders and childhood adverse mental health outcomes, and ADHD is a disorder with relevance when considering infant and preschool mental health. ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S271-S272.

PARENTAL ADHD AND THEIR OFFSPRING FROM THE PERINATAL PERIOD TO EARLY CHOLDHOOD.

Joseph HM, Chronis-Tuscano A.

Objectives: ADHD is a common neurodevelopmental disorder that has been increasingly recognized as persisting into adulthood. ADHD has high heritability, and parental behaviors influence child ADHD symptoms and impairment. In fact, parent behavior training is the primary treatment modality for preschool-aged children with ADHD. Thus, examining offspring at familial risk for ADHD from infancy to preschool and the impact of parental ADHD on early parenting could elucidate potential intervention targets to decrease the prevalence of ADHD and/or reduce impairment for children born to parents with ADHD.

Methods: Allison Baker, MD, will present the trajectory of ADHD symptoms across pregnancy. Heather Marie Joseph, DO, will describe findings regarding predictors of parental distress across the first year of parenthood for parents with ADHD and their co-parents. Mai Uchida, MD, will report on ADHD symptoms among preschool-aged offspring of parents with ADHD. Joyce Lui, PhD, will review thematic analyses from stakeholder meetings regarding identification and treatment of African American families, both parents and children, with ADHD in pediatric primary care.

Results: Pregnant women with ADHD had a significant increase in symptom scores across pregnancy, regardless of medication ($p = 0.027$), and women returning to work postpartum had an increase in total functional impairment score ($p = 0.043$). A cohort of mother-father-infant triads found that families with parent ADHD experienced greater parental distress ($p < 0.05$). Both parent sleep ($p < 0.01$) and infant temperament, surgency ($p = 0.03$) and effortful control ($p < 0.01$), were associated with parental distress. Among a sample of preschool-aged children, those born to parents with ADHD had significantly higher rates of attention problems compared to the children of control parents (OR = 2.37, $p = 0.04$). Stakeholders identified 6 themes of importance when approaching African American families in pediatric primary care settings regarding screening for parent ADHD and treatment of both the parent and child.

Conclusions: The impact of parent ADHD on early parenting and offspring development has been underrecognized. These presentations provide new insights into potential intervention targets to reduce the familial transmissions of ADHD as well as early markers of risk for developing childhood ADHD. ADHD, PAT, PSC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S268.

BROAD-SPECTRUM MULTINUTRIENTS FOR ADHD AND EMOTIONAL DYSREGULATION: A RANDOMIZED CONTROLLED TRIAL.

Arnold LE, Jensen PS.

Objectives: This session aims to examine the effects of a broad-spectrum multinutrient formula containing all known vitamins and essential minerals on ADHD and emotional dysregulation.

Methods: Jeanette Johnstone, PhD, presents primary outcomes of a recently completed randomized controlled trial of broad-spectrum multinutrients. In secondary results from this trial, Gene Arnold, MD, presents the effects of multinutrients on parent-selected target problems (PTPs) quantified by structured interview and rated by blinded psychiatrists, and then Andrew Hughes, MD, and Barbara Gracious, MD, present safety and selected micronutrient results. Irene Hatsu, PhD, presents new analyses from baseline data on the relationship of food insecurity and emotional dysregulation. Peter Jensen, MD, is the discussant.

Results: In the 3-site 8-week randomized controlled trial of 135 children aged 6-12 years with ADHD and emotional dysregulation (N = 126, intention-to-treat), 54% of the multinutrient group and 18% of the placebo group were responders by blinded Clinical Global Impression-Improvement (CGI-I) of 1 or 2 (Cramer's V = 0.37; $p < 0.001$). On another primary outcome, a parent-rated composite score of ADHD, ODD, DMDD, and peer-conflict symptoms and impairment, both treatment groups improved significantly. The average of each parentΓÇÖs first-nominated PTP showed significantly greater improvement with multinutrients than with placebo ($p = 0.02$). Multinutrient supplementation significantly increased blood levels of vitamins D, B6, and

B12 and decreased homocysteine ($p < 0.001$). No toxic blood levels were detected, and there were no clinically concerning effects on complete blood count, complete metabolic panel, or urinalysis. Adverse events with multinutrients were similar to those with placebo. In 8 weeks, children taking multinutrients grew 6 mm more than those taking placebo ($p = 0.002$). Emotional and conduct problems and hyperactive/impulsive, ODD, and DMDD severity were significantly associated with household food insecurity status at baseline.
Conclusions: A broad-spectrum multinutrient appears safe and effective for ADHD with emotional dysregulation, replicating 2 smaller randomized controlled trials. The response rate (54%) is somewhat lower than stimulant medication, but without growth suppression or cardiovascular risk. Food insecurity appears to be a risk factor for emotional dysregulation. ADHD, DMDD, RCT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S272.

9.2 PARENT AND INFANT FACTORS ASSOCIATED WITH EARLY PARENTING DISTRESS AMONG FAMILIES WITH ADHD.

Joseph HM.

Objectives: ADHD is a highly heritable disorder. Thus, offspring of parents with ADHD are at high risk for ADHD. Early parenting influences brain development and may contribute to the expression of inherited vulnerability to ADHD. However, little is known about factors affecting parenting of infants in families with ADHD. Parental stress is linked to less sensitive parenting and, therefore, may be one such factor. Given impairments associated with ADHD, including greater interpersonal dysfunction, we hypothesized that parents with ADHD and their co-parents would report greater parenting stress compared to families without ADHD. Because infants at high risk for ADHD may have more difficult temperament, we aimed to examine both parent and infant factors associated with parenting stress.
Methods: Seventy-three families (N = 146 parents) enrolled in a longitudinal study. Half of the families had at least 1 parent with ADHD. Parents completed questionnaires regarding stress, sleep, parenting satisfaction, and infant temperament when their children were approximately 8 months (M = 8 months). Correlations among these variables and t tests were used to compare families with and without ADHD. Hypothesized predictors of early parenting stress including ADHD family status, mother vs father, parent education, social support, infant temperament, and both parent and infant sleep were assessed using multilevel models.
Results: Stress was positively correlated with poor sleep quality ($p < 0.001$) and negatively correlated with parenting satisfaction ($p < 0.001$). Families with ADHD reported greater stress ($p = 0.015$), lower satisfaction ($p = 0.023$), and poorer sleep ($p = 0.018$). Sleep quality ($p < 0.01$) was associated with stress and accounted for the variance in ADHD status. Parent ADHD remained significant ($p = 0.04$) when considering infant factors. Surgency ($p = 0.03$) and effortful control ($p < 0.01$) were both negatively associated with stress.
Conclusions: Parents with ADHD and their partners experience increased stress in the first year of their child's life. Greater parenting stress is known to impact the developing brain and may be one mechanism by which parent ADHD increases the risk for development of ADHD symptoms in offspring. Addressing parent ADHD symptoms and comorbidity (ie, sleep disturbances) is a potential target for early interventions for infants at familial high risk for ADHD. ADHD, INF, PAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S257.

IMPROVEMENTS IN EMOTIONAL LABILITY WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDTE TREATMENT IN CHILDREN WITH ADHD.

Arnold V, Lopez F, Childress A, et al.

Objectives: Emotional lability (EL) is common in individuals with ADHD, with reported prevalence rates ranging from 38% to 75%. Pharmacologic treatments for ADHD have been shown to improve EL with modest effect sizes. This post hoc analysis examined the effect of HLD200, an evening-dosed delayed-release and extended-release methylphenidate (DR/ER-MPH; tradename: JORNAY PM-«), on EL in children (6-12 years) with ADHD in 2 randomized, double-blind, phase 3 trials (HLD200-107 [NCT02493777] and HLD200-108 [NCT02520388]).

Methods: EL was measured with the 3-item Connors Global Index–Parent (CGI-P) EL subscale, which was recorded weekly in the 6-week, open-label phase of HLD200-107, and at baseline and study endpoint (Week 3) in HLD200-108. In HLD200-107, mean scores were compared to baseline at each week using paired t test (N = 117). In HLD200-108, mean scores in the DR/ER-MPH (n = 79) and placebo (n = 76) groups at Week 3 were compared using ANCOVA analysis. Correlations were determined between CGI-P EL scores and the following measures/items: Clinical Global Impression-Severity (CGI-S), CGI-Improvement (CGI-I), Caregiver Strain Questionnaire (CGSQ), and the ΓÇ£arguing/strugglingΓÇØ items in the Morning (item 3) and Evening (item 8) subscales of the Parent Rating of Evening and Morning BehaviorΓÇôRevised (PREMB-R) scale.
Results: In HLD200-107, CGI-P EL scores improved after 1 week of DR/ER-MPH treatment and remained improved vs baseline in each week ($p < 0.0001$). In HLD200-108, CGI-P EL scores were significantly improved after 3 weeks of DR/ER-MPH treatment compared to placebo ($p < 0.01$). Significant positive correlations ($p < 0.005$) were found between CGI-P EL scores and CGSQ, CGI-S, CGI-I, and the arguing/struggling items in both the Morning and Evening subscales of the PREMB-R.
Conclusions: DR/ER-MPH treatment improved EL scores in two phase 3 trials of children aged 6-12 years with ADHD. EL was positively correlated with ADHD symptoms and functional impairment in children with ADHD and with strain on caregivers. Due to its pharmacokinetic profile and dose-dependent duration of effect that can provide consistent treatment effects from early morning to late afternoon/evening, DR/ER-MPH is predicted to be an effective treatment for ADHD patients with EL

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J Am Acad Child Adolesc Psychiatry. 2021;60:S258.

EFFICACY OF LONG-TERM TREATMENT WITH VILOXAZINE EXTENDED-RELEASE CAPSULES (QELBREE) IN CHILDREN AND ADOLESCENTS WITH ADHD: AN OPEN-LABEL EXTENSION STUDY.

Nasser A, Hull J, Chaturvedi S, et al.

Objectives: Viloxazine extended-release capsules (viloxazine ER; QelbreeΓäó) is a novel nonstimulant recently approved for the treatment of ADHD in children and adolescents based on results from 3 pivotal Phase 3 trials. Here, we report efficacy results of the ADHD Rating Scale, 5th Edition (ADHD-RS-5) and Clinical Global Impression-Improvement (CGI-I) assessed during the long-term open-label extension (OLE) safety study of viloxazine ER.
Methods: The change from baseline (pivotal; CFB) in ADHD-RS-5 Total score, 50% ADHD-RS-5 Responder Rate (percentage of subjects with a 50% reduction in their CFB ADHD-RS-5 Total score), and CGI-I Responder Rate (percentage of subjects with a CGI-I score of 1 or 2) were analyzed by visit from pivotal to last visit in an OLE trial. Subjects were grouped based on pivotal trial treatment assignment (pivotal-placebo or pivotal-viloxazine ER). In the OLE trial, subjects aged 6-11 years were dosed at 100 mg/day or titrated up (100 mg/day/week) to optimal dose at or below 400 mg/day, and subjects aged 12-17 years were dosed at 100 mg/day or titrated up (100 or 200 mg/day/week) to optimal dose at or below 600 mg/day.
Results: Of the 1170 subjects who completed a pivotal trial, 1100 subjects were dosed in the OLE (323 pivotal-placebo and 777 pivotal-viloxazine ER). The median dose of viloxazine ER was 300 mg in children aged 6-11 years and 400 mg in adolescents aged 12-17 years. ADHD symptoms improved in the first month and continued improving over time during OLE in both pivotal-placebo and pivotal-viloxazine ER subjects. The mean (-¦SD) CFB in ADHD-RS-5 Total score at last visit during OLE was significantly improved in the pivotal-viloxazine ER group (ΓÇô19.3 -¦ 13.22; $p < 0.0001$) and in the pivotal-placebo group (ΓÇô18.0 -¦ 13.17; $p < 0.0001$). For both groups, ADHD-RS-5 and CGI-I responder rates were above 50% within the first 3 months, remained above 65% after 3 months, and remained above 75% after 18 months of treatment.
Conclusions: ADHD symptoms significantly improved and the number of subjects experiencing a clinically meaningful improvement increased over time during long-term viloxazine ER treatment. These data indicate that viloxazine ER treatment can provide sustained efficacy, further improve ADHD symptoms, and increase the responder rates even after 8 weeks of treatment

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J Am Acad Child Adolesc Psychiatry. 2021;60:S269-S270.

7.4 FIID INSECURITY AND EMOTIONAL SYSREGULATION IN CHILDREN WITH ADHD: THE MADDY STUDY.

Hatsu I, Johnstone JM, Leung B, et al.

Objectives: This session aims to examine the association between household food insecurity, pediatric ADHD, and co-occurring emotional dysregulation. Food insecurity affects 13 million children in the United States. Defined as the limited or uncertain availability or access to adequate and safe foods, food insecurity can have both physical and mental health consequences. The mental health consequences of food insecurity have yet to be fully explored, especially among children with ADHD.

Methods: This analysis used baseline data of children aged 6-12 years enrolled in a randomized controlled trial of Micronutrients for ADHD in Youth (MADDY), a sample with co-occurring emotional dysregulation. The 18-Item US Household Food Security Survey Module (HFSSM) was used to assess household food security. Symptoms of ADHD and comorbid symptoms of ODD and DMDD were assessed using the Child and Adolescent Symptom Inventory-5 (CASI-5). Other emotional dysregulation symptoms were assessed using the SDQ. Associations were determined through multiple linear regression models with appropriate covariates.

Results: Household food insecurity prevalence was found to be 11.2% in this sample. It was significantly associated with severe emotional problems (+¦ = 1.75; 95% CI, 0.40-3.10; p = 0.011), conduct problems (+¦ = 1.38; 95% CI, 0.30-2.45; p = 0.012), and total difficulties score (+¦ = 4.07; 95% CI, 1.41-6.73; p = 0.003) after adjusting for covariates (sex, income, and parental education). Household food insecurity was also associated with increased symptom severity of hyperactivity/impulsivity (+¦ = 0.46; 95% CI, 0.06-0.85; p = 0.024), ODD (+¦ = 0.50; 95% CI, 0.14-0.86; p = 0.007), and DMDD (+¦ = 0.60; 95% CI, 0.13-1.08; p = 0.014) after adjusting for sex. In the subsequent adjustment of 2 covariates highly associated with food insecurity (income p < 0.001; and parent education p = 0.009), the latter associations attenuated to nonsignificance.

Conclusions: Household food insecurity was significantly associated with severe emotional dysregulation. Asking about and addressing food insecurity may be appropriate in pediatric populations with emotional dysregulation. ADHD, ODD, DMDD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S49.

MANAGEMENT OF COMPLEX PEDIATRIC ADHD.

Baweja R, Waxmonsky JG.

Objectives: In the United States, over 10% of school-aged children are diagnosed with ADHD. The disorder has a significant impact on functioning at school, at home, and in social relationships. Multiple evidence-based pharmacological and psychosocial interventions exist for ADHD. However, many youths with ADHD have elevated levels of mood and anxiety symptoms, irritability, aggression, or autism spectrum disorder that can complicate treatment. This presentation highlights the assessment and treatment of ADHD comorbid with other common mental health symptoms or disorders.

Methods: Presenters use a combination of reviewing current research literature, clinical case examples, and best clinical practices. Presenters will discuss the assessment and management of complex ADHD by a multimodal approach including pharmacological and psychosocial interventions.

Results: In the first talk, Rasim Diler, MD, presents an assessment and management of ADHD with comorbid mood disorders. In the second talk, J. Bhagia, MD, discusses assessment and management of ADHD with comorbid anxiety disorders. Raman Baweja, MD, presents an assessment of chronic irritability and aggression in youth with ADHD. Linda Halldner, MD, discusses the assessment and management of ADHD symptoms in children with autism spectrum disorder. In the final talk in the session, James G. Waxmonsky, MD, integrates these presentations and discusses their clinical implications with a focus on how they inform office-based management of ADHD.

Conclusions: A systematic multimodal approach can be feasibly accomplished in routine clinical care that improves the detection and management of common mental health comorbidities that complicate the course of ADHD. This Clinical Perspectives will have senior child and adolescent psychiatrists present their care models with the goal of expanding providersΓÇÖ knowledge, skill, and comfort in managing children and adolescents with ADHD and complex comorbidity. ADHD, PPC, TREAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S130.

5.1 WHAT'S NEW IN ADHD, ANXIETY DISORDERS, AND DMDD?

Wilens T.

Objectives: ADHD, anxiety, and mood disorders are among the most prevalent disorders that child and adolescent psychiatrists treat. This talk provides a timely update on contemporary data related to the care of youth with these disorders.

Methods: A selected review of the literature focused on ADHD, anxiety, and DMDD was undertaken. Studies and editorials focusing on relevant issues related to the prevention and care of young people with these disorders were reviewed.

Results: This talk will focus on the longer-term outcomes of treated ADHD including effects on injuries, mood comorbidity, and growth. Recent guidelines on the treatment of anxiety disorders will be highlighted. The treatment of youth with DMDD will be reviewed.

Conclusions: Emerging findings related to ADHD, anxiety, and mood dysregulation, and their overlap, will be presented. ADHD, AD, DMDD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S69.

47.1 CHALLENGES IN PRESCRIBING AND OPTIMIZING PHARMACOTHERAPY IN ADOLESCENTS WITH ADHD DURING COVID-19.

Newcorn JH.

Objectives: Pharmacotherapy in adolescents with ADHD poses unique challenges and is less studied than the treatment of children and adults. Moreover, issues related to psychological independence and control significantly impact provision of care, as do increasing rates of comorbid mood, anxiety, and substance use disorders. Most importantly, the shift from a parent-centered to an adolescent-centered approach has major implications for treatment adherence. These issues are magnified by changes in peer interactions, demands of online learning, variable schedules, the need to extend or contract medication duration, and shifts in family dynamics in the post-COVID-19 world. This presentation will provide a mix of clinical and research-informed expertise on the use of medication in adolescents with ADHD, highlighting new information regarding pharmacotherapy during the COVID-19 pandemic.

Methods: A review of recent literature and experience in conducting clinical trials with adolescents will be utilized to generate specific recommendations. Guidelines for pharmacotherapy of ADHD during the pandemic, and new research on the impact of the pandemic on ADHD and its treatment, will be presented.

Results: Stimulant and nonstimulant effect sizes in clinical trials are often lower in adolescents than in children; adolescents typically require higher absolute doses and lower weight-based doses of stimulants. Effect sizes for alpha-2 agonists are smaller, and dosing needs to be increased to account for weight. Similar issues impact treatment with atomoxetine. Combining treatment with medications that target comorbidity offers opportunities but also complicates the therapeutic approach. Risks related to the abuse and/or diversion of drugs are often not considered well enough. Particular problems during the pandemic include changes in the duration of medication coverage needed, dose adjustments for online learning, and shifts in the proportion of extended-release and immediate-release medications used.

Conclusions: Treatment of adolescents with ADHD requires sensitivity to myriad psychological, developmental, diagnostic, and pharmacokinetic considerations that impact treatment response. These issues are often augmented during the COVID-19 pandemic. The art of managing these issues to therapeutic advantage will be illustrated in this presentation. ADHD, PPC, ADOL

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J Am Acad Child Adolesc Psychiatry. 2021;60:S234.

43.8 CHANGES IN CANNABIS AND ALCOHOL USE AND THEIR IMPACT ON ADHD SYMPTOMS IN ADOLESCENTS RECEIVING ADHD PHARMACOTHERAPY AND SUBSTANCE USE TREATMENT.

Pink A, Rizwan B, Park G, et al.

Objectives: Adolescents with ADHD commonly use and co-use cannabis and alcohol. Whether these substances act as complements vs substitutes is debated in the literature. Little is known about the impact of cannabis use on alcohol use disorder (AUD) treatment outcomes (and vice versa) in ADHD youth.

Methods: The present study used data from the NIDA-CTN-0028 trial to investigate the relationships between change in cannabis use (CU) and alcohol use (AU) and their impact on ADHD outcomes in 303 adolescents (aged 13-18 years) meeting DSM-IV criteria for ADHD and substance use disorder (SUD) who participated in a 16-week randomized controlled multisite trial of osmotic-controlled release oral delivery system methylphenidate (OROS-MPH) vs placebo with both groups receiving CBT for SUD.
Results: In the ADHD/SUD sample, cannabis use disorders (89%) and AUD (60%) were the most common SUD diagnoses. During treatment, 79% and 48% of participants reduced and 12% and 24% of participants increased their CU and AU, respectively. After controlling for age, race, and sex, during treatment, reduction in the amount of cannabis used was positively correlated with during-treatment reductions in the number of drinks (r = 0.14; p = 0.02) and drinking days (r = 0.14; p = 0.02). Reduction in drinking days was associated with reductions in ADHD symptoms (+¦ = 0.26; p = 0.04), and reductions in both CU and AU were associated with improvements in global functioning (+¦ΓÇÖs = 0.26-0.44; all p s < 0.05) during treatment.
Conclusions: Our findings indicate that reductions in CU track with reductions in AU during SUD treatment with both contributing to posttreatment improved functioning in youth with ADHD/SUD. These results provide preliminary support for a complementary relationship between CU and AU in this population. Additional research is warranted to clarify the clinical implications of different patterns of change in cannabis and alcohol use across the continuum of co-use in ADHD and non-ADHD samples. SUD, CM, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S150.

5.1 D-AMPHETAMINE TRANSDERMAL SYSTEM (D-ATS) IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ADHD: SECONDARY ENDPOINT RESULTS FROM A PHASE 2 TRIAL.

Cutler AJ, Suzuki K, Starling B, et al .

Objectives: Amphetamines are a first-line treatment for ADHD. The dextroamphetamine transdermal system (d-ATS) was developed as an alternative to oral amphetamine formulations. A randomized controlled trial of d-ATS in children and adolescents with ADHD was conducted, and its primary and key secondary endpoints were met. Here, we report the secondary endpoints of the study, further assessing the efficacy and safety of d-ATS.
Methods: This study comprised a 5-week, open-label dose-optimization period (DOP) followed by a 2-week, randomized, crossover double-blind treatment period (DBP). All eligible subjects received d-ATS 5 mg/9 hours (hr) and were evaluated weekly for possible dose increase to 10 mg/9 hr, 15 mg/9 hr, and 20 mg/9 hr (DOP). Once reached, the optimal dose was maintained for the DOP and utilized for the DBP. The secondary objectives for this study included an assessment of efficacy via Permanent Product Measure of Performance-Attempted and -Correct (PERMP-A, PERMP-C), ADHD Rating Scale-IV (ADHD-RS-IV), ConnersΓÇÖ Parent Rating ScaleΓÇôRevised: Short Form (CPRSΓÇôR:S), and Clinical Global Impression (CGI) scores in a laboratory classroom setting. A mixed-model repeated-measures (MMRM) approach was used to analyze efficacy. Safety assessments included treatment-emergent adverse events (TEAEs) and dermal safety.
Results: In total, 110 subjects were enrolled in the DOP, and 106 subjects were randomized in the DBP. Subjects receiving d-ATS demonstrated significant improvement vs placebo in PERMP-A and -C scores in the DBP consistently from 2 to 12 hours postdose (p < 0.001 for all timepoints). ADHD-RS-IV total scores improved during the DOP and improved further during the DBP, with a least-squares (LS) mean (95% CI) difference for d-ATS vs placebo of ΓÇô13.1 (ΓÇô16.2 to ΓÇô10.0; p < 0.001). Significant differences between placebo and d-ATS in the DBP were also observed for the CPRS-R:S and CGI scales (p < 0.001). Most TEAEs were mild or moderate, with 3 TEAEs (abdominal pain, irritated mood, and appetite loss) leading to study discontinuation in the DOP and none in the DBP. No patients discontinued due to dermal reactions across both phases.
Conclusions: d-ATS was effective in the treatment of ADHD in children and adolescents, meeting its primary endpoint (reported elsewhere) and all secondary endpoints. d-ATS was safe and well tolerated, with minimal dermal reactions. ADHD, RCT, STIM

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J Am Acad Child Adolesc Psychiatry. 2021;60:S273.

9.4 CHALLENGES AND CONSIDERATIONS FOR SCREENING FOR PARENT ADHD IN PEDIATRIC PRIMARY CARE.

Lui JHL.

Objectives: ADHD is common in both parents and children, yet African American families are less likely to be diagnosed or treated, or to participate in clinical trials. Parent ADHD can significantly impact child development and treatment response. Most children receive primary care annually, presenting an opportunity to screen for ADHD in children and parents. Although pediatric providers are familiar with screening and managing ADHD in children, there is little guidance on how to effectively approach parents about their own ADHD. The current qualitative study describes challenges encountered and lessons learned when implementing a parent ADHD screening protocol in primary care serving a large population of African American youth and families.

Methods: The study occurred within the context of a hybrid effectiveness-implementation trial treating parents and children with ADHD with parental stimulant medication and behavioral parent training. To guide study implementation, a stakeholder advisory group was formed including pediatricians, behavioral health providers, clinic staff, and parents with ADHD or with a child with ADHD. Meetings were held before and during the study to seek feedback from stakeholders regarding factors that may influence recruitment and implementation of the treatment trial. Two meetings were held with 9 stakeholders during June and November 2020. Meetings were recorded, transcribed, coded, and analyzed for themes. Stakeholder members were predominantly female (89%) and White (44%).

Results: Thematic analyses identified 6 themes: 1) centering Black people's experiences with mental health care; 2) the value of integrating parent mental health with child mental health care; 3) sensitivity required when talking about parent mental health; 4) attention to medication hesitation; 5) effective vs ineffective strategies to identify parent mental health; and 6) structural barriers for screening parent ADHD in pediatric primary care.

Conclusions: Findings provide suggestions (eg, describing symptoms vs using clinical labels, having conversations initiated by trusted providers) for pediatricians on how to engage parents effectively and sensitively in discussions about their own ADHD in the context of working with underserved multiplex families in primary care. ADHD, PAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S272-S273.

9.3 EARLY MANIFESTATIONS OF RISK FOR ADHD IN AT-RISK PRESCHOOL-AGED CHILDREN.

Uchida M.

Objectives: While ADHD is most commonly diagnosed around 8 years of age, emerging ADHD symptoms are frequently seen as early as during the preschool years. This gap between the onset of ADHD symptomatology and its eventual identification results in significant delays to receiving early intervention and treatment. Thus, the main aim of this study was to examine the early manifestations of ADHD in preschool children. To this end, we studied emergent symptoms of ADHD in the preschool offspring of parents with ADHD and compared them to the offspring of parents without ADHD.

Methods: Our sample was derived from a longitudinal study of 331 offspring of parents with and without MDD and ADHD. The study recruited parent-child dyads from families in which at least 1 parent had been treated for one, both, and neither of these disorders. To be eligible for inclusion, parents had to have at least 1 biological child between 2 and 5 years of age. Parents and children were assessed using the Child Behavior Checklist (CBCL). A syndromal score was defined as a t score of 70 on a CBCL subscale, and a subsyndromal score was defined as a t score <70.

Results: Our final groups comprised 68 children from 56 families with at least 1 parent with ADHD, and 91 children from 76 control families. Children of parents with ADHD had significantly higher rates of elevated CBCL Attention Problems t scores compared to children of control parents (OR = 2.37; 95% CI, 1.01-5.57; p = 0.04). Restricting our analyses to children with elevated CBCL Attention Problems t scores, children of parents with ADHD had, on average, significantly more additionally elevated CBCL clinical scales compared to children of control parents.

Conclusions: We found that preschool children of parents with ADHD were at significantly elevated risk for subsyndromal and syndromal symptoms of ADHD than control children. ADHD symptomatology in high-risk offspring was associated with significantly higher levels of comorbid symptoms of anxiety, depression, and

aggression compared to control children with ADHD symptoms. These findings suggest that ADHD symptoms are prevalent in high-risk preschoolers and are associated with well-known correlates of the disorder. ADHD, PSC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S69.

47.2 ENGAGEMENT STRATEGIES TO PROMOTE TREATMENT ADHERENCE AND LONG-TERM SUCCESS IN ADOLESCENTS WITH ADHD.

Sibley MH.

Objectives: There is a noted age-based disparity in the delivery of pediatric ADHD treatments, with adolescents receiving far fewer services than children. Families of teens with ADHD often experience barriers to successful engagement in behavior therapy that include motivation deficits, inconsistent family routines, intrusive parenting, regulating electronics, and skepticism about the efficacy of behavioral techniques.

Methods: In this presentation, we will provide an overview of an evidence-based behavior therapy for adolescents with ADHD that emphasizes youth engagement (Supporting Teens Autonomy Daily [STAND]). We will discuss specific techniques that clinicians can use to increase medication and psychosocial treatment engagement among adolescents with ADHD.

Results: We will review key engagement strategies for adolescents with ADHD and discuss recent longitudinal findings on the complementary effects of medication and evidence-based psychosocial treatment. These findings are from the ADHD Teen Integrative Data Analysis Longitudinal (ADHD-TIDAL) study (N = 854), a recent RCT (N = 278) of STAND compared to community-based usual care, and 4-year follow-up of an RCT of high- vs low-intensity behavior therapy for adolescents with ADHD (N = 325).

Conclusions: We will summarize the key goals when treating teenagers with ADHD and discuss why adolescence may be an excellent window for promoting long-term treatment effects. We will share information about delivering STAND via video conferencing and during COVID-19, sharing resources with attendees to promote application of the presented material in their practice. ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S46.

LOOKING AT ADULT OUTCOME OF CHILDREN WITH ADHD VIA DIFFERENT LENSES.

Hechtman L, Sonuga-Barke E.

Objectives: The objective of this Clinical Perspectives is to explore the adult outcome of ADHD with a variety of lenses, for example, exploring patterns of persistence and remission over time, comparing findings from controlled prospective follow-up studies vs registry studies, and identifying benefits and limitations of qualitative interviews of adults with childhood ADHD and their families.

Methods: Margaret Sibley, PhD, will present on the variable patterns of remission of ADHD of 558 participants in the MTA. Lily Hechtman, MD, FRCP, will compare various adult outcomes in individuals with childhood ADHD from controlled prospective follow-up studies vs registry studies from Denmark and Norway. Peter Jensen, MD, will present benefits and limitations of qualitative interventions of adults with childhood ADHD and their families.

Results: Dr. SibleyΓÇÖs study shows that remission is often not permanent but many adults with ADHD may have a period of remission that may be followed by recurrence depending on environmental demands. A small percent (9%) show recovery and 10% show persistence of ADHD across study time points. Dr. Jensen will outline the benefits (in-depth information from the subjects and families perspectives) of qualitative interviews and the challenge of synthesizing a coherent picture when perspectives of the patients and families differ. Qualitative interviews provide a personal view of turning points from the perspective of the person and family that may not be supported by objective measures. However, objective measures do not provide the patient's views, feelings, or understanding of the challenges that he and his family face. Dr. Hechtman will review adult outcomes from controlled prospective studies that show that outcomes differ across domains and are different for those in which ADHD symptoms persist vs desist. It is clear that registry studies capture the population that is still in difficulty with diagnosis, medication, hospitalization, and public assistance payments, but not more subtle emotional, work, and relationship outcomes.

Conclusions: The outcome in adults with childhood ADHD varies depending on how and when it is explored. It may also vary depending on environmental demands and available support. Finding ways to support adult patients in these changing environments remains a clinical challenge. ADHD, LONG

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J Am Acad Child Adolesc Psychiatry. 2021;60:S117.

1.2A RANDOMIZED CONTROLLED TRIAL OF INTERVENTIONS FOR GROWTH SUPPRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH CENTRAL NERVOUS SYSTEM.

Waxmonsky J.

Objectives: To examine the impact of central nervous system (CNS) stimulants on the growth of children with ADHD, and to assess the efficacy and feasibility of weight recovery interventions on growth.

Methods: A total of 230 children aged 5 to 12 years with ADHD with no history of chronic CNS stimulant use were randomly assigned to receive daily CNS stimulants (78%, primarily osmotic release oral system-methylphenidate [OROS-MPH]) or behavioral treatment (22%) for 30 months. After 6 months, children evidencing a decline in body mass index (BMI) of >0.5 z-units were randomized to 1 of 3 weight recovery treatments (WRTs): monthly monitoring of height/weight (MON) plus continued daily medication; drug holidays (DH) with medication limited to school days; or daily caloric supplementation (CS) with a 150-kcal supplement plus daily medication.

Results: Before WRT assignment, medication was associated with significant reductions in standardized weight and height (p values < 0.01). Adherence to CS and DH during WRT was high, with significant increases in daily caloric intake and decreases in weekly medication exposure (p values < 0.05). Across all WRT participants (n = 71), weight velocity increased significantly after WRT randomization (+¦2 = 0.271, SE = 0.027, p < 0.001). When analyzed by what parents did (versus what they were assigned to), CS (p < 0.01) and DH (p < 0.05) increased weight velocity more than MON. No increase in height velocity was seen after randomization to any WRT. Over the entire study, WRT participants declined in standardized weight (0.44 z-units) and height (0.20 z-units).

Conclusions: Drug holidays, caloric supplementation, and increased monitoring all led to increased weight velocity in children taking CNS stimulants, but none led to increased height velocity. ADHD, SAC, STIM

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J Am Acad Child Adolesc Psychiatry. 2021;60:S166.

6.25 CHARACTERIZING THE AUTISM SPECTRUM DISORDERΓÇôADHD PHENOTYPE: MEASUREMENT STRUCTURE AND INVARIANCE IN A CLINICAL SAMPLE.

Krakowski A, Cost K, Szatmari P, et al.

Objectives: Autism spectrum disorder (ASD) and ADHD have considerable overlap, supporting the need for a dimensional framework that examines neurodevelopmental domains that cross traditional diagnostic boundaries. In the following study, we use factor analysis to deconstruct the ASD-ADHD phenotype into its underlying phenotypic domains and test for measurement invariance across adaptive functioning, age, gender, and ASD/ADHD clinical diagnoses.

Methods: Participants included children and youth (aged 3-20 years) with a clinical diagnosis of ASD (n = 770) or ADHD (n = 727) for a total of 1497 participants. Parents of these children completed the Social Communication Questionnaire (SCQ), a measure of ASD symptoms, and the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire, a measure of ADHD symptoms. An exploratory factor analysis (EFA) was performed on combined SCQ and SWAN items. This was followed by a confirmatory factor analysis (CFA) and tests of measurement invariance.

Results: The EFA revealed a 4-factor solution (inattention, hyperactivity/impulsivity, social-communication, and restricted, repetitive, behaviors and interests [RRBIs]), and a CFA confirmed good model fit. This solution also showed good model fit across subgroups of interest.

Conclusions: Our study shows that a combined ASD-ADHD phenotype is characterized by 2 latent ASD domains (social communication and RRBIs) and 2 latent ADHD domains (inattention and hyperactivity/impulsivity). We established measurement invariance of the derived measurement model across adaptive functioning, age, gender, and ASD/ADHD diagnoses. Our study encourages the use of a dimensional approach when assessing children with suspected ASD or ADHD, and it reassures clinicians

that variation on these dimensional phenotypes is not due to measurement differences across age, gender, adaptive functioning, and ASD/ADHD diagnosis. ADHD, ASD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S100.

68.1 ASSESSMENT OF YOUNG CHILDREN WITH DISRUPTIVE BEHAVIORS.

Misch DM.

Objectives: Disruptive behavior plays a central role in developmental sequences of psychopathology. It is antecedent to up to 60% of common mental disorders across the life span, often emerges in early childhood, and is the most prevalent disorder of the preschool period with estimates between 9% and 15%. This presentation suggests use of a multidimensional, multisession, developmental framework for early childhood assessment of disruptive behavior. It addresses key challenges in distinguishing developmentally normative from atypical behaviors, categorical vs dimensional models of childhood psychopathology, and psychosocial moderators and mediators of disruptive behavior.

Methods: A summary of practice guidelines on mental health assessment of the young child will be reviewed. It will highlight the intricacies and skill needed to complete a thorough evaluation. Use of stop-and-think questions, vignettes, visuals, real-life cases, and video clips will engage the audience in the presentation.

Results: Integrating the body of evidence that links environmental, physiologic, genetic, and relational contributions to individual differences can determine significant self-control problems, suggest underlying cause, and can guide the use of targeted interventions. An understanding of this information provides practical strategies for successful assessments in most mental health outpatient settings.

Conclusions: Problematic levels of disruptive behavior, especially when accompanied by functional impairment and distress of the child and/or primary caregiver, should be identified early using a systematic developmentally informed mental health examination including standardized measures, collateral resources, and multiple sessions to improve outcome trajectories. ADHD, PSC, EC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S78.

53.1 TEACHING ADHD TO INDIAN REACHERS AND PARENTS.

Yehudian S, Neelgund P.

Objectives: The prevalence of ADHD in India is reported to be 1.6% to 17.9%. This large spread is likely due to the unevenness in diagnosis of this common mental health disorder and the lack of familiarity with interventions. Indian teachers in lower resourced areas recognize problems associated with ADHD-inattentiveness, impulsivity, and disorganization but may attribute them to lack of interest or motivation and noncompliance with the rules of the classroom. Although ADHD is highly heritable, deficits in the core competencies necessary for academic success are also linked with environmental stressors such as poverty, especially when experienced in the first months of life. It is prudent to inform teachers about ADHD so that the child's behavior is not misapprehended solely as intentional, thereby allowing for the possibility of intervention.

Methods: A child and adolescent psychiatry fellow gives remote lectures on ADHD to teachers in rural India, with an Indian educator as a collaborator and translator. Case discussions of problem children presented by the teachers serve to develop the content of the lecture and to illuminate cultural differences in meanings attributed to ADHD and culturally congruent interventions. Informational videos are shown to highlight insights gained by the teachers on ADHD.

Results: Working with a translator/collaborator, the child and adolescent psychiatry fellow learns lecturing and consultation skills in this experience with teachers from a different culture and country. He offers helpful information to the teachers while challenging the Western bias of his medical model and experiments with the use of visual media in teaching.

Conclusions: This presentation demonstrates learning how to teach and consult important skills in child and adolescent psychiatry to teachers. It also explores Western bias in the diagnosis and intervention of ADHD and uses media to communicate mental health knowledge to teachers in India. ADHD, CUL, PRE

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J Am Acad Child Adolesc Psychiatry. 2021;60:S268-S269.

7.1RANDOMIZED CONTROLLED TRIAL OF MULTINUTRIENTS FOR ADHD WITH EMOTIONAL DYSREGULATION.

Johnstone JM, Tost G, Hatsu I, et al.

Objectives: This session aims to examine the efficacy of broad-spectrum multinutrients for ADHD and emotional dysregulation.

Methods: In the Micronutrients for ADHD in Youth (MADDY) randomized controlled trial, unmedicated children (N = 135) aged 6-12 years with ADHD and emotional dysregulation (based on parent reports) at 3 sites (Oregon, Ohio, Canada) were randomized to a 36-ingredient multinutrient supplement (vitamins + minerals) or placebo (3:2 ratio) for 8 weeks. The primary outcomes were the clinician-rated Clinical Global ImpressionΓÇôImprovement (CGI-I; 1 or 2 = responder), and the parent-rated Child and Adolescent Symptom Inventory-5 (CASI-5) composite score comprised of ADHD, ODD, DMDD, and peer-conflict symptoms, including impairment scores for each. A teacher also completed the CASI-5.

Results: With a mean age of 9.8 years, 93% (N = 126) of the 135 randomized children comprised the intention-to-treat population. Participants demographic and baseline clinical characteristics were well matched between treatment groups, with no significant differences (all $p > 0.05$). On the CGI-I, 54% of those assigned micronutrients vs 18% of the placebo group were responders (Cram®rs V = 0.37; $p < 0.001$). However, parent-rated CASI-5 composite scores did not differ between groups ($p = 0.70$); both improved from baseline ($p < 0.01$). Teacher reports showed significant between-group difference favoring micronutrients on the Peer Conflict subscale, which was 0.13 points lower for micronutrients (95% CI, 0.26 to 0.01, $p = 0.04$; Cohen's d = 0.16). The micronutrient group grew 6 mm more than the placebo group ($p = 0.002$; Cohen's d = 1.15). Blinding was maintained.

Conclusions: Micronutrients showed global improvement over placebo by blinded clinician rating and teacher reports of peer conflict, but not by parent report on the CASI-5 in children with ADHD and irritability. The micronutrient group showed greater height growth velocity. Micronutrients were well tolerated, and the majority of children adhered to the treatment. This randomized controlled trial replicates the efficacy reported for ADHD in 2 smaller RCTs of a similar formula, containing all vitamins and known essential minerals in therapeutic amounts between the Recommended Dietary Allowance and Tolerable Upper Intake Level. ADHD, RCT, IMD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S100.

68.2 TREATMENTS GUIDELINES FOR PHARMACOLOGICAL MANAGEMENT OF DISRUPTIVE BEHAVIORS AND ADHD.

Romanowicz M.

Objectives: There is a high comorbidity between ADHD and disruptive behavior problems in young children. The AAP recommends behavioral parent training and/or behavioral therapy as a first-line treatment of preschool-aged children with ADHD. Based on literature review, behavioral therapy in young children is the most efficacious in the treatment of ADHD symptomatology, particularly when it is comorbid with disruptive behaviors; however, if it fails or is inadequate in managing symptomatology, stimulant medications are considered. Dextroamphetamine is FDA approved for the treatment of ADHD in children aged 3 years and older, vs methylphenidate, which has a warning to not be used in children younger than 6 years old. Data on medication use in this patient population are limited and risk assessment is complex due to lack of full appreciation of potential long-term side effects and consequences on the developing brain. It is also unclear which children would respond better to therapy and which ones would respond better to medication management. There are also no guidelines regarding combined treatment, medication plus therapy, for children with severe symptomatology.

Methods: This presentation will focus on a literature review of studies discussing various treatment modalities for disruptive behaviors in young children with ADHD. We will discuss challenges of combined treatment: psychotherapy and medication management. We will focus on available literature on the use of psychotropic medications in children aged 2 to 7 years. We will review available treatment guidelines and offer provisional guidelines, based on available literature on when to use behavior treatment alone vs in combination with medication.

Results: Participants will learn treatment recommendations for young children with ADHD and disruptive behaviors. They will gain an understanding of the pros and cons of using medications in this patient population. They will have an opportunity to present their challenging cases and ask questions.

Conclusions: First-line treatment of disruptive behaviors in kids with ADHD is with behavioral therapies. Data on medication use are very limited in this patient population. PPC, DBD, PSC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S78-S79.

53.3 TEACHING ADHD TO PHYSICIANS IN EL SALVADOR.

Mayen Lainez AV, Marquez-Castro H.

Objectives: Whereas the incidence of ADHD in El Salvador is reported as 6.7%, it is likely that in sections of this traumatized country burdened by a recent civil war, gang violence, and chronic poverty, early neurodevelopment has been disproportionately affected and ADHD is more prevalent. In addition, much of the population-especially in rural areas-does not have ready access to specialty care. It is therefore important for Salvadoran primary care physicians (PCPs), teachers, and parents to learn about the diagnosis and treatment of ADHD. Similarly, US child and adolescent psychiatry trainees who are evaluated for teaching ability must learn to communicate medical knowledge to child caregivers, including professionals and parents from different cultures. Finally, many children requiring mental health care in the United States come from immigrant populations from El Salvador and other Latin American countries. Understanding cultural elements of ADHD in El Salvador will enhance their capacity to treat these children.

Methods: A child and adolescent psychiatry fellow gives remote lectures on ADHD to PCPs in San Salvador, with a Salvadoran physician as collaborator and translator. Extended discussion periods serve not only to elaborate the content of the lecture, but also as focus groups to consider cultural differences in perceptions and treatment preferences of ADHD. Informational TikTok videos are made as a result of this insight into Salvadoran perspectives on ADHD.

Results: The child and adolescent psychiatry trainee practices teaching skills of lecturing, leading discussion, and working with a translator. He delivers helpful scientific information to PCPs, evaluates his previous understanding of this disorder, and collaborates in the creation of user-friendly informational videos on ADHD.

Conclusions: This presentation demonstrates learning teaching skills in child and adolescent psychiatry, identifying and challenging Western bias in the diagnosis and intervention of ADHD, and illustrates innovative methods of communicating mental health knowledge to child caregivers in El Salvador. ADHD, CUL

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J Am Acad Child Adolesc Psychiatry. 2021;60:S101.

68.3 LONG-TERM OUTCOME OF PARENT-CHILD INTERACTION THERAPY ON ADHD SYMPTONS.

Bussing R, Eyberg S, Guzick A, et al.

Objectives: This study examines the long-term effects of Parent-Child Interaction Therapy (PCIT) on female and male caregiver ratings of ADHD symptoms, as well as on observational interaction measures in preschoolers randomized to individual or group PCIT.

Methods: Data from 128 children participating in treatment were examined (mean age at study entry = 4.8 years). Children with ADHD, half of whom also met the criteria for disruptive behavior disorder (DBD), were randomized to group or individual PCIT and outcomes were assessed posttreatment as well as 1 and 2 years after treatment completion. Pretreatment and posttreatment measures included: 1) parent rating scales, like the Child Behavior Checklist (CBCL) Externalizing Problems Subscale; the SNAP-IV; the Eyberg Child Behavior Inventory (ECBI) Intensity Score; and the Columbia Impairment Scale (CIS); and 2) observations of the parent-child interaction using the Dyadic Parent-Child Interaction Coding System (DPICS).

Results: PCIT results in clinically and statistically significant improvements in ADHD symptoms and reductions in impairment as rated by female and male caregivers. There are no differences in outcomes at posttreatment between children with and without DBD, or between those in individual or group PCIT. For both PCIT treatment formats, improvements are maintained at 1- and 2-year follow-up on all caregiver measures, including ADHD-specific ratings, externalizing behavior ratings, CIS scores, and observational measures of parent-child interactions.

Conclusions: ADHD symptom reduction is not an original goal of PCIT intervention, yet significant improvements occur in ADHD symptoms based on both caregivers reports and observational data. These findings suggest that PCIT may be an effective treatment for the behavioral and attentional symptoms of

ADHD in preschoolers with or without DBD and that it merits further study as a promising intervention for preschoolers with ADHD. ADHD, PAT, RCT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S151.

5.5 DIFFERENCES IN PARENTAL AND PERCEIVED STRESS IN PARENTS OF CHILDREN WITH AND WITHOUT BEHAVIORAL DISORDER DURING THE COVID-19 PANDEMIC IN THE MEXICAN POPULATION.

Corral-Frias M, Grijalva-Mart+¡nez A, Corral-Frias N, et al.

Objectives: Our objective was to conduct a cross-sectional study using surveys to determine if parents of children with behavior problems will report a higher level of stress during the COVID-19 pandemic.

Methods: Participants included both parents of children (6-17 years old) who have been diagnosed with behavioral disorders such as ADHD, conduct disorder, and ODD, as well as parents of children who have not been diagnosed with any behavioral disorder. The sample included parents seeking treatment in our institution and parents who self-reported the child's diagnosis. Participants were separated into 3 groups: children with diagnosis (n = 58), children with no diagnosis (n = 105), and those who were not sure (n = 12). The previously Spanish-validated Perceived and Parental Stress was administered online to assess differences in stress among participants. The questionnaire also included demographic characteristics, parent and children psychopathological history, and quarantine situation. The Shapiro-Wilk Test was utilized considering the nonnormal distribution of the data.

Results: There were significant differences between groups in both perceived stress (H[3] = 12.67; p = 0.005) and parental stress (H[3] = 20.49; p < 0.001). Post hoc analyses showed that these differences were only significant between the no diagnosis (Median = 25) and diagnosis (Median = 27) groups for perceived stress (adjusted p = 0.024). Conversely, for parental stress, post hoc analyses demonstrated that these differences were significant between the no diagnosis (Median = 35) and diagnosis (Median = 38) groups for perceived stress (adjusted p = 0.026) and between the no diagnosis (Median = 25) and not sure (Median = 28) groups for perceived stress (adjusted p = 0.004).

Conclusions: Our results show that parents with children who have been diagnosed with behavioral disorders report higher levels of perceived and parental stress. Exploratory analyses suggest that parents who report being unsure of their child's diagnosis reported even higher levels of parental stress. These results should be taken with caution given the small sample size. The present research is significant because children with behavioral problems and their parents continue to represent a vulnerable population, even when considering the overall high report of stress among study participants. ADHD, STRESS, PAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S87.

59.1 ADHD IN AUTISM SPECTRUM DISORDER.

Wilens T.

Objectives: The objective of this presentation is to assess the evidence for the comorbidity, impact, and treatment of ADHD in populations with autism spectrum disorder (ASD).

Methods: A database search of peer-reviewed literature was conducted. Selected studies examining the prevalence, characteristics, and impact of ASD in ADHD were reviewed. Controlled trials published in English with sample sizes 10 examining the safety and efficacy of anti-ADHD medication in populations with ASD were analyzed. Data were extracted on relevant variables of study design, demographics, associated psychopathology, medication dose, efficacy, and tolerability.

Results: Because of the previous prohibition of the diagnosis of ASD and ADHD, most studies are contemporary. Up to three-quarters of young people with ASD have ADHD. Conversely, ASD traits are noted in up to 30% of youth with ADHD and are associated with poorer socialization and functioning. Nine controlled trials met the criteria: 5 with methylphenidate, 3 with atomoxetine, and 1 with guanfacine. Sample sizes ranged from 10 to 128, with a total (N) of 430 children. In all of the trials, the treatment response was significantly superior to placebo. However, almost all trials assessed only hyperactivity, and most included only participants with intellectual disability with high levels of irritability. While the response on hyperactivity for methylphenidate and atomoxetine was less than that observed in the neurotypical population, the response for guanfacine surpassed the results observed in neurotypical populations. More traditional

response rates were noted in patients with normal IQ. Treatment-emergent mood effects were associated with methylphenidate and guanfacine treatments. Worse treatment outcomes were associated with lower intellectual capability compared to higher IQs, for both efficacy and adverse outcomes.
Conclusions: There is an important bidirectional overlap between ADHD and ASD. Individuals with both disorders manifest more functional impairment necessitating treatment. There is a scarcity of controlled trials examining ADHD treatments in populations with ASD, particularly in intellectually capable individuals with ASD and in adults. Response to ADHD medications in ASD appears similar to neurotypical ADHD samples with higher IQs; however, it was adversely moderated by the presence of intellectual disability and mood lability. ASD, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S185.
13.1 CELIAC DISEASE ASSOCIATED WITH MENTAL ILLNESS IN CHILDREN AND CORRELATED SCREENING PRACTICES.
Anderson S, McKinnis E, Dyer B, et al.
Objectives: Celiac disease (CD) and non-celiac gluten sensitivity (NCGS) are associated autoimmune manifestations that can lead to psychiatric and neurological disorders, as well as treatment resistance. Mental illness is often the primary expression of CD or NCGS. Up to 85% of patients with histologically proven CD have no gastrointestinal symptoms. Untreated CD can lead to serious behavioral disorders, including a higher suicide risk. Child and adolescent psychiatrists treat such cases daily but may fail to screen for and/or recognize the association. We examine the literature on mental illness associated with CD and NCGS in the pediatric population to inform screening in psychiatry.
Methods: A literature search using PubMed, Cochrane, and Google Scholar for CD or NCGS-related psychiatric comorbidities in the pediatric population aged 2 to 22 years using the terms psychiatric, celiac, gluten, child OR adolescent OR pediatric, and mental illness to include depression, anxiety, mood disorders, attention deficit hyperactivity disorder, psychosis, and "eating disorders" located 30 relevant articles (19 cohort studies, 2 observational studies, 2 case-control studies, 4 case reports, and 3 systematic reviews).
Results: Mental illness symptoms often precede a diagnosis of CD in children; however, we found only 2 articles on screening practices, limited to eating disorders. One study, a small clinical trial, recommended screening patients with severe anorexia nervosa. Another study, a retrospective chart review, surveyed emergency department visits for patients with eating disorders and did not recommend screening for CD. Conversely, a 2019 systematic review stressed the importance of screening for CD in outpatient psychiatric clinics, because the overall prevalence of psychiatric comorbidities is higher in those with CD or NCGS.
Conclusions: CD is a common childhood autoimmune disease, with 1 in 100 children being affected. At least 1 out of 3 cases of CD are undiagnosed, suggesting a higher prevalence of mental health disorders linked to CD than expected. More studies are needed to inform screening practices for CD and NCGS in children and adolescents with mental illness. Understanding this association aids clinicians in diagnostic and treatment clarity and could result in mental illness symptom remission with the gluten-free diet. CAM, PSP, PYI

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J Am Acad Child Adolesc Psychiatry. 2021;60:S269.
7.2 MULTINUTRIENT EFFECT ON PARENT-SELECTED TARGET PROBLEMS IN ADHD AND EMOTIONAL DYSREGULATION.
Arnold LE, Tost G, Srikanth P, et al.
Objectives: The objective of this presentation is to examine the effect of broad-spectrum multinutrients on symptoms of specific concern to each parent of a child with ADHD and emotional dysregulation.
Methods: In the Micronutrients for ADHD in Youth (MADDY) RCT, 126 children aged 6 to 12 years were randomized to 8 weeks of a 36-ingredient multinutrient with all the known vitamins and essential minerals (n = 71) vs matched placebo (n = 55). A secondary measure was the blinded clinician rating of change in quantified parent-selected target problems (PTPs). The parent was asked to describe the 1 or 2 problems s/he was most concerned about (most parents nominated 2), and these were quantified with structured questions regarding frequency, duration, cumulative minutes/hours per day, intensity (scale of 1-10), and consequences. At subsequent visits (weeks 4 and 8), PTPs were requantified. Blinded psychiatrists who had

no contact with the families rated each problem at weeks 4 and 8 relative to baseline quantification on a 9-point scale (1 = problem gone; 2 = much improved; 3 = definitely improved; 4 = minimally improved; 5 = no change; and 6-9 = worse). A 2-sample t test compared outcome by treatment at 4 and 8 weeks.
Results: At 4 weeks, treatments were not significantly different. At 8 weeks, the average of the first-nominated PTPs was significantly better (p = 0.02) for micronutrients (3.73) than for placebo (4.23). The average of both PTPs was also significantly better (p = 0.05) for micronutrients (3.85) than for placebo (4.25). Thus, the multinutrient average was between minimally improved and definitely improved, while the placebo was between no change and minimally improved. When the PTPs were classified into 9 categories, the most numerous were inattention, hyperactivity/impulsivity, and emotional dysregulation. All 3 of these tended to favor multinutrients over placebo, but only emotional dysregulation was significant (3.2 vs 3.8, p = 0.05).
Conclusions: In this double-blinded assessment, broad-spectrum multinutrients significantly improved the problems of most concern to parents of children with ADHD and emotional dysregulation, especially mood and emotional regulation problems. ADHD, RI, TREAT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S152.
5.9 Single-Dose Pharmacokinetics of Serdexmethylphenidate/d-Methylphenidate Capsules in Children and Adolescents With ADHD and Healthy Adults: An Evaluation of Age and Body Weight.
Braeckman R, Guenther S, Barrett A, et al.
Background: Serdexmethylphenidate (SDX)/d-methylphenidate (d-MPH) capsules are an approved ADHD product designed to provide rapid onset and extended duration of symptom improvement. SDX/d-MPH capsules contain 70% SDX, a prodrug of d-MPH that is gradually converted to d-MPH, and 30% d-MPH, which provides rapid exposure to d-MPH after administration.
Objectives: The objectives of these studies were to: 1) in study 1, examine the single-dose (SD) pharmacokinetics (PK) of SDX/d-MPH and determine the effect of body weight (BW) on the PK properties in children and adolescents with ADHD; and 2) in study 2, examine SD PK of SDX/d-MPH in healthy adults under fed conditions.
Methods: Both studies were phase 1, open-label, SD oral administration of SDX/d-MPH capsules. After a standardized meal in study 1, subjects (aged 6-17 years, N = 30) received treatments stratified into 3 age and 2 dose groups: 6- to 8-year-olds (Cohort 1, n = 10) received 26.1/5.2 mg, 9- to 12-year-olds (Cohort 2, n = 10) received 52.3/10.4 mg, and 13- to 17-year-olds (Cohort 3) received either 26.1/5.2 mg (n = 5) or 52.3/10.4 mg (n = 5). Blood samples for PK were collected predose and at multiple time points postdose. In study 2, adults (N = 28) received SDX/d-MPH 52.3/10.4 mg after a high-fat meal. Results: In study 1, dose-normalized (to the 52.3/10.4 mg dose) peak and overall exposure to d-MPH was highest in Cohort 1 (Cmax = 34.4 ng/mL; AUC0-24 = 362.0 h*ng/mL), followed by Cohort 2 (Cmax = 25.9 ng/mL; AUC0-24 = 294.1 h*ng/mL), and lowest in Cohort 3 (Cmax = 17.8 ng/mL and 14.0 ng/mL; AUC0-24 = 195.0 ng/mL and 171.1 h*ng/mL, for the low and high doses, respectively). When normalized for both dose and BW, mean Cmax and AUC0-24 values were similar across cohorts. Clearance (CL/F) values were lower in Cohorts 1 and 2 (96.85 and 97.44 L/h, respectively) than Cohort 3 (170.3 L/h for low dose and 172.3 L/h for high dose). When adjusted for BW differences, CL/F values were similar. A nonlinear regression model indicated a moderate correlation (R2 = 0.628) between d-MPH CL/F and BW. In adults (study 2), the shape of the PK curve was comparable to those obtained in children and adolescents when administered under the same conditions.
Conclusions: BW is an appropriate scaling factor for d-MPH exposure after oral SDX/d-MPH dosing in children, adolescents, and adults. ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S156.
5.20 Clinical and Neuropsychological Characteristics of Child and Adolescent Offspring of Patients With Schizophrenia: The Role of ADHD.
De La Serna E, Camprodon-Boadas P, Sugranyes G, et al.
Objectives: The present study is part of the Bipolar and Schizophrenia Young Offspring Study (BASYS). In the current study, we analyze the clinical and cognitive characteristics of a sample of child and adolescent

offspring of patients with schizophrenia (SZoff) diagnosed with ADHD (SZoff-ADHD) compared to a sample of children with ADHD without a family history of psychotic disorders and a sample of healthy controls (HCs).
Methods: A sample consisted of 22 SZoff-ADHD children, 15 children with ADHD with no familial history of psychotic disorders, and 40 HCs between 6 and 17 years old. All subjects completed clinical and neuropsychological assessments. The clinical assessment included: the K-SADS, the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms (SIPS/SOPS), and the Global Assessment Functioning (GAF). The neuropsychological assessment included the following areas: intelligence, working memory, processing speed, verbal memory, and executive functions.
Results: Significant differences between groups were found in socioeconomic status, which was lower in the SZoff-ADHD group than in the other 2 groups ($F = 15.886$; $p < 0.001$). Moreover, the SZoff-ADHD group also showed a higher percentage of males (90.9%) compared with the ADHD group (62.5%) and the HCs (45%) ($F = 12.647$; $p = 0.002$). Regarding clinical assessments, the SZoff-ADHD group obtained higher scores than the HC group on all SIPS/SOPS subscales and lower scores in the GAF. The ADHD group obtained significantly higher scores than the HC group in disorganized and total symptoms of the SOPS and lower scores on the GAF. Significant differences were detected between the SZoff-ADHD and ADHD groups in the positive, disorganized, and total subscales of the SOPS, whereas the SZoff-ADHD group obtained higher scores than the ADHD group. Regarding cognition, the SZoff-ADHD group scored lower than the HC group in intelligence, working memory, processing speed, and verbal memory, while the ADHD group only obtained lower scores than the HC group in verbal memory. The SZoff-ADHD group scored lower than the ADHD group in intelligence and working memory.
Conclusions: Compared with the HC group, the SZoff-ADHD group displayed more subclinical psychotic symptoms and worse psychosocial functioning. The ADHD group showed an intermediate pattern between the SZoff-ADHD and HC groups. ADHD, SZ, BRD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S269.

7.3 SAFETY LABS AND NUTRIENT-LEVEL CHANGES IN CHILDREN WITH ADHD TAKING A MULTINUTRIENT SUPPLEMENT.

Hughes AJ, Gracious B, Srikanth P, et al.

Objectives: This session aims to examine the safety and nutrient-level effects of supplementation with multinutrients active vs placebo in children with ADHD and emotional dysregulation.
Methods: In the multisite Micronutrients for ADHD in Youth (MADDY) randomized controlled trial, blood and urine samples from US participants (active n = 50; placebo n = 38) were collected at baseline and week 8 (end of randomized controlled trial). Safety labs included complete blood count, metabolic profile, iron panel, and urinalysis. Research labs obtained at the Oregon Health & Science University (OHSU) site only (active n = 26; placebo n = 20) included an iron panel; vitamins B6, B12, and 25-OH D; and homocysteine. Parent reports on the 44-question Pediatric Adverse Events Rating Scale (PAERS) detected adverse events (AEs). Analyses included within- and between-group changes.
Results: Between-group comparisons of blood safety labs revealed significant changes for 3 liver function tests active vs placebo, respectively: AST (3.70; 2.93 U/L; $p < 0.001$), ALT (7.33; 2.31 U/L; $p < 0.001$), and ALP (ΓÇô13.67; 5.72 U/L; $p < 0.01$). No within-group changes reached clinical significance. Creatinine had a statistically, but not clinically, significant within-group increase over time of 0.02 mg/dL ($p < 0.05$) in the active group. Labs showed significant between-group differences for vitamins B6, B12, and D (all $p < 0.001$), and homocysteine ($p = 0.005$), with vitamin increases in the active group over time (vitamin B6 = 327.1 nmol/L; vitamin B12 = 631.6 pg/mL; vitamin D = 7.2 ng/mL) and no changes for placebo. Homocysteine decreased 0.5 mmol/L for active, with no change for placebo. No changes were found for urine. No AEs is possibly attributable to the treatment being significantly different between groups ($p = 0.13$): 32% of the active group and 45% of the placebo group reported at least 1 AE.
Conclusions: Multinutrient supplementation increased blood vitamin levels and decreased homocysteine, compared to placebo. The remaining labs were within normal limits, with no significant changes or clinical concerns. These results replicate previous randomized controlled trial findings and suggest that multinutrient supplementation is generally safe, while raising vitamin levels and reducing oxidative stress. ADHD, TREAT, IMD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S151.

5.4 DBT-BASED SKILLS TRAINING FOR ADOLESCENTS WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.

Meyer J, Ramklint M, Hallerb+ñck M, et al.

Objectives: The objective of this presentation is to evaluate the effectiveness and acceptance of an age-adapted structured skills training group (SSTG) for adolescents with ADHD in a clinical setting.

Methods: Adolescents (n = 184, ages 15-18 years) with a diagnosis of ADHD were randomly assigned to either the SSTG, a group treatment based on DBT, or an active control group based on psychoeducation. Symptoms of ADHD, behavioral and emotional problems, functional impairment, and health-related outcomes were assessed with self-ratings and parental ratings 2 weeks before, 2 weeks after, and 6 months after treatment. All participants who completed the pretreatment measurements (n = 164) were included in the main analyses, which were conducted using a linear mixed model, adjusted for major changes in ADHD medication.

Results: Significant decreases in ADHD symptoms, functional impairment, and behavioral and emotional problems were observed in both groups (d = 0.25 to 0.69). However, no group differences were found for any of the study outcomes (d = 0.01 to 0.36). A majority of the participants in both groups reported that they had increased their knowledge about ADHD, improved their ability to manage problems related to the diagnosis, and would recommend the treatment to others.

Conclusions: Although the SSTG seems to be an acceptable treatment for adolescents with ADHD, it was not proved to be more effective or more acceptable than psychoeducation. The lack of group differences and the rather modest symptom decrease indicate that further adaption of the SSTG should be considered, including involvement of parents and more extensive practice. The study population was rather heterogenous, and more research is needed to explore if the SSTG is more beneficial for certain subgroups of adolescents with ADHD. In addition, the use of an active control group precluded an evaluation of the absolute effects of the SSTG; therefore, further studies are needed. ADOL, RCT, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S157.

5.23 UNDERSTANDING PARENT-CHILD COMMUNICATION IN THE CONTEXT OF ADHD.

Duncan A, Yamin E, Nandi S, et al.

Objectives: Adolescents with ADHD are at higher risk for health risk behaviors and adverse consequences. Their parents, in turn, experience greater parenting stress and lower quality of life. The objective of this study is to conduct a needs assessment of parent-adolescent communication (PAC) in this population, which will in turn be used to develop a parenting skills class that includes motivational interviewing (MI) skills to address the challenges in PAC in a developmentally appropriate way.

Methods: We recruited 22 parents and 17 adolescents through outpatient clinics in an urban safety net health system. Participants engaged in interviews about PAC and a health risk discussion. In addition, they answered surveys covering demographic information, parenting stress, parenting styles, adolescent symptom burden, and MI.

Results: There are many notable sample characteristics. Twenty-seven percent of parents had taken a parenting class for children with ADHD or for divorced parents in the past; 87% of parents reported that they were having a close and supportive relationship with their adolescents; and 50% of parents felt that a parenting class should target PAC. Other common concerns included coping with mental health problems, behavioral issues, and how to provide support for the adolescents. Fifty-five percent of parents are interested or extremely interested in taking a parenting class designed for the parents of teenagers with ADHD. The Helpful Responses Questionnaire was scored on 3 dimensions of MI (MI Spirit [SP], MI Skills [MI], and promoting change talk [CT]) according to MI adherent responses (1), neutral responses (0), or MI nonadherent responses of persuasion and confrontation (1). The average scores were 0.67 for SP, 0.79 for MI, and 0.55 for CT. Parents scored an average of 4.6 out of 16 on the MI Knowledge and Attitudes Test (MIKAT). The majority of the parents had an involved and positive parenting style as measured by the Alabama Parenting Questionnaire.

Conclusions: Parents expressed a high level of interest in taking a parenting class that targets PAC. The parents have a low level of knowledge of or alliance with MI, despite positive and involved styles. Future directions include qualitative analysis of the parent and adolescent interviews to guide the development of a parenting class including MI skills for parents. ADHD, PAT, ADOL

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J Am Acad Child Adolesc Psychiatry. 2021;60:S46-S47.

31.1 VARIABLE PATTERNS OF REMISSION FROM ADHD IN THE MULTIMODAL TREATMENT STUDY OF ADHD (MTA).

Sibley MH.

Objectives: It is estimated that childhood ADHD remits by adulthood in approximately 50% of cases; however, this conclusion is typically based on single endpoints, failing to consider longitudinal patterns of ADHD expression. We investigated the extent to which children with ADHD experience recovery and variable patterns of remission by adulthood.

Methods: Children with ADHD (N = 558) in the MTA study were administered 8 assessments from 2-year (M age = 10.44 years) to 16-year follow-up (AI age = 25.12 years). We identified participants with fully remitted, partially remitted, and persistent ADHD at each time point based on parent, teacher, and self-reports of ADHD symptoms and impairment, treatment utilization, and substance use and mental disorders. Longitudinal patterns of remission and persistence were identified that considered context and timing.

Results: Approximately 30% of children with ADHD experienced full remission at some point during the 14-year follow-up period; however, a majority (60% of these) experienced recurrence of ADHD after the initial period of remission. Only 9% of the sample demonstrated recovery from ADHD by study endpoint, and only 10.8% demonstrated stable ADHD persistence across study time points. Instead, most participants with ADHD (64%) demonstrated fluctuating periods of persistence and remission over time.

Conclusions: The MTA findings challenge the notion that approximately 50% of children with ADHD outgrow the disorder by adulthood. Most cases demonstrated fluctuating symptoms that may be environmentally modulated. Although 9% of children with ADHD continued to struggle with residual ADHD through young adulthood, intermittent periods of remission can be expected in most cases. We will share visual depiction of longitudinal and cross-sectional patterns of symptom remission, recovery, and persistence in the MTA, as well as case examples for patterns of recovery. These findings emphasize that childhood-onset ADHD is a chronic but waxing/waning disorder with periods of full remission that are more often temporary than sustained. ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S145.

2.2 ACCELEROMETRY-BASED CHARACTERISTICS ASSOCIATED WITH AGGRESSIVE BEHAVIOR IN CHILDREN WITH ADHD.

Park C, Mishra R, Najafi B, et al.

Objectives: Children with ADHD often display aggression. Ascertaining aggressive episodes in an objective manner reduces the need for relying on informants and maximizes the opportunities for targeted interventions. As such, this study sought to examine whether physical activity (PA), quantified using a wearable sensor, can reliably predict aggressive behavior in children with ADHD.

Methods: Children diagnosed with ADHD (n = 11; aged 8.5 -¦ 1.0 years; 27% female; BMI: 16.7 -¦ 1.5 kg/m2) participated. A wearable sensor (ActiGraph GT3X+, Pensacola, FL, USA) attached to the waist was used to remotely monitor PA per hour for 7 days. Parents completed the Retrospective-Modified Overt Aggression Scale (R-MOAS). Five PA variables, including light PA (%), moderate PA (%), MVPA (%) (ie, averaged sum of moderate and vigorous PA), steps per minute, and average steps, were extracted from the wearable sensor using ActiLife (Pensacola, FL, USA). To compare PA level between hours over the no-aggression episode and aggressive episode, and at 1, 2, 3, and 4 hours before the aggressive episode, all PA variables were assessed statistically using generalized estimating equations analysis.

Results: All participants exhibited aggressive outbursts at least once (mean number of outbursts = 6.3 -¦ 7.3). All PA variables were significantly higher during the aggressive outbursts compared to other times when no aggression occurred ($p < 0.0001$). Multiple pairwise comparisons revealed that all PA variables at 1 hour

and 2 hours prior to the aggressive outbursts were significantly higher compared to times outside the aggressive outbursts but no difference to times when an outburst was occurring.
Conclusions: Our data suggest that tracking PA variables may enable identifying an aggressive outburst with a 2-hour lead time. Future studies are needed to further validate these findings and to examine their potential to improve treatment of aggression. ADHD, AGG

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J Am Acad Child Adolesc Psychiatry. 2021;60:S307.

32.1 NEUROPSYCHIOLOGICAL PATTERNS ACROSS DISTINCT PSYCHOPHARMACOLOGY PROFILES IN THE LONGITUDINAL ASSESSMENT OF MANIC SYMPTOMS (LAMS) STUDY.

Frazier T.

Objectives: The primary objective is to describe neuropsychological patterns across empirically identified psychopathology profiles from the Longitudinal Assessment of Manic Symptoms (LAMS) study. The secondary aim was to examine relationships between psychopathology domains and neuropsychological measures.
Methods: Distinct psychopathology classes previously identified using latent profile analysis were scored for this study. A set of 13 neuropsychological measures evaluating processes relevant to ADHD and mood disorder were selected from the LAMS battery. Measures assessed reaction time, sustained attention, and impulsive responding to neutral stimuli (standard CPT) and to affectively laden words (affective go/no-go), set shifting (intra/extra-dimensional shift task), long-term verbal memory (list learning free recall), and affective prosody recognition. To evaluate patterns across latent profiles, a series of univariate ANOVAs were computed with latent classes (psychopathology profiles) as the independent variable and neuropsychological measures as the dependent variables in separate analyses. Bivariate correlations examined relationships between psychopathology dimensions and neuropsychological measures.
Results: Latent profiles showed different reaction times to positively and negatively valenced words ($p = 0.020$ and $p = 0.006$, respectively) and to prosody recognition ($p = 0.034$). Profiles with mild symptoms and significant depression showed slower response times to emotional words, while profiles with significant hyperactivity/impulsivity, aggression with impulsivity and reactivity, and severe mood symptoms showed faster response speeds to emotional words. Prosody accuracy also differed across classes ($p = 0.034$); accuracy was higher in children with moderate hyperactivity/impulsivity and lower in children with aggression with impulsivity and reactivity with severe mood symptoms. Specific bivariate relationships between psychopathology domains and neuropsychological measures were identified.
Conclusions: Psychopathology profiles show distinct neuropsychological patterns that highlight cognitive contributions to these patterns. These profiles and their neuropsychological correlates may be helpful in tailoring interventions and, in some cases, for tracking treatment response. IMD, NEPSYC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S305.

30.4 UNDERLYNG COGNITIVE COMPONENTS RESPOND TO NEUROFEEDBACK FOR ADHD AND MODERATE CLINICAL OUTCOME.

Ging-Jehli N, Arnold LE, deBeus R, et al.

Objectives: The objective of this presentation is to explore whether cognitive characteristics improve with neurofeedback treatment (NF) for childhood ADHD and whether they moderate clinical behavioral outcomes.
Methods: In an RCT, 133 children aged 7 to 10 years with ADHD received either active NF (N = 78) or sham NF (N = 55) of equal appearance, intensity, and frequency, and performed the Integrated Visual and Auditory Continuous Performance Test (IVA2-CPT) at baseline, midtreatment, and end of treatment. A diffusion decision model analysis (DDM) applied to the IVA2-CPT data quantified cognitive components deficient in ADHD, namely efficiency and context sensitivity of the processes involved in integrating stimulus information. We explored whether these cognitive components improved with NF and whether the baseline efficiency component and/or context sensitivity component moderated the improvement in parent- and teacher-rated inattention (primary clinical outcome).
Results: 1) Children who received active NF improved significantly more in both efficiency of information integration ($p = 0.044$) and context sensitivity ($p = 0.002$) than those with sham NF. 2) Improvement in

efficiency from baseline to midtreatment was positively associated with improvement in primary clinical outcome at treatment end (+¦standardized = 0.189; p = 0.036). 3) Baseline cognitive characteristics moderated the primary clinical outcome: the interaction of the baseline efficiency and context sensitivity components moderated the effects of NF on the improvement in inattention (p = 0.006). Children with either the most or least severe deficits (but not those with moderate deficits) in these 2 cognitive components benefitted from active NF: they showed moderate improvement in inattention (Cohen's d = 0.59), while those with similar cognitive components assigned to sham NF showed mild deterioration in attention (Cohen's d = 0.21).
Conclusions: NF for ADHD improves efficiency and context sensitivity of information processing and may be clinically effective for children with either severely deficient or intact cognitive components involved in information processing. Pretreatment cognitive testing, together with computational modeling, may provide a valuable tool in the selection of effective treatments. ADHD, COG, CAM

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J Am Acad Child Adolesc Psychiatry. 2021;60:S285.
18.3 MINDFULNESS-BASED ADHD TREATMENT FOR CHILDREN: A PILOT FEASIBILITY STUDY.
Saunders DC.
Objectives: ADHD is a neurodevelopmental disorder associated with myriad adverse outcomes. Medication is known to be effective but is limited by side effects. Mindfulness improves attention in healthy adults, as well as adults with ADHD, and 2 small studies in teenagers with ADHD have shown preliminary evidence of efficacy. To our knowledge, however, there are no standardized mindfulness interventions for children with ADHD, nor has it been studied in a rigorous research setting in children.
Methods: We developed a novel mindfulness-based intervention for children with ADHD-Mindfulness-Based ADHD Treatment for Children (MBAT-C)-and conducted a single-arm pilot study (N = 10) to: 1) evaluate acceptability and feasibility of MBAT-C as measured by attendance, retention, homework completion, and engagement; and 2) test for preliminary efficacy on multiple objective and subjective indices of ADHD symptoms, including attention, behavior, executive function, and clinical severity by self- and parent report, and neuropsychiatric assessment.
Results: For Aim 1, multiple indices of feasibility and acceptability exceeded pretrial benchmarks, including attendance (65.9%), retention (75%), homework completion (66.1%), and engagement. For Aim 2, multiple subjective and objective indices of ADHD symptoms showed improvement, including: ADHD symptoms measured by the ADHD Rating Scale; attention, problem behaviors, and anxiety measured by the Child Behavior Checklist; and working memory as assessed on the NIH Toolbox List Sorting Working Memory Test.
Conclusions: These data suggest that MBAT-C is a feasible and acceptable intervention for children with ADHD and that it may be efficacious. Further study is warranted to assess efficacy. The next phase of this study, which is presently ongoing, is a 3-arm, randomized controlled trial comparing MBAT-C to medication and a combined intervention. ADHD, RCT, R

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J Am Acad Child Adolesc Psychiatry. 2021;60:S290.
21.2 MULTIMETHOD INVESTIGATION OF THE NEUROBIOLOGICAL BASIS OF ADHD SYMPTOMATOLOGY IN CHILDREN AGES 9 AND 10: BASELINE DATA FROM THE ABCD STUDY.
Owens M.
Objectives: ADHD is associated with numerous neurocognitive deficits, including poor working memory and difficulty inhibiting undesirable behaviors that cause academic and behavioral problems in children. Prior work has attempted to determine how these differences are instantiated in the structure and function of the brain, but much of that work has been done in small samples, focused on older adolescents or adults, and used statistical approaches that were not robust to model overfitting.
Methods: The current study used cross-validated elastic net regression to predict a continuous measure of ADHD symptomatology using brain morphometry and activation during tasks of working memory, inhibitory control, and reward processing, with separate models for each MRI measure.

Results: The best model using activation during the working memory task to predict ADHD symptomatology had an out-of-sample R2 of 2% and was robust to residualizing the effects of age, sex, race, parental income and education, handedness, pubertal status, and internalizing symptoms from ADHD symptomatology. This model used reduced activation in task-positive regions and reduced deactivation in task-negative regions to predict ADHD symptomatology. The best model with morphometry alone predicted ADHD symptomatology with an R2 of 1%, but this effect dissipated when including covariates. The inhibitory control and reward tasks did not yield generalizable models.
Conclusions: In summary, these analyses show, with a large and well-characterized sample, that the brain correlates of ADHD symptomatology are captured best by brain morphometry and activation during a working memory task. ADHD, NEPSYC, IMAGS

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J Am Acad Child Adolesc Psychiatry. 2021;60:S124.

2.5 PSYCHOPHARMACOLOGICAL TREATMENT OF COMORBID PSYCHIATRIC DISORDERS IN PATIENTS WITH ADHD.

Pliszka SR.

Objectives: Half or more of patients with ADHD have a comorbid mental health disorder. Clinicians must be able to treat these wide-ranging conditions in addition to treating the ADHD in order to obtain an optimal therapeutic outcome. The presentation will focus on several major comorbidities: ODD, DMDD and aggression, tic disorders, and mood and anxiety disorders.
Methods: This presentation will review literature, clinical presentation, and multiple studies examining ADHD comorbid with ODD, DMDD, tic disorders, and affective and anxiety disorders. A review of treatment sequencing and algorithms will be emphasized.
Results: An evidence-based, transdiagnostic approach will be used, focusing on optimal control of symptoms of aggression, depression, or anxiety across DSM-5 categories. Several cases will be presented. The presentation will distinguish when psychosocial or psychopharmacological approaches should be used to treat ODD in the presence of ADHD. The differential diagnosis of impulsive aggression/emotional dysregulation in ADHD is important in dictating the selection of treatments. The talk will describe and make use of a stepwise psychopharmacological approach to treating impulsive aggression/emotional dysregulation in ADHD. It will describe difficulties in diagnosing depression or anxiety in the presence of ADHD and discuss the use of antidepressants concurrently with ADHD medication. Finally, the talk will discuss the treatment of ADHD and PTSD when these conditions are comorbid.
Conclusions: In conclusion, ADHD plus one or more comorbid disorders are commonly presented in child and adolescent psychiatry practices. Becoming comfortable with managing and treating ADHD in the context of other disorders ensures that children will have optimal treatment of their presenting symptoms to ensure improved functioning at school, at home, and with peers. ADHD, CM, PPC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S285.

18.2 ASSOCIATION OF PRENATAL ACETAMINOPHEN WITH CHILD ADHD IS MEDIATED BY FUNCTIONAL BAIN CONNECTIVITY BUT NOT BIRTH OUTCOMES.

Baker B.

Objectives: This presentation aims to evaluate associations of prenatal acetaminophen exposure measured in meconium with child ADHD, and to test birth outcomes and functional brain connectivity as potential mediators.
Methods: Mothers were enrolled into this birth cohort study in Sherbrooke, Quebec, Canada at their first prenatal care visit or delivery. Acetaminophen was measured in the meconium. A physician diagnosis of ADHD was determined at follow-up when children were 6 to 7 years old or from medical records. When children were 9 to 11 years old, resting-state brain connectivity was assessed with MRI, and attention problems and hyperactivity were assessed with the Behavioral Assessment System for Children Parent Report Scale. Associations between the meconium, acetaminophen, and outcomes were estimated with linear, logistic, and cox proportional hazards models. Birth outcomes and resting-state brain connectivity were tested as mediators of the association between prenatal acetaminophen exposure and ADHD.

Results: Among 345 children included in the analysis, acetaminophen was detected in 199 meconium samples (57.7%), and ADHD was diagnosed in 33 children (9.6%). Detection of acetaminophen in meconium was associated with increased odds of ADHD (OR = 2.43; 95% CI, 1.41-4.21). Prenatal acetaminophen was associated with negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices, which mediated an indirect effect on increased child hyperactivity (14% mediation; 95% CI, 1-26). Although prenatal acetaminophen exposure was associated with decreased birthweight by 128 grams (+¦ = 128; 95% CI, 221 to 36), and 22% increased weekly hazard of delivery (hazard ratio = 1.22; 95% CI, 1.06-1.40), birth outcomes did not mediate an effect on ADHD.
Conclusions: Although unobserved confounding and confounding by indication are possible, these results warrant further investigation into adverse perinatal effects of prenatal acetaminophen exposure. ADHD, NEURODEV, EPI

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J Am Acad Child Adolesc Psychiatry. 2021;60:S47.

31.3 COMPARISON OF ADULT OUTCOME IN PEOPLE WITH CHILDHOOD ADHD FROM CONTROLLED PROSPECTIVE FOLLOW-UP STUDIES VS SCANDINAVIAN REGISTRY STUDIES.

Hechtman L.

Objectives: This presentation aims to compare ADHD persistence, comorbidity, educational, occupational, substance use, driving, and justice involvement in adult outcomes of children diagnosed with ADHD as described in controlled prospective follow-up studies vs Scandinavian registry studies.
Methods: Findings from a number of controlled prospective follow-up studies of children with ADHD followed into adulthood will be compared to the Scandinavian registry studies from Denmark and Norway. The prospective follow-up studies include the Montreal, New York, Milwaukee, Pittsburgh, Massachusetts General, Berkley, and multisite MTA. Registry studies have larger samples, can generate larger matched-control groups, and have little attrition or missing data. However, past patients who are no longer affected and who are functioning well are rarely identified and the point of focus.
Results: Both types of studies show that some adults with ADHD continue to have emotional, educational, occupational, substance, driving, and justice problems in adulthood. The controlled prospective follow-up studies are more likely to also identify subjects who are no longer disabled by ADHD symptoms and therefore functioning better.
Conclusions: Both registry and controlled prospective follow-up studies identify adults who continue to have ADHD symptoms and who are impaired in many functional spheres. However, the controlled prospective follow-up studies also identify individuals who no longer have symptoms and are not significantly impaired. Registry studies could also identify these individuals but rarely focus on them. ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S150.

5.2 PHARMACOTHERAPY OF ADHD AND THE RISK OF NEW-ONSET PSYCHOSIS IN A GEOGRAPHICALLY DEFINED COHORT OF YOUTH.

Elmaghraby R, Pines A, Markota M, et al.

Objectives: Epidemiological studies suggested increased risk of psychosis in youth with ADHD who are treated with psychostimulants. A recent study by Moran and colleagues found that youth with ADHD had a higher risk of psychosis when treated with amphetamines compared to methylphenidate. The risk of developing psychosis in other groups of ADHD medications is poorly understood. This population-based study aims to compare the risk of new-onset psychosis between 4 different groups of ADHD medications.
Methods: We used the Rochester Epidemiology Project (REP) to evaluate patients between January 1, 2005 and December 31, 2018 who were 6 to 18 years old, diagnosed with ADHD, and prescribed amphetamine, methylphenidate, atomoxetine, or alpha-2 agonists. All subjects with psychotic or substance use diagnoses prior to receiving their first qualifying ADHD medication were excluded. The primary outcome was a newly diagnosed psychosis, defined as having a relevant ICD-9 and ICD-10 diagnosis. The risk of psychosis conditioned on ADHD medication class was estimated using a time-varying covariate Cox proportional hazard regression model.

Results: We identified 5171 youth (3545 male) who met the inclusion criteria, of which 134 (95 males, 70.9%) were classified as having new-onset psychosis. Male sex was a significant predictor of psychosis (hazard ratio [HR] = 1.904; 95% CI, 1.909-2.783; p = 0.0009). Exposure to atomoxetine was the strongest predictor of psychosis (HR = 2.009; 95% CI, 1.382-2.921; p = 0.0003). Exposure to amphetamines was also found to be a significant predictor of psychosis (HR = 1.612; 95% CI, 1.148-2.263; p = 0.0058). Exposure to methylphenidate was not found to be a significant predictor (HR = 1.022; 95% CI, 0.701-1.491; p = 0.9083). Exposure to alpha-2 agonists trended toward significance as a predictor of the absence of a diagnosis of psychosis (HR = 0.668; 95% CI, 0.421-1.059; p = 0.0860).
Conclusions: Our results agree with previously published findings that amphetamines are associated with increased risk for new-onset psychosis. Interestingly, we found the risk of new-onset psychosis to be greatest with atomoxetine and lowest with alpha-2 agonists, which are novel additions to the literature from a large cohort. Finally, we found that male sex is a significant predictor of later diagnosis of psychosis in pediatric patients taking ADHD medication. ADHD, PPC, PSY

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J Am Acad Child Adolesc Psychiatry. 2021;60:S211.

30.3 ADOLESCENT BORDERLINE PERSONALITY SYMPTOMS AND INTERACTIONS WITH CO-OCCURRING PSYCHOPATHOLOGY PREDICT FUNCTIONAL OUTCOMES.

Babinski D, Langfus J, Youngstrom E, et al.

Objectives: Borderline personality disorder (BLP) symptoms emerge in youth and are associated with poor outcomes. However, since BLP symptoms often co-occur with other mental health problems, it is unclear to what extent BLP symptoms uniquely influence functional outcomes or how BLP symptoms interact with these more commonly identified problems to influence functioning. This study examines the unique effect of adolescent BLP symptoms in predicting functional outcomes 2 years later.
Methods: Data from the Longitudinal Assessment of Manic Symptoms (LAMS) Study, a prospective study of 621 clinical youth with elevated mania and 86 clinical youth without elevated mania symptoms (Mage = 9.4 years; SD = 2.0), were examined. For this study, 152 youth with available data at the 48- and 72-month follow-up waves were identified. Dimensional ratings of BLP, inattention and hyperactive/impulsive symptoms of ADHD, depression, and mania were collected at the 48-month follow-up wave. Functional outcomes, including emotional and physical well-being, self-esteem, family, friend, and school functioning, as well as overall functioning were collected at the 72-month follow-up wave. Regression analyses were conducted with BLP, inattention, hyperactivity/impulsivity, depression, mania, age, and sex as independent variables. Interactions between BLP and inattention, hyperactivity/impulsivity, depression, mania, age, and sex were tested. Due to the number of tests, $p < 0.01$ identified significance.
Results: Interactions between BLP and inattention emerged. At higher levels of inattention, BLP was associated with poorer physical (partial r = 0.21), emotional (partial r = 0.37), and overall functioning (partial r = 0.32), whereas at lower levels of inattention, BLP was associated with better functioning. Significant interactions at the $p < 0.01$ level did not emerge between BLP and inattention in predicting self-esteem, school, or friend functioning, or between BLP and other measures of psychopathology. Main effects of psychopathology on functional outcomes did not emerge.
Conclusions: Inattentive symptoms of ADHD moderated the prospective association between BLP symptoms and functional outcomes. Future research that attends to the complex and heterogeneous presentations of youth with BLP symptoms is needed to develop targeted interventions to improve clinical outcomes. PED, ADHD

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J Am Acad Child Adolesc Psychiatry. 2021;60:S183.

12.1 RELATIONSHIP BETWEEN IQ AND INTERNALIZING AND EXTERNALIZING SYMPTOMS IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND CHILDREN WITH ADHD.

Baweja R, Mayes S, Waschbusch D, et al.

Objectives: Research (based on generally small samples) has yielded inconsistent findings regarding the relationship between IQ, intellectual disability (ID), and mental health comorbidity in autism spectrum disorder

(ASD) and ADHD. Ours is the first large study to analyze multiple symptoms and their association with IQ and ID.
Methods: Mothers rated 1436 children with ASD and 1056 with ADHD without ASD (IQs 9-149; ages 2-17 years) on 15 Pediatric Behavior Scale externalizing and internalizing symptoms.
Results: Correlations and t tests (controlling for age and the number of comparisons) indicated that decreasing IQ and/or ID was associated with decreasing ODD (oppositional behavior, irritability, tantrums), conduct problems (mean/bully, lie/cheat, steal), generalized anxiety, social anxiety, and depression, and with increasing inattention, hyperactivity, aggression, self-injurious behavior (SIB), and separation anxiety ($p < 0.05$). Children with ADHD inattentive presentation (ADHD-I) had less comorbidity than children with ASD in all domains except social anxiety compared to ACHD-Combined (ADHD-C; binomial $p < 0.001$). Almost all children with ASD and with ADHD-C and ADHD-I across IQ groups had inattention rated as often or very often a problem. Most with ASD and with ADHD-C also had impulsivity and hyperactivity. The majority with ASD and ADHD-C who had ID had ODD symptoms, and almost half without ID had ODD. ODD was rare in ADHD-I but was higher in those without ID. Conduct disorder symptoms were far less common (3%-19% across groups). Aggression and SIB were most prevalent in ASD (27% and 16%), followed by ADHD-C (19% and 6%) and ADHD-I (2% and 1%). For children with and without ID, generalized, separation, and social anxiety were more common in ASD (24%-47%) than in ADHD-C (15%-32%) and ADHD-I (15%-25%). Depression was far less common, was most prevalent in ASD, and occurred less frequently in children with ID.
Conclusions: Because of the high prevalence of ADHD symptoms in ASD, ADHD needs to be ruled in or out in children referred for possible ASD. ASD also needs to be assessed in children referred for ADHD because many children with ASD are initially diagnosed with only ADHD. Given the high frequency of many comorbid symptoms, clinicians assessing and treating children with ASD, ADHD, and ID should assess for mental health comorbidity and provide intervention as needed. ADHD, ASD, ID

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J Am Acad Child Adolesc Psychiatry. 2021;60:S78.

53.2 A DISCUSSION WITH AN ISRAELI PROFESSOR: THE IMPACT OF CULTURAL AND SOCIOECONOMIC FACTORS ON ADHD IN ISRAEL.

Yehudian M.

Objectives: Undiagnosed ADHD can have significant negative impacts on a childΓÇÖs academic, social, and financial success. Early screening and intervention have been associated with better outcomes in an Israeli study, in which the cost-benefit ratio for treating ADHD in childhood was found to be more than 7-fold. A professor of psychiatry in Israel shares his perspectives on the cultural and socioeconomic factors that influence the diagnosis and treatment of ADHD in Israel. Despite increased awareness of this treatable disorder, as well as a significant body of ADHD literature coming from Israel, ADHD goes unrecognized in certain subpopulations in Israel. Specifically, the Arab-Israeli and religious Jewish Israeli populations in Israel are less likely to seek treatment for ADHD due to unnoticed symptoms, lack of perceived importance in treating this disorder, and the stigmas associated with mental illness. In a retrospective study of children with ADHD, mental health comorbidities were less prevalent in an Arab population than in a Jewish population, presumably because of Arab families propensity to not address symptoms as problematic or their discomfort with disclosing this information. This discrepancy underscores the importance of educating parents on ADHD and emphasizing the need for culturally sensitive clinical assessments. Families of low socioeconomic status tend to be underdiagnosed with ADHD due to the lack of importance they tend to place on academics. Similarly to the US, families with higher socioeconomic status tend to be overdiagnosed with ADHD due to their increased access to health care and high importance placed on academic achievements. By learning from and exchanging ideas with Israeli psychiatrists, our aim is to address the cultural and socioeconomic gaps with the goal of promoting accurate and culturally-sensitive diagnoses, and partner with families to promote early intervention in populations that are left untreated.
Methods: A child and adolescent psychiatry trainee has a remote discussion about ADHD with an Israeli psychiatrist to broaden their current understanding of ADHD symptomatology and prevalence in Israel, highlighting the complexities of accurately diagnosing ADHD in distinct subpopulations in Israel, and highlighting the importance of cultural-sensitivity in early screening and diagnosis of ADHD in Israel.

Results: The child and adolescent psychiatry trainee learns how to integrate culturally-sensitive and socioeconomic factors that play a role in accurately diagnosing and effectively treating ADHD.
Conclusions: This presentation demonstrates consulting and exchanging ideas with psychiatrists in Israel, which are important skills in child and adolescent psychiatry. It also explores some of the complexities in diagnosing ADHD in certain subpopulations in Israel, and the bias of Western culture that may present as a barrier to diagnosis and intervention. ADHD, CUL

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J Am Acad Child Adolesc Psychiatry. 2021;60:S304.

30.2 MODERATIONG EFFECTS OF PSYCHIATRIC DIAGNOSES ON NEUROFEEDBACH FOR ADHD AT 25 MONTH FOLLOW-UP.

Roley-Roberts M, Kerson C, Ging-Jehli N, et al.

Objectives: Childhood ADHD commonly co-occurs with comorbidities, suggesting that ADHD treatments should consider these. A 2-site, double-blind RCT comparing neurofeedback (NF) to control found delayed treatment effects. We examined whether comorbid diagnoses enhanced or impaired NF effects.
Methods: Children aged 7-10 years with DSM-5 defined ADHD presentationsΓÇöinattentive (n = 51) or combined (n = 91) received either NF (n = 84) or control treatment (n = 58). Their inattentive symptoms were assessed at baseline, treatment (Tx) end, and 13- and 25-month follow-ups. Among those children, 70% had a comorbidity: 50% met criteria for ODD, 27% for specific phobias, 23% for generalized anxiety, and 16% for separation anxiety. Based on comorbid diagnoses, children were grouped into: anxiety disorders (ANX) only, ODD only, neither, or both to assess whether comorbidity moderated outcomes.
Results: Those with ANX alone improved less with NF than with control (item mean difference 0.410; CI, 0.029 to 0.791; p = 0.035) from baseline to Tx end. In contrast, those with ODD improved more with NF than control (0.378; CI, 0.027 to 0.729; p = 0.035) from baseline to 13 months. Irrespective of treatment, youth with ANX had less inattention improvement from baseline to Tx end (item mean difference 0.547; CI, 0.996 to 0.127; p = 0.011); and from baseline to 13 months (item mean difference 0.467; CI, 0.909 to 0.025; p = 0.038) than other comorbidity groups. At 25 months, the significant time*treatment*comorbidity interaction attenuated to nonsignificance (p = 0.1435), leaving a trend for youth with neither comorbidity to have more inattention improvement with control than with NF from baseline to 25-month follow-up (item mean difference 0.310; CI, 0.627 to 0.048; p = 0.089).
Conclusions: Theta-beta NF is contraindicated for youth with ANX without ODD and appears to have a delayed specific benefit for ADHD with ODD that is not sustained to 25 months. The loss of significant moderation at 25 months appears to be due to a combination of reduced power to detect effects, those with ANX recovering from impaired NF response between Tx end and 25 months, and those with neither comorbidity doing worse after NF than control from Tx end to 25 months. ADOL, PTSD, RCT

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J Am Acad Child Adolesc Psychiatry. 2021;60:S304-S305.

30.3 EEG CONNECTIVITY IN ADHD COMPARED TO A NORMATIVE DATABASE AND INTERACTION WITH NEUROFEEDBACK RESPONSE.

Kerson C, Lubar J, deBeus R, et al.

Objectives: This study explores how EEG connectivity measures in a large group of children with ADHD aged 7 to 10 years differ from an age-matched data set. The children (N = 142) were in the International Collaborative ADHD Neurofeedback (ICAN) study, which examined the efficacy of neurofeedback (NFB) for ADHD. Inclusion criteria were mainly rigorously diagnosed ADHD and an EEG theta/beta ratio (TBR) of at least 4.5. The differences in specific connectivity networks, including dorsal attention, ventral attention, default mode network, and executive function were evaluated in quantitative EEGs.
Methods: Pretreatment and posttreatment EEGs were de-artifacted to create clean records for analyses; technicians were blinded to subject and treatment assignment. Connectivity values were extracted in coherence, phase, and lagged coherence at all Brodmann areas, and in many subcortical and cerebellar locations in each of the main frequency bands. Values from pretreatment EEGs were compared to a normative database. The pretreatment and posttreatment EEGs were compared for changes dependent on the assigned treatment group (NFB or control) and the scalp site (Fz or Cz).

Results: Initial connectivity analyses revealed the need to explore deeper. To date, we found a significant pre-to-post difference in theta (4-8 Hz) and alpha-1 (8-10 Hz) bands (effect size d = 1.0 and 0.84, respectively), regardless of treatment group, in subjects who trained at scalp site Fz. In addition, some exploration showed that certain pairs of connection sites were specific to the ADHD group and that some were positively affected by the NFB. Analyses are ongoing, and the results will be presented.
Conclusions: The preliminary results of the training at Fz are promising, albeit still partial due to the amount of work to analyze the myriad components of the human EEG by hand and statistical interpretation alone. Therefore, machine learning algorithms are being explored to capture the meaningful properties of the over 7500 possible connectivity variables and how they are populated in this data set of 142 children with ADHD, each with 4 multichannel recordings (pre-, mid-, and posttreatment, and 13-month follow-up). With machine learning algorithms, we plan to present patterns distinguishing ADHD, which are important for diagnostic and prognostic understanding. ADHD, COG, SAC

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J Am Acad Child Adolesc Psychiatry. 2021;60:S285.

18.1 ADHD AND RISK FOR ADVERSE CHILDHOOD EXPERIENCES: A PATHWAY FOR THE PERPETUATION OF ADVERSITY.

Lugo-Candelas C.

Objectives: The present study aimed to examine if children with ADHD are at an increased risk for subsequent adverse childhood experiences (ACEs) in a prospective, longitudinal, population-based study of Puerto Rican children and adolescents in the South Bronx, New York, and Puerto Rico. Prior work has shown that children with ACEs are more likely to develop ADHD, yet the reverse relationship-ADHD predicting subsequent ACEs'is vastly understudied. By leveraging a study design with 3 recurrent ADHD and ACEs assessments, we were able to establish a clear temporal sequence that allowed us to examine if children were at increased risk for ACEs after ADHD symptoms were present.
Methods: Participants were 5 to 15 years old (48% females) with (10%) and without ADHD. Exposure to 11 ACEs (10 classic ACEs covering parental loss and maladjustment and child maltreatment plus exposure to violence) were examined in 3 yearly assessments (Waves 1-3). Logistic regression models examined ADHD and subsequent risk for ACEs. Also considered were ADHD subtype differences, as well as interactions by age, sex, number of Wave 1 ACEs, and recruitment site.
Results: Children with Wave 1 ADHD were more likely to experience subsequent adversity (OR = 1.63; 95% CI, 1.12-2.37) controlling for child age, sex, public assistance, maternal education, site, disruptive behavior disorders, and Wave 1 ACEs. Inattentive (OR = 2.00; 95% CI, 1.09-3.66), but not hyperactive/impulsive or combined ADHD, predicted ACEs.
Conclusions: This is the first study to test whether ADHD increases the likelihood of experiencing ACEs in a longitudinal, probability-based sample of children highly exposed to ACEs. We show that ADHD predicts increased likelihood of accruing subsequent ACEs and that inattentive ADHD subtype predicted ACEs. Inattentive ADHD could pose a bigger risk given differences in symptom persistence, latency to access to treatment, and often shorter treatment duration. This study suggests a pathway for the perpetuation of adversity, in which bidirectional relationships between ADHD and ACEs may ensnare children in developmental pathways predictive of poor outcomes. Understanding the underlying mechanism will be critical to developing interventions. ADHD, EC, RF

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J Am Acad Child Adolesc Psychiatry. 2021;60:S125-S126.

3.2 ADHD COMORBIDITY WITH AUTISM SPECTRUM DISORDER AND BURDEN OF TRAITS OF AUTISM SPECTRUM DISORDER IN ADHD.

Biederman J.

Objectives: Both autism spectrum disorder (ASD) and ADHD are severely impairing chronic conditions with high prevalence rates that manifest in early childhood. The reciprocal presence of ADHD and ASD further worsens academic and social functioning. The objective of this presentation is to highlight the burden of ADHD psychopathology in youth with ASD and to examine its clinical presentation and neural correlates, as well as the stability and predictive utility of autistic traits (ATs) in youth with ADHD.

Methods: This presentation will offer an up-to-date review of the emerging evidence on the prevalence, clinical, and neural characteristics of ADHD in youth with ASD. In addition, this presentation will address the comorbidity of significant ATs in individuals with ADHD as indexed through the Child Behavior Checklist (CBCL) consisting of an aggregate T score of 195 on the Withdrawn, Social, and Thought Problems subscales (CBCL-AT profile).
Results: Nearly two-thirds of the psychiatrically referred populations of youth (ranging from 59% to 83%) and adults (ranging from 37% to 68%) with ASD suffer from ADHD. The phenotypic expression of ADHD in individuals with ASD is strikingly similar to the presentation in the typical population. The aberrant neural profile typically observed with ADHD is also observed in youth with ASD who have ADHD. The CBCL-AT profile was positive in 18% of the youth with ADHD. At the follow-up, 83% of the youth with ADHD who had ATs continued to have a positive CBCL-AT profile. The presence of a positive CBCL-AT profile in youth with ADHD heralded a more compromised course characterized by higher levels of psychopathology and adverse interpersonal, educational, and neurocognitive outcomes.
Conclusions: ADHD is the most frequent psychopathology associated with ASD. The clinical and neural presentation of ADHD in youth with ASD is substantially similar to typical expression of ADHD, suggesting that the available diagnostic criteria for ADHD can be applied to identify ADHD in populations with ASD. Furthermore, findings indicate a high level of persisting ATs in youth with ADHD over time, and that its presence prognosticates a compromised course in adult life in multiple domains of functioning. ASD, ADHD

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J Neurol Sci. 2021;429.
A NOVEL WDR45 MUTATION IN A 6-YEAR-OLD BOY WITH AUTISM, LENNOX-GASTAUT SYNDROME, AND ADHD .
Baek W, Wang H.
Background and aims: Beta-propeller protein-associated neurodegeneration, i.e., neurodegeneration with brain iron accumulation type 5, is due to mutations in the WDR45 gene. We report a case where a novel pathogenic mutation was discovered. Methods: Case Report.
Results: A 6-year-old boy presented with autism, developmental delay, seizures, and aggression. Details of his birth history were unknown. He had been on levetiracetam since 3. His parents first witnessed near-daily drop attacks. Valproic acid was added to tolevetiracetam, which resolved his drop attacks but head banging increased, hence discontinued. He was 117 cm (7th percentile) and weighed 23.5 kg (39th percentile). Head circumference was 50 cm (17th percentile). He was not dysmorphic, but very hyperactive and disruptive. EEG was indicative of Lennox-Gastaut syndrome. MRI showed neurodegeneration with iron accumulation. Amphetamine-dextroamphetamine and Methylphenidate for ADHD did not help. Levetiracetam was increased and valproic acid was restarted, which had resolved his seizures. Risperdone was started for aggression. Genetic testing revealed a novel pathogenic variant (c.577C > T, p.Gln193) in WDR45. Allele fraction was 46%, suggesting mosaicism. At 8 his verbal communication improved, and he was seizure-free.
Conclusions: A novel pathogenic variant (c.577C > T, p.Gln193) was found in the WDR45 gene as a mosaic with an allele fraction of 46%. The clinical features of our case were unique; he clearly did not have cerebral palsy nor was he bedridden. To date, at age 8, he still does not exhibit any signs of parkinsonism or dystonia. Whether this was due his mosaicism or the specific novel mutation remains unclear. Postzygotic mosaicism might explain why his phenotype was not as severe

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J Neurol Sci. 2021;429.
STUDY OF SELF CONCEPT AND SOCIAL SUPPORT PERCEPTION: NEURODEVELOPMENTAL DISORDERS.
Akyurek G, Muratto-Ƒlu H.
Background and aims: This study were planned to investigate self-perception, self-esteem, and social support perception among children with Attention Deficit and Hyperactivity Disorder (ADHD) and/or Specific Learning Disabilities (SLD).
Methods: In this study, 31 children with ADHD and/or SLD between the ages of 9-13 who are registered in Hacettepe University Faculty of Health Sciences, Department of Occupational Therapy were included as a research group (RG). Thirty typically developed children between the same age (9-13 years old) were included as the control group (CG). For this study, Self-Perception Profile for Children (SPPC), Coopersmith

Self-Esteem Inventory (CSEI), and Social Support Questionnaire for Children (SSQC) were used. Mann-Whitney U test was used for analysis.
Results: The analyses showed that the SPPC score of the RG was significantly lower than that for CG (Z = -3.125; p = 0.002); the CSEI score of the RG was significantly lower than that for CG (Z = 2.464; p = 0.014) and the SSQC score of the RG was significantly lower than that for CG (Z = 2.887; p = 0.004).
Conclusions: In this study, it was found that self-concept, self-esteem, and social support are low from the typical developed peers. Children with ADHD with/or SLD have problems these psychosocial areas and need support. Therefore, it is important to include practices that support their identity development and social support in their rehabilitation programs

Lupus. 2021 Feb;30:228-37.
SYSTEMIC LUPUS ERYTHEMATOSUS DURING PREGNANCY IS NOT ASSOCIATED WITH SCHOOL PERFORMANCE IN OFFSPRING - A DANISH POPULATION-BASED STUDY.
Knudsen SS, Simard JF, Knudsen JS, et al.
INTRODUCTION: Systemic lupus erythematosus (SLE) in pregnancy is considered a risk factor for a range of adverse outcomes in the offspring. Studies have indicated increased risk of neurodevelopmental disorders such as autism spectrum disorders, dyslexia and ADHD. However, the overall long-term cognitive development of children born to women with SLE has scarcely been examined. In this study, we compare test scores from the Danish National School Tests of children born to women SLE with children of the background population.
METHODS: We included all singleton children born in Denmark between 1995 and 2008, who were listed in the Danish National School Test Register (n=738,862). Children born to women with SLE were identified through linkage of national healthcare registers. We assessed the children's performance in the national school tests between 2nd and 8th grade, in reading and mathematics. Information on the mothers' redeemed prescriptions in pregnancy was included in stratified analyses. Differences of mean test scores were derived from linear regressions and compared according to maternal SLE status, and predefined categories of medication exposures.
RESULTS: In total, 312 (0.04%) children were born to mothers with SLE. There were no differences in performance in neither reading nor mathematics tests between those born to mothers with SLE and children born to mothers without SLE. When stratifying on medication exposures among children whose mothers had SLE, there was a non-significant tendency towards poorer results among those exposed to hydroxychloroquine and/or immunosuppressants (n=31), compared to those not exposed to these medications. A similar tendency was not observed among children whose mothers received hydroxychloroquine for non-SLE reasons (n=1,235).
CONCLUSION: This study indicates no major harmful effect on the child's neurocognitive development from exposure in utero to SLE, hydroxychloroquine and/or immunosuppressants, as measured by school performance

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Med Lett Drugs Ther. 2021 Oct;63:157-59.
AZSTARYS (SERDEXMETHYLPHENIDATE/DEXMETHYLPHENIDATE) FOR ADHD.
Anon.

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Molecular Autism. 2021;12.
EXPLORING SENSORY PHENOTYPES IN AUTISM SPECTRUM DISORDER.
Scheerer NE, Curcin K, Stojanoski B, et al.
Background: Atypical reactions to the sensory environment are often reported in autistic individuals, with a high degree of variability across the sensory modalities. These sensory differences have been shown to promote challenging behaviours and distress in autistic individuals and are predictive of other functions including motor, social, and cognitive abilities. Preliminary research suggests that specific sensory differences may cluster together within individuals creating discrete sensory phenotypes. However, the

manner in which these sensory differences cluster, and whether the resulting phenotypes are associated with specific cognitive and social challenges is unclear.
Methods: Short sensory profile data from 599 autistic children and adults-ábetween the ages of 1 and 21-áyears were subjected to a K-means cluster analysis. Analysis of variances compared age, adaptive behaviour, and traits associated with autism, attention-deficit and hyperactivity disorder, and obsessive and compulsive disorder across the resultant clusters.
Results: A five-cluster model was found to minimize error variance and produce five sensory phenotypes: (1) sensory adaptive, (2) generalized sensory differences, (3) taste and smell sensitivity, (4) under-responsive and sensation seeking, and (5) movement difficulties with low energy. Age, adaptive behaviour, and traits associated with autism, attention-deficit and hyperactivity disorder, and obsessive and compulsive disorder were found to differ significantly across the five phenotypes. Limitations: The results were based on parent-report measures of sensory processing, adaptive behaviour, traits associated with-áautism, attention-deficit and hyperactivity-ádisorder, and obsessive and compulsive disorder, which may limit the generalizability of the findings. Further, not all measures are standardized, or psychometrically validated with an autism population. Autistic individuals with an intellectual disability were underrepresented in this sample. Further, as these data were obtained from established records from a large provincial database, not all measures were completed for all individuals.
Conclusions: These findings suggest that sensory difficulties in autistic individuals can be clustered into sensory phenotypes, and that these phenotypes are associated with behavioural differences. Given the large degree of heterogeneity in sensory difficulties seen in the autistic population, these sensory phenotypes represent an effective way to parse that heterogeneity and create phenotypes that may aid in the development of effective treatments and interventions for sensory difficulties

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Molecular Autism. 2021;12.

INDIVIDUALS WITH FOXP1 SYNDROME PRESENT WITH A COMPLEX NEUROBEHAVIORAL PROFILE WITH HIGH RATES OF ADHD, ANXIETY, REPETITIVE BEHAVIORS, AND SENSORY SYMPTOMS.

Trelles MP, Levy T, Lerman B, et al.

Background: FOXP1 syndrome is an autosomal dominant neurodevelopmental disorder characterized by intellectual disability, developmental delay, speech and language delays, and externalizing behaviors. We previously evaluated nine children and adolescents with FOXP1 syndrome to better characterize its phenotype. We identified specific areas of interest to be further explored, namely autism spectrum disorder (ASD) and internalizing and externalizing behaviors.
Methods: Here, we assess a prospective cohort of additional 17 individuals to expand our initial analyses and focus on these areas of interest. An interdisciplinary group of clinicians evaluated neurodevelopmental, behavioral, and medical features in participants. We report results from this cohort both alone, and in combination with the previous cohort, where possible.
Results: Previous observations of intellectual disability, motor delays, and language deficits were confirmed. In addition, 24% of the cohort met criteria for ASD. Seventy-five percent of individuals met DSM-5 criteria for attention-deficit/hyperactivity disorder and 38% for an anxiety disorder. Repetitive behaviors were almost universally present (95%) even without a diagnosis of ASD. Sensory symptoms, in particular sensory seeking, were common. Limitations: As FOXP1 syndrome is a rare disorder, sample size is limited.
Conclusions: These findings have important implications for the treatment and care of individuals with FOXP1 syndrome. Notably, standardized testing for ASD showed high sensitivity, but low specificity, when compared to expert consensus diagnosis. Furthermore, many individuals in our cohort who received diagnoses of attention-deficit/hyperactivity disorder or anxiety disorder were not being treated for these symptoms; therefore, our findings suggest that there may be immediate areas for improvements in treatment for some individuals

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Molecular Genetics and Metabolism. 2021.

NATURAL HISTORY OF CHILDREN AND ADULTS WITH PHENYLKETONURIA IN THE NBS-PKU CONNECT REGISTRY.

Kenneson A, Singh RH.

Purpose: Phenylalanine hydroxylase deficiency, or phenylketonuria (PKU), is a rare autosomal recessive metabolic disorder. Early diagnosis via newborn screening (NBS) and initiation of treatment prevent the development of cognitive impairment and other co-morbidities. The purpose of this study is to describe the natural history of PKU in the United States, including prevalence of co-morbidities and predictors of outcomes.

Methods: We analyzed data from a self-report survey in the NBS-PKU Connect online registry. We describe the participants' nutrition management strategies, barriers to management, outcomes of bone disorders, skin, and psychological co-morbidities, and the use of special education or other special services. Predictors of outcomes were identified and assessed, including the impact of sex, age, age at diagnosis, blood phenylalanine concentration, use of sapropterin, use of medical food, adherence to prescribed diet, use of low protein modified foods, whether they had ever been off-diet, and use of tyrosine supplementation.

Results: The 219 respondents included individuals with PKU or hyperphenylalanemia (n = 78), or their caregivers (n = 141). Most (84.3%) started treatment before the age of two weeks. About one-third indicated that they had been off-diet at some point in their lives, and 81.4% reported that they currently adhered to their prescribed diet, with adherence to prescribed diet decreasing with age. Blood phenylalanine concentration was under the recommended threshold of 360 ++mol/L for 68.5% of participants. One-quarter of respondents reported psychological co-morbidities, with anxiety and ADD/ADHD being the most common. The incidence of psychological co-morbidities increased with age and with ever having been off diet. Special education or other special services were more likely to be reported by individuals who were diagnosed after one week of age. Skin disorders such as acne and eczema were more common in females than males, and a minority of participants reported bone disorders.

Conclusions: Despite recommendations to maintain blood phenylalanine concentrations in the therapeutic range throughout life, it is not uncommon for adults with PKU to discontinue dietary management of their disorder. Early diagnosis was associated with reduced need for special education or other special services, and continuous treatment was associated with decreased psychological co-morbidities

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Movement Disorder. 2021;36:S91.

EXCESSIVE DIRECTIONAL ANTISACCADE ERRORS IN TOURETTE SYNDROME WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A CASE REPORT.

Sandoval-Lopez DSL, Ortega-M+írquez JOM, et al.

Objective: To describe a case of a young man diagnosed with Tourette syndrome and Attention-Deficit Hyperactivity Disorder, where oculomotor tics were observed as the main clinical affection.

Background: Tourette syndrome (TS) is a neurodevelopmental and neuropsychiatric disorder mainly characterized by motor and phonic tics. Children and adolescents are the most affected with a prevalence of 0.3-0.9% (1). Although the pathophysiology of TS is still unclear, it has been suggested that it is produced by the dysfunction of cortico-striato-pallido- thalamo-cortical networks (2), which in relation with superior colliculi, modulate voluntary saccadic movements (3). Most TS patients have at least one association with additional psychiatric comorbidities, especially with Attention Deficit Hyperactivity Disorder (ADHD) (1). These findings suggest that patients with TS+ADHD have abnormalities in prefrontal-striatal circuits, which explains excessive antisaccade errors.

Methods: A 23-year-old Mexican man with a 16-year history of TS and ADHD. At the age of 7, started with involuntary stereotyped movements, exacerbated under psychological stress, and decreased by exercising or playing music. By age 11, abrupt neck movements, clearing of the throat, ocular supraversion and intense blinking. 6 years later, he was diagnosed and started treatment based on risperidone (1mL/day) with a clear improvement of oculomotor tics. However, after 1 year the patient abandoned the treatment because of side effects. Management was changed to paroxetine (10mg/day). At present, the patient reports amelioration of oculomotor tics and ADHD symptoms, without relevant side effects.

Results: Oculomotor tics were the main clinical features, managed with risperidone as initial treatment, yet because of the side effects, there was poor adherence to treatment. Paroxetine was established instead, with noticeable improvement of the movement disorders.

Conclusions: The association of TS+ADHD remains underestimated in clinical practice. This leads to a suboptimal diagnosis and treatment of these patients who present typical symptoms of TS, but also show oculomotor pathway impairments (uncontrolled saccadic involuntary movements) as the main clinical affection (4,5,6). Thus, it is essential to see TS as a multidimensional disease, where other comorbidities could not only be associated but may even mark the clinical course of the disease

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MSMR. 2021 Jan;28:2-8.

ATTRITION RATES AND INCIDENCE OF MENTAL HEALTH DISORDERS IN AN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) COHORT, ACTIVE COMPONENT, U.S. ARMED FORCES, 2014-2018.

Sayers D, Hu Z, Clark LL.

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood diagnosis and affects the pool of potential military applicants. Early detection and treatment of ADHD may decrease the risk of developing comorbidities; however, accession policy in place during this study period (2014-2018) disqualified applicants who used ADHD medication for more than 24 months cumulative after age 14. The objective of this study was to assess attrition from military service in newly accessed active component service members diagnosed with ADHD as compared to controls. In addition, attrition rates and incidence rates of mental health diagnoses were assessed in service members with ADHD by treatment status (i.e., treated vs untreated ADHD) where treatment was defined as being dispensed an FDA-approved ADHD medication at least twice within 181 days. Almost two-thirds (64.8%) of newly accessed ADHD cases in 2014 were identified after enlistment medical screening at Military Entrance Processing Stations (MEPS) (i.e., post-MEPS). These post-MEPS ADHD cases accounted for 99.1% of the treated ADHD cases. The vast majority of treated cases (91.0%) were dispensed ADHD medication within 6 months of accession. The treated ADHD group had higher rates of attrition and incidence of mental health disorders during the followup period. These study findings highlight the problem of nondisclosure of ADHD among military applicants. Future changes to enlistment standards should consider the optimal way to promote applicant disclosure of ADHD during MEPS screening or for medical waiver review and should discourage withholding an ADHD diagnosis during enlistment

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MSMR. 2021 Jan;28:9-14.

THE PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND ADHD MEDICATION TREATMENT IN ACTIVE COMPONENT SERVICE MEMBERS, U.S. ARMED FORCES, 2014-2018.

Sayers D, Hu Z, Clark LL.

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Multisens Res. 2020 Oct;33:599-623.

AUDIOVISUAL MULTISENSORY PROCESSING IN YOUNG ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McCracken HS, Murphy BA, Burkitt JJ, et al.

Multisensory integration is a fundamental form of sensory processing that is involved in many everyday tasks. Those with Attention-Deficit/Hyperactivity Disorder (ADHD) have characteristic alterations to various brain regions that may influence multisensory processing. The overall aim of this work was to assess how adults with ADHD process audiovisual multisensory stimuli during a complex response time task. The paradigm used was a two-alternative forced-choice discrimination task paired with continuous 64-electrode electroencephalography, allowing for the measurement of response time and accuracy to auditory, visual, and audiovisual multisensory conditions. Analysis revealed that those with ADHD (n=10) respond faster than neurotypical controls (n=12) when presented with auditory, visual, and audiovisual multisensory conditions, while also having race model violation in early response latency quantiles. Adults with ADHD also had more prominent multisensory processing over parietal-occipital brain regions at early post-stimulus latencies, indicating that altered brain structure may have important outcomes for audiovisual multisensory processing. The present study is the first to assess how those with ADHD respond to multisensory conditions during a complex response time task, and demonstrates that adults with ADHD have unique multisensory processing

when assessing both behavioral response time measures and neurological measures

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NeuroImage. 2021 Aug;236:118072.

BRAIN STATE-BASED DETECTION OF ATTENTIONAL FLUCTUATIONS AND THEIR MODULATION.

Yamashita A, Rothlein D, Kucyi A, et al.

In the search for brain markers of optimal attentional focus, the mainstream approach has been to first define attentional states based on behavioral performance, and to subsequently investigate "neural correlates" associated with these performance variations. However, this approach constrains the range of contexts in which attentional states can be operationalized by relying on overt behavior, and assumes a one-to-one correspondence between behavior and brain state. Here, we reversed the logic of these previous studies and sought to identify behaviorally-relevant brain states based solely on brain activity, agnostic to behavioral performance. In four independent datasets, we found that the same two brain states were dominant during a sustained attention task. One state was behaviorally optimal, with higher accuracy and stability, but a greater tendency to mind wander (State1). The second state was behaviorally suboptimal, with lower accuracy and instability (State2). We further demonstrate how these brain states were impacted by motivation and attention-deficit/hyperactivity disorder (ADHD). Individuals with ADHD spent more time in suboptimal State2 and less time in optimal State1 than healthy controls. Motivation overcame the suboptimal behavior associated with State2. Our study provides compelling evidence for the existence of two attentional states from the sole viewpoint of brain activity

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Neuropharmacology. 2021 Feb;184:108370.

DNA METHYLATION ASSOCIATED WITH PERSISTENT ADHD SUGGESTS TARBP1 AS NOVEL CANDIDATE.

WeiÃŸ AL, Meijer M, Budeus B, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate symptoms of inattention and/or hyperactivity and impulsivity. ADHD is highly prevalent in childhood and often persists into adulthood. Both genetic variants and environmental factors play a role in the onset and persistence of ADHD, and epigenetic changes, such as DNA methylation are considered as a link for their interplay. To investigate this, we studied DNA methylation in 37 candidate genes by performing targeted bisulfite sequencing of DNA isolated from whole blood of N = 88 individuals diagnosed with adult ADHD and N = 91 unaffected individuals (mean age 34.2 years). Differentially methylated sites were assessed by generalized linear models testing ADHD status and ADHD symptoms, accounting for a methylation-based smoking score, age, sex, and blood cell count. DNA methylation of single sites within DRD4 and KLDR1 was associated with adult ADHD status, and multiple DNA methylation sites within TARBP1 were associated with ADHD symptoms in adulthood and childhood. Awaiting replication, findings of this pilot study point to TARBP1 as a new candidate gene for ADHD symptoms. Our work also stresses the need for research to further examine the effects of environmental factors, such as nicotine exposure, on epigenetic modifications associated with psychiatric traits

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Neuropsychol Rev. 2021 Sep;31:422-46.

CEREBELLAR-SUBCORTICAL-CORTICAL SYSTEMS AS MODULATORS OF COGNITIVE FUNCTIONS.

Clark SV, Semmel ES, Aleksonis HA, et al.

Over the past few decades, research has established that the cerebellum is involved in executive functions; however, its specific role remains unclear. There are numerous theories of cerebellar function and numerous cognitive processes falling under the umbrella of executive function, making investigations of the cerebellum's role in executive functioning challenging. In this review, we explored the role of the cerebellum in executive functioning through clinical and cognitive neuroscience frameworks. We reviewed the neuroanatomical systems and theoretical models of cerebellar functions and the multifaceted nature of executive functions. Using attention deficit hyperactivity disorder and cerebellar tumor as clinical developmental models of cerebellar dysfunction, and the functional magnetic resonance imaging literature, we reviewed evidence for cerebellar involvement in specific components of executive function in childhood,

adolescence, and adulthood. There is evidence for posterior cerebellar contributions to working memory, planning, inhibition, and flexibility, but the heterogeneous literature that largely was not designed to study the cerebellum makes it difficult to determine specific functions of the cerebellum or cerebellar regions. In addition, while it is clear that cerebellar insult in childhood affects executive function performance later in life, more work is needed to elucidate the mechanisms by which executive dysfunction occurs and its developmental course. The limitations of the current literature are discussed and potential directions for future research are provided

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Neuropsychol Rehabil. 2021 Oct;31:1466-94.

IMPLEMENTATION OF AN ATTENTION TRAINING PROGRAMME WITH A SAMPLE OF CHILDREN WHO HAVE SUSTAINED TRAUMATIC BRAIN INJURIES IN SOUTH AFRICA: A PILOT STUDY .

Lanesman TH, Schrieff LE.

This pilot study evaluated the feasibility of implementing an attention-training programme for children who have sustained moderate-to-severe traumatic brain injuries (TBIs) in a South African context. We compared the performance on the programme of children with TBI (TBI Intervention Group) to children who had been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD Intervention Group), a TBI Art group and a TBI No-intervention Group (n = 5 in each group) in this preliminary study. Children in the two Intervention Groups participated in the 'Pay Attention!' programme for 45 minutes twice a week for 12 weeks. All children were aged 6–8 years and underwent neuropsychological testing pre- and post-intervention. Behavioural data were collected from parents. Children in the ADHD Intervention Group showed individual clinically significant attentional improvements on measures of the Conners' Continuous Performance Test II using the Reliable Change Index (= 2.58 SD). Despite mixed results, the pilot study demonstrates that implementing a cognitive rehabilitation programme in South Africa is feasible and necessary, despite limited infrastructure and access to resources

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Neuropsychopharmacology Reports. 2021.

EFFECT OF ANTI-ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) MEDICATION ON CLINICAL SEIZURES AND SLEEP EEG: A RETROSPECTIVE STUDY OF JAPANESE CHILDREN WITH ADHD.

Yamamoto H, Nakagawa E, Kita Y, et al.

Aims: Patients with attention-deficit hyperactivity disorder (ADHD) often exhibit basic or paroxysmal wave abnormalities on electroencephalography (EEG). Methylphenidate (MPH), an anti-ADHD stimulant, has been reported to lower the seizure threshold. However, there have been no reports comparing EEG changes before and after administration of the central nervous system (CNS) stimulant MPH, or atomoxetine (ATX) hydrochloride, a non-CNS stimulant. In this study, we investigated changes in sleep EEG before and after the administration of ADHD treatment drugs.

Method: With the approval of the ethics committee, the medical records of 28 children with ADHD (23 men and 5 women) who gave consent were retrospectively investigated. The appearance of sudden abnormal waves during a 10-minute sleep EEG recording was measured in 0.1-second units, and the duration of these waves was calculated as the paroxysmal index (PI).

Results: Paroxysmal index did not differ significantly between patients who received MPH and those who received ATX. In addition, there were no exacerbations of clinical seizures.

Conclusion: It was concluded that ADHD medications do not have an adverse effect on epileptic seizures or abnormal sleep EEGs

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Neurotoxicol Teratol. 2021;88.

NO ASSOCIATION BETWEEN MATERNAL AND CHILD PFAS CONCENTRATIONS AND REPEATED MEASURES OF ADHD SYMPTOMS AT AGE 2-¢ AND 5 YEARS IN CHILDREN FROM THE ODENSE CHILD COHORT.

Dalsager L, Jensen TK, Nielsen F, et al.

Introduction: The potential impact of exposure to perfluoroalkyl substances (PFAS) on childhood Attention-Deficit Hyperactivity-Disorder (ADHD) is unclear and deserves scrutiny. The majority of previously conducted

longitudinal studies found no association between maternal serum-PFAS concentrations and ADHD symptoms in the offspring, but some studies observed possible associations with postnatal PFAS exposures, mainly in girls.
Objective: To investigate the association between maternal and child serum concentrations of five PFAS and symptoms of ADHD at ages 2-¢ and 5 years.
Methods: In the Odense Child Cohort (OCC) women were recruited in early pregnancy in 2010-12 and their children are being prospectively followed. Mothers donated serum samples in the first trimester and children at age 18 months to be analyzed for perfluorohexane sulfonic acid (PFHxS), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA). Parents completed the Child Behavior Check List for ages 1.5-5 years (CBCL/1-¢-5), including a 6-item ADHD symptom scale at age 2-¢ years and again at 5 years. Negative binomial and logistic regression models taking account of repeated measures were used to investigate the association between maternal and child serum-PFAS concentrations and the ADHD symptom score. Effect modification by child sex was investigated as well.
Results: A total of 1138 mother-child pairs were included. At age 2-¢ years, 17.4% of the children had an ADHD scale score 5 (equivalent to the 90th percentile), whereas the proportion was 15.8% at age 5. We found no association between either maternal or child PFAS concentrations in serum and symptoms of ADHD at age 2-¢ or 5 years, and no evidence of effect modification by sex.
Conclusion: We found no evidence of an association between early-life PFAS exposure and the risk of developing symptoms of ADHD

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Neurourology and Urodynamics. 2021.
NEURODEVELOPMENTAL DISORDERS AND INCONTINENCE IN CHILDREN AND ADOLESCENTS: ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AUTISM SPECTRUM DISORDER, AND INTELLECTUAL DISABILITYΓÇöA CONSENSUS DOCUMENT OF THE INTERNATIONAL CHILDREN'S CONTINENCE SOCIETY.
Von Gontard A, Hussong J, Yang SS, et al.
Aims: Neurodevelopmental disorders (NDs) are incapacitating disorders, which begin early in life, are mainly caused by genetic and neurobiological factors, and show a tendency to persist. They are associated with higher rates of incontinence in children and adolescents, including nocturnal enuresis, daytime urinary incontinence, fecal incontinence, and constipation. Without diagnosis and treatment, they will interfere with incontinence treatment leading to less favorable outcomes. The aim of this-International Children's Continence Society (ICCS) document is to provide an overview of the three most important NDs, that is, attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), and intellectual disability (ID).
Methods: This consensus paper was commissioned by the ICCS. A selective, nonsystematic review was performed. Guidelines, reviews, and selected studies were included. The recommendations are consensus-based.
Results: ADHD is the most common ND with special relevance in clinical practice. ASD and ID are less common, but more severe disorders than ADHD. Basic principles of the assessment and treatment of NDs are provided. Incontinence is common among patients with NDs. Specific modifications and practical approaches in the treatment of incontinence in children with NDs are outlined.
Conclusions: Incontinence in children and adolescents with NDs is common. Effective treatment of incontinence should be adapted and modified to the specific needs of patients with NDs. A multiprofessional approach is recommended

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Nord J Psychiatry. 2021.
REMARKABLE HIGH FREQUENCY OF INSECURE ATTACHMENT IN CHILDREN WITH ADHD PERSISTS IN A THREE-YEAR FOLLOW-UP.
Darling Rasmussen P, Elmose M, Lien G, et al.
Background: Studies have pointed to a complicated and mutual relationship between attention deficit hyperactivity disorder (ADHD) and attachment. In an observational follow-up study conducted in 2015 60 children from 7 years to 12 years recently diagnosed with ADHD were included and assessed according to

attachment representation showing 85% of the children to be insecurely attached. Aim: The aim of this study was to investigate the stability of this remarkably high frequency of insecure attachment in the same cohort of children.
Methods: Children previously assessed using the child attachment interview (CAI) when diagnosed with ADHD were contacted three years later for a follow-up CAI assessment.
Results: At follow-up, 31 children participated in the CAI-interviews. Since their diagnosis with ADHD, the children had received treatment as usual. The CAI-interviews showed a continued high rate of insecure attachment with 90% of the children classifying as insecurely attached compared to expected 38% in the normal population. Of these, the majority of children (77%) were classified as dismissing.
Conclusion: Our findings suggest that targeting ADHD-symptoms with our current treatment strategies does not in itself improve attachment security. Attachment security may in turn be a factor of importance when evaluating general functioning and prognosis

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Nord J Psychiatry. 2021.
CHALLENGES OF CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING THE COVID-19 PANDEMIC.
Kuygun Karci C, Arici Gurbuz A.
Objective: We aimed to understand the challenging effect of the pandemic on children and adolescents with ADHD.
Methods: 100 children and adolescents with ADHD aged 7-18 years were included in the study. They were evaluated in terms of internet addiction diagnostic criteria. Symptom severity was assessed using the CBCL, CPRS, and SNAP-IV.
Results: We found that 42% spent less time outdoors, and 26% spent more time watching TV. 57% had increased internet use and 28% were diagnosed as having internet addiction. There was a significant difference in terms of symptom severity between the groups depending on whether the children took part in sports activity before the pandemic.
Conclusions: Children and adolescents with ADHD have experienced challenges in many areas, especially internet use in the pandemic. The positive long-term effects of exercise in children with ADHD are thought to be protective in terms of symptom management during the COVID-19 pandemic

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Orphanet Journal of Rare Diseases. 2021;16.
METHYLPHENIDATE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PATIENTS WITH SMITHΓÇôMAGENIS SYNDROME: PROTOCOL FOR A SERIES OF N-OF-1 TRIALS.
Muller AR, Zinkstok JR, Rommelse NNJ, et al.
Background: SmithΓÇôMagenis syndrome (SMS) is a rare genetic neurodevelopmental disorder characterized by intellectual disability and severe behavioural and sleep disturbances. Often, patients with SMS are diagnosed with attention-deficit/hyperactivity disorder (ADHD). However, the effectiveness of methylphenidate (MPH), the first-line pharmacological treatment for ADHD, in patients with SMS is unclear. Our objective is to examine the effectiveness of MPH for ADHD symptoms in individuals with SMS, proposing an alternative trial design as traditional randomized controlled trials are complex in these rare and heterogeneous patient populations.
Methods and analysis: We will initiate an N-of-1 series of double-blind randomized and placebo-controlled multiple crossover trials in six patients aged 6 years with a genetically confirmed SMS diagnosis and a multidisciplinary established ADHD diagnosis, according to a power analysis based on a summary measures analysis of the treatment effect. Each N-of-1 trial consists of a baseline period, dose titration phase, three cycles each including randomized intervention, placebo and washout periods, and follow-up. The intervention includes twice daily MPH (doses based on age and body weight). The primary outcome measure will be the subscale hyperactivity/inattention of the Strengths and Difficulties Questionnaire (SDQ), rated daily. Secondary outcome measures are the shortened version of the Emotion Dysregulation Inventory (EDI) reactivity index, Goal Attainment Scaling (GAS), and the personal questionnaire (PQ). Statistical analysis will

include a mixed model analysis. All subjects will receive an assessment of their individual treatment effect and data will be aggregated to investigate the effectiveness of MPH for ADHD in SMS at a population level.
Conclusions: This study will provide information on the effectiveness of MPH for ADHD in SMS, incorporating personalized outcome measures. This protocol presents the first properly powered N-of-1 study in a rare genetic neurodevelopmental disorder, providing a much-needed bridge between science and practice to optimize evidence-based and personalized care.
Trial registration: This study is registered in the Netherlands Trial Register (NTR9125)

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Orv Hetil. 2021 Oct;162:1703-08.

POSSIBLE ASSOCIATION BETWEEN METHYLPHENIDATE TREATMENT IN A CHILD WITH AUTISM SPECTRUM DISORDER AND SUBSEQUENT GYNECOMASTIA.

Kollrovics N, Nagy P, Balazs J.

Summary. Although gynecomastia associated with methylphenidate monotherapy in the treatment of attention deficit hyperactivity disorder has already been reported in some adverse event databases, based on a review of the literature it appears that only five case reports have been published. In our study, we present the case of a child diagnosed with both autism spectrum disorder and attention deficit/hyperactivity disorder, who developed bilateral gynecomastia in association with continuous methylphenidate monotherapy for 6 months. With immediate cessation of methylphenidate therapy, clomiphene treatment was given for 10 days. A total of 14 days after cessation of methylphenidate treatment gynecomastia receded on both sides. After a methylphenidate drug-free period of 3 months, methylphenidate therapy was restarted, but 1 month later the side effect reappeared. The relationship between methylphenidate and the development of gynecomastia raises questions about a number of mechanisms. From a child psychiatrist point of view, it is an interesting question whether the presence of comorbid autism spectrum disorder and attention deficit/hyperactivity disorder may be relevant in the onset of adverse events by medication. The phenomenon may also be caused by altered regulation of the neuroendocrine-immune system. Our case report draws the attention of practicing physicians to monitoring of potential gynecomastia during methylphenidate therapy.

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Pediatr Ann. 2020 Oct;49:e431-e435.

MANAGEMENT OF ADVERSE EFFECTS OF PSYCHOTROPIC MEDICATIONS.

Romba C, Perez-Reisler M.

Psychotropic medications are an essential component of treating pediatric mental health disorders, and pediatricians are increasingly likely to prescribe them. Commonly used psychotropic medications include stimulants and nonstimulants used in the treatment of attention-deficit/hyperactivity disorder (ADHD); antidepressants used in the treatment of anxiety and depression; and antipsychotics indicated for use in autism, schizophrenia, mood disorders, severe impulsivity, and aggression. Stimulants are commonly associated with appetite suppression and initial insomnia and nonstimulants for ADHD are associated with sedation. Antidepressants are generally well tolerated; adverse effects include behavioral activation early in treatment and, rarely, treatment-emergent mania and suicidal ideation. Potential adverse effects of atypical antipsychotics include weight gain and metabolic syndrome. Monitoring strategies are reviewed

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Pediatr Transplant. 2020 Dec;24:e13832.

EARLY SCHOOL-AGE COGNITIVE PERFORMANCE POST-PEDIATRIC HEART TRANSPLANTATION.

Gold A, Bondi BC, Ashkanase J, et al.

BACKGROUND: As survival in pediatric heart transplantation (HTx) has improved due to medical advances, the analysis of long-term outcomes impacting quality of life such as cognition and development becomes increasingly important. Neuropsychological assessments provide a comprehensive understanding of individual needs, allowing for the development of tailored recommendations and interventions.
METHODS: Routine neuropsychological assessment was completed between 5 and 7 years of age in this cohort of pediatric HTx recipients at our center (Jan 2014-Oct 2018), including tests of general intellect

(WPPSI-IV, WISC-V), academics (WIAT-II/III), perceptual-motor abilities (Beery VMI), and memory (CMS). Relevant medical variables were collected.
RESULTS: Among 25 children, the median age at testing was 6.7 (IQR:5.8-7.4) years, with a median time since HTx of 5.2 (IQR:4.8-6.8) years. Medical diagnoses included congenital heart disease (CHD; 56%) and cardiomyopathy (44%). Cognitive functioning across the intellectual, academic, and perceptual-motor domains fell within the low-average range, while memory abilities fell within the average range. DSM-5 clinical diagnoses were provided for 14 (56%) children: Intellectual Disability-Mild (20%), Learning Disability (20%), Language Disorder (8%), and Attention-Deficit/Hyperactivity Disorder (12%). The presence of neurological issues and/or CHD predicted poorer performance on various neuropsychological domains.
CONCLUSIONS: Over 50% of this cohort of pediatric heart transplant recipients seen for routine post-HTx neuropsychological assessment received a clinical psychological diagnosis, notably higher than rates in the general population. This population requires monitoring to ensure that high risk children are identified and successfully supported in school and their community

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Pediatric Radiology. 2021;51:S43.

CORPUS CALLOSUM THICKNESS IN NF1 AND ITS CORRELATION WITH COGNITIVE, DEVELOPMENTAL, INTELLECTUAL ASSESSMENT, AUTISM SPECTRUM, AND ADHD.

Miranda Schaeubinger M, Tierradentro Garcia L, Kim J, et al.

Purpose: A number of neurological disorders are associated with Neurofibromatosis type I (NF1). Studies seeking to establish associations between these and brain characteristics lack sufficient sample sizes for robust statistical conclusions. Thickened corpus callosum (CC) is a known feature of NF1. We explored CC thickness and its association with cognitive, learning and developmental disorders, intellectual assessment, autism spectrum disorder (ASD) and attention-deficit/hyperactivity (ADHD).
Materials and Methods: CC thickness of NF1 patients aged 1 to 15 years was retrospectively measured from midline T1 sagittal MR images using a customized semi-automated MATLAB tool. Thickness at each location was compared to age-appropriate reference standards. Patient demographics and clinical evaluations were obtained from the electronical medical record.Mann-Whitney tests were used to compare the CC thickness at the level of the genu, body, isthmus, and splenium with different evaluation parameters.
Results: Ninety patients were included (median age 7 [5-7 IQR], 48 female [53.3%]). CC median thickness at all locations was significantly thicker than reference standards, except for the body in infancy and the splenium in early adolescence. Notable differences in CC thickness were found at the isthmus in infancy (1.9 mm median difference, p value = 0.037), splenium in infancy (3.1 mm median difference, p value = 0.037) and early childhood (1.7 mm median difference, p value = 0.003), and genu in infancy (3.9 mm median difference, p value = 0.037). Eleven children (12.2%) had ASD, and 38 (42.2%) ADHD; of these, 6 children (6.7%) had both ASD and ADHD. Median CC thicknesswas significantly larger at the genu (p=0.005) and body (p=0.005) in children with learning disorders; and at the body in children with behavioral or cognitive disorders (p=0.07) and those with global cognitive delay (p=0.044). Median isthmus was thicker in children with ADHD (p=0.008).
Conclusion: Semi-automated evaluation of CC thickness demonstrated thicker CC median values than published reference standards. The CC was significantly thicker in patients with learning disorders, behavioral or cognitive development disorders, and ADHD. Further studies with larger sample sizes, longitudinal assessments, and control comparison could expound the relationship between CC thickness and these disorders in children with NF1

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Pediatrics. 2021;148.

SIX STAGES OF ENGAGEMENT IN ADHD TREATMENT DESCRIBED BY DIVERSE, URBAN PARENTS.

Spencer AE, Sikov J, Loubeau JK, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental condition in children. Although ADHD is treatable, barriers remain to engagement in treatment, especially among socioeconomically disadvantaged and racial and ethnic minority families. Our goal was to examine the

process by which families engage in ADHD treatment and to identify targets for an intervention to improve engagement in care.
METHODS: We conducted in-depth semistructured qualitative interviews with 41 parents of diverse youth aged 3 to 17 years old in treatment of ADHD at an urban safety net hospital. Parents were asked about their journey through diagnosis and treatment, community attitudes about ADHD, and other factors influencing treatment access and decision-making. Transcripts were analyzed by using thematic analysis.
RESULTS: Of children with ADHD, 69.2% were male, 57.7% were Black or African American, and 38.5% were of Hispanic, Latino, or Spanish origin. Parents were 92.7% female, were 75.6% English speaking, and had a median income of $20 000. Parents described 6 stages to the process of engaging in care for their child's ADHD, which unfolded like a developmental process: (1) normalization and hesitation, (2) fear and stigmatization, (3) action and advocacy, (4) communication and navigation, (5) care and validation, and (6) preparation and transition. Barriers often occurred at points of stage mismatch between parents and providers and/or systems. Difficulty resolving an earlier stage interfered with the progression through subsequent stages.
CONCLUSIONS: The 6 stages framework could be used to develop new strategies to measure engagement and to design family-centered interventions to facilitate engagement in ADHD treatment

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Pharmacoepidemiol Drug Saf. 2021;30:166-67.

CHILDREN'S RELATIVE AGE AND MEDICINE TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) ACROSS AUSTRALIAN JURISDICTIONS WITH DIFFERENT SCHOOL ENROLMENT POLICIES.

Bruno C, Havard A, Hanly M, et al.

Background Objective: Children who are relatively young for their school grade are more likely to receive treatment for attention-deficit/hyperactivity disorder (ADHD); this is known as the relative age effect. Objectives: We described the association between children's relative age and initiation of ADHD medicines across six Australian jurisdictions with different school enrolment ages and options to delay school entry.
Methods: We used Australia-wide dispensing data for a 15% random sample of children aged 4-9 years in 2013-2017. We assumed children started school in the year that they first met the school starting age criterion in their jurisdiction of residence. We did not consider this a reasonable assumption in NSW where 27% of children delay school entry, thus we used a separate linkage of prescribing and education data for NSW residents starting school in 2009 and 2012. We estimated incidence rate ratios (IRRs) for ADHD treatment using Poisson regression across children's birth month, sex and jurisdiction of school enrolment. We used asthma medicines as a negative control.
Results: We observed a relative age effect among girls in Victoria, Queensland, and Western Australia with an IRR of 2.1 (95% CI: 1.09-4.10), 1.9 (95% CI: 1.19-2.92), and 1.9 (95% CI: 0.96-3.88), respectively. We also observed a relative age effect among boys in Western Australia (IRR=1.7, 95% CI: 1.15-2.59), and borderline effect in the Australian Capital Territory and South Australia (IRR=1.9, 95% CI: 0.97-3.67). In NSW, the youngest were half as likely to initiate stimulant medicines than the relatively oldest who delayed school entry (girls: IRR = 0.7, 95% CI: 0.24-1.75 and boys IRR = 0.5, 95% CI: 0.29-0.78). We did not observe a relative age effect for the initiation of asthma medicines in any jurisdiction.
Conclusions: In jurisdictions with low rates of delayed school entry, relatively young children were more likely to initiate medicine treatment for ADHD than their older classmates. The association was more pronounced among girls than boys. The inverse association observed among boys in NSW warrants further investigation as it is likely a reflection of the characteristics and needs of the children who delay school entry and become the oldest children in the grade. Increased awareness around children's maturity differences and school readiness may enhance appropriate diagnosis and treatment of ADHD

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Pharmacoepidemiol Drug Saf. 2021;30:118.

PEDIATRIC OFF-LABEL ANTIPSYCHOTIC USE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A TIME-TO-EVENT ANALYSIS.

Lee H, Reis SD, Zhang C, et al.

Background: Off-label antipsychotic use for behavioral symptoms in pediatric attention-deficit/hyperactivity disorder (ADHD) poses safety concerns and has limited evidence of effectiveness. Objectives: We tested a hypothesis that the diagnosis of a disruptive behavior disorder (DBD) increases the risk of initiating an antipsychotic among a cohort of youth with ADHD.

Methods: A population-based, retrospective cohort study was conducted using the 2007-2015 IQVIA PharMetrics Plus data. To be included in the cohort, youth had to be aged 5-15 years old at the time of the ADHD diagnosis. To confirm that youth were receiving care for ADHD, there had to be evidence of 1) at least one inpatient visit, 2) two outpatient visits within three months, or 3) one outpatient visit and a stimulant medication within one month. A six-month baseline period preceded the index ADHD diagnosis. We excluded youth who, at baseline, had a diagnosis of DBD and evidence of bipolar disorder, schizophrenia and other psychosis, or autism, which are FDA approved indications for antipsychotic medication. Youth were followed until antipsychotic initiation or were censored at loss of coverage, receipt of an FDA-indicated diagnosis, or December 2015 (end of study). Cox proportional hazards models estimated the risk of antipsychotic use following the ADHD diagnosis. DBD diagnosis was modeled as a time-varying covariate such that person-time after the DBD diagnosis was considered 'exposed' time. We adjusted for other psychiatric and learning disorder diagnoses and other psychotropic medication use at baseline.

Results: In a cohort of 50,272 youth diagnosed with ADHD, 5,213 were diagnosed with DBD during the follow-up. The incidence rate of antipsychotic initiation was 19.4 (95% CI, 18.6 - 20.2) per 1000 person-years. A DBD diagnosis was associated with significantly elevated risk of antipsychotic initiation. Adjusting for demographics and baseline psychiatric diagnoses and psychotropic medication use, the risk of antipsychotic initiation after being diagnosed with DBD was 4.91 (95% CI, 4.45 - 5.42) times that without DBD. Risperidone, aripiprazole, and quetiapine were the most frequently prescribed antipsychotic drugs.

Conclusions: The risk of antipsychotic use among youth with ADHD is higher in the presence of DBD, suggesting that off-label use is for behavior problems

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Pharmacoepidemiol Drug Saf. 2021;30:372.

TREATMENT FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND THE RISK OF POISONING IN CHILDREN AND ADOLESCENTS.

Gao L, Man KK, Chan EW, et al.

Background: Children and adolescents with attention deficit hyperactivity disorder (ADHD) are at higher risk of poisoning. Currently, there is limited data on the association between ADHD treatment and poisoning.

Objectives: To investigate the association between methylphenidate (MPH) use and poisoning in children and adolescents.

Methods: Patients aged 5-18 years with methylphenidate (MPH) prescription and incident poisoning diagnosis between Jan 2001 and June 2020 were identified from the Hong Kong Clinical Data Analysis and Reporting System. A self-controlled case series study design was used to compare the incidence rate ratios (IRRs) of poisoning during different risk windows (30 days before the first MPH prescription, exposure periods within 30 days of the first prescription, and periods of subsequent exposure) compared to the reference window (other non-exposure periods).

Results: 42,203 patients were prescribed ADHD medications in Hong Kong, of which 417 were included in the analysis. Compared to other non-exposed periods, a higher risk of poisoning was found in 30 days before the first prescription (IRR=2.64, 95% confidence interval [CI] 1.33 to 5.22), and exposure periods within 30 days of the first prescription (IRR=2.18, 95% CI 1.06 to 4.48), but not during prolonged exposure. However, compared with 30 days before the first prescription as well as exposure periods within 30 days of the first prescription, there was a lower risk during the subsequent exposure (IRRs=0.49 and 0.60, respectively).

Conclusions: The risk of poisoning was higher shortly before and after the first MPH prescription and became lower during the subsequent prescription. Our results do not support an association between MPH treatment and increased risk of poisoning

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Pharmacoepidemiol Drug Saf. 2021;30:58-59.

PRENATAL ANALGESIC OPIOID EXPOSURE AND RISK OF ADHD IN CHILDHOOD.

Tronnes JN, Lupattelli A, Handal M, et al.

Background: In recent years, use of prescribed analgesic opioids has increased. Prior studies have reported that use of illicit opioids during pregnancy is associated with increased risk of attention-deficit/hyperactivity disorder (ADHD); however, knowledge regarding the effect of analgesic opioids is limited. Objectives: To examine the association between prenatal analgesic opioid exposure and ADHD in children, measured as parentalreported symptoms at child age 5 years, and ICD-10 diagnosis.

Methods: We used data from the Norwegian Mother, Father and Child Cohort Study (1999-2008) linked to other national health registries. The study included 73784 live-born singletons born to 62013 mothers who reported a pain related condition before and/or during pregnancy. Exposure to analgesic opioids was self-reported and classified according to timing (early or mid/late pregnancy) and duration (5 weeks vs 1-4 weeks). Two comparator groups were included; i) unexposed during pregnancy or ii) pre-pregnancy users only. Inverse probability of treatment weights was used to control for measured confounding. Cox regression were used to estimate Hazard Ratios (HR) and 95% confidence intervals (CI).

Results: Overall, 2.3% of children were prenatally exposed to analgesic opioids at least once during pregnancy. Exposure in early and mid/late pregnancy was borderline associated with an increased risk of child ADHD (early: wHR: 1.34, 95% CI: 0.90-2.02; mid/late: wHR: 1.32, 95% CI: 0.92-1.89) compared to unexposed, but not when prepregnancy users only acted as comparator (early: wHR: 1.13, 95% CI: 0.71-1.79; mid/late: wHR: 1.08, 95% CI: 0.70-1.68). Exposure in five or more weeks was associated with an increased risk of child ADHD (wHR: 1.60, 95% CI: 1.04-2.47) compared to exposure in 1-4 weeks. We found no association between timing or duration of prenatal analgesic opioid exposure and ADHD symptoms in 5-year-old children.

Conclusions: We found no associations between timing of analgesic opioid exposure during pregnancy and ADHD, both as diagnosis or symptoms. The risk of child ADHD was however elevated after exposure in five or more weeks, compared to exposure in 1-4 weeks. We cannot rule out the possibility of residual confounding by severity of the underlying pain conditions or other unmeasured confounders on our results. Adequate pain management in pregnancy should be discussed on an individual patient level bearing in mind the pros and cons of different analgesics

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Pharmacol Rep. 2021 Apr;73:386-404.

EFFECTS AND MECHANISMS OF PHTHALATES' ACTION ON NEUROLOGICAL PROCESSES AND NEURAL HEALTH: A LITERATURE REVIEW.

Hlisna-kova H, Kolena B, et al.

During the period of mass industrial production of plastic products, the quality of human health has decreased significantly, especially in children's neurodevelopmental disorders. Phthalates are endocrine-disrupting chemicals that can induce neurological disorders. This review aims to compile evidence concerning the associations between neurological disorders, such as attention-deficit/hyperactivity disorder, autism spectrum disorder, decreased masculine behavior, and phthalate exposure. Phthalates dysregulate the hypothalamic-pituitary-gonadal, adrenal, and thyroid axis, which is crucial for the neurodevelopmental process. Phthalates interfere with nuclear receptors in various neural structures involved in controlling brain functions and the onset of neurological disorders at the intracellular level. It is critical to increase the current knowledge concerning phthalates' toxicity mechanism to comprehend their harmful effect on human health

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Physiol Res. 2020 Dec;69:S513-S521.

CENTRAL AUTONOMIC REGULATION ASSESSED BY PUPILLARY LIGHT REFLEX IS IMPAIRED IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hamrakova A, Ondrejka I, Sekaninova N, et al.

It is assumed that the Attention Deficit Hyperactivity Disorder is associated with the central autonomic dysregulation, however, the studies are rare. Analysis of pupillary light reflex represents a non-invasive tool to provide information related to the central autonomic regulation; thus, we aimed to evaluate potential

disturbances in the central autonomic integrity using pupillary light reflex examination in Attention Deficit Hyperactivity Disorder. We have examined 20 children with Attention Deficit Hyperactivity Disorder (10 boys, 13.0+/-2.3 years) and 20 age/gender-matched healthy subjects. Pupillary light reflex was examined at rest for both eyes using Pupillometer PLR-2000 (NeurOptics, USA). Evaluated parameters were: diameter of the pupil before the application of light stimulus and after illumination at the peak of the constriction, the percentual change of the pupil diameter during constriction, average constriction velocity, maximum constriction velocity and average dilation velocity. We found significantly lower percentual change of the pupil diameter during constriction for both eyes in Attention Deficit Hyperactivity Disorder group compared to controls (right eye: -25.81+/-1.23 % vs. -30.32+/-1.31 %, p<0.05, left eye: -25.44+/-1.65 % vs. -30.35+/-0.98 %, p<0.05). The average constriction velocity and maximum constriction velocity were significantly shortened in left eye in Attention Deficit Hyperactivity Disorder group compared to controls (p<0.05). Our findings revealed altered pupillary light reflex indicating abnormal centrally-mediated autonomic regulation characterized by parasympathetic underactivity associated with relative sympathetic predominance in children suffering from Attention Deficit Hyperactivity Disorder

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PLoS Genet. 2021 Jun;17:e1009590.

GENETIC SENSITIVITY ANALYSIS: ADJUSTING FOR GENETIC CONFOUNDING IN EPIDEMIOLOGICAL ASSOCIATIONS.

Pingault JB, Rijsdijk F, Schoeler T, et al.

Associations between exposures and outcomes reported in epidemiological studies are typically unadjusted for genetic confounding. We propose a two-stage approach for estimating the degree to which such observed associations can be explained by genetic confounding. First, we assess attenuation of exposure effects in regressions controlling for increasingly powerful polygenic scores. Second, we use structural equation models to estimate genetic confounding using heritability estimates derived from both SNP-based and twin-based studies. We examine associations between maternal education and three developmental outcomes - child educational achievement, Body Mass Index, and Attention Deficit Hyperactivity Disorder. Polygenic scores explain between 14.3% and 23.0% of the original associations, while analyses under SNP- and twin-based heritability scenarios indicate that observed associations could be almost entirely explained by genetic confounding. Thus, caution is needed when interpreting associations from non-genetically informed epidemiology studies. Our approach, akin to a genetically informed sensitivity analysis can be applied widely

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PLoS ONE. 2021;16.

OUTCOMES OF A 12-WEEK ECOLOGICALLY VALID OBSERVATIONAL STUDY OF FIRST TREATMENT WITH METHYLPHENIDATE IN A REPRESENTATIVE CLINICAL SAMPLE OF DRUG NA+»VE CHILDREN WITH ADHD.

Kaalund-Brok K, Houmann TB, Hebsgaard MB, et al.

Randomized placebo-controlled trials have reported efficacy of methylphenidate (MPH) for Attention-deficit/hyperactivity disorder (ADHD); however, selection biases due to strict entry criteria may limit the generalizability of the findings. Few ecologically valid studies have investigated effectiveness of MPH in representative clinical populations of children. This independently funded study aims to describe treatment responses and their predictors during the first 12 weeks of MPH treatment using repeated measurements of symptoms and adverse reactions (ARs) to treatment in 207 children recently diagnosed with ADHD. The children were consecutively included from the Child and Adolescent Mental Health Centre, Mental Health Services, The Capital Region of Denmark. The children (mean age, 9.6 years [range 7-12], 75.4% males) were titrated with MPH, based on weekly assessments of symptoms (18-item ADHD-rating scale scores, ADHD-RS-C) and ARs. At study-end 187 (90.8%) children reached a mean end-dose of 1.0 mg/kg/day. A normalisation/borderline normalisation on ADHD-RS-C was achieved for 168 (81.2%) children on the Inattention and/or the Hyperactivity-Impulsivity subscale in week 12, and 31 (15.0%) children were nonresponders, which was defined as absence of normalisation/borderline normalisation (n = 19) or discontinuation due to ARs (n = 12), and eight (3.8%) children dropped out from follow- up. Nonresponders were characterised by more severe symptoms of Hyperactivity- Impulsivity and global impairment before the treatment. ARs were few; the most prominent were appetite reduction and weight loss. A decrease in AR-like symptoms during the treatment period questions the validity of currently available standard instruments

designed to measure ARs of MPH. This ecologically valid observational study supports prior randomized placebo-controlled trials; 81.2% of the children responded favourably in multiple domains with few harmful effects to carefully titrated MPH.
Clinical trial registration: ClinicalTrials.gov with registration number NCT04366609

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PLoS ONE. 2021;16:e0258959.

PARENTS' PERSPECTIVES ON A SMARTWATCH INTERVENTION FOR CHILDREN WITH ADHD: RAPID DEPLOYMENT AND FEASIBILITY EVALUATION OF A PILOT INTERVENTION TO SUPPORT DISTANCE LEARNING DURING COVID-19.

Cibrian FL, Monteiro E, Ankrah E, et al.

Distance learning in response to the COVID-19 pandemic presented tremendous challenges for many families. Parents were expected to support children's learning, often while also working from home. Students with Attention Deficit Hyperactivity Disorder (ADHD) are at particularly high risk for setbacks due to difficulties with organization and increased risk of not participating in scheduled online learning. This paper explores how smartwatch technology, including timing notifications, can support children with ADHD during distance learning due to COVID-19. We implemented a 6-week pilot study of a Digital Health Intervention (DHI) with ten families. The DHI included a smartwatch and a smartphone. Google calendars were synchronized across devices to guide children through daily schedules. After the sixth week, we conducted parent interviews to understand the use of smartwatches and the impact on children's functioning, and we collected physiological data directly from the smartwatch. Our results demonstrated that children successfully adopted the use of the smartwatch, and parents believed the intervention was helpful, especially in supporting the development of organizational skills in their children. Overall, we illustrate how even simple DHIs, such as using smartwatches to promote daily organization and task completion, have the potential to support children and families, particularly during periods of distance learning. We include practical suggestions to help professionals teach children with ADHD to use smartwatches to improve organization and task completion, especially as it applies to supporting remote instruction

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PLoS ONE. 2021;16:e0248864.

PREVALENCE OF PSYCHIATRIC DISORDERS IN NORWEGIAN 10-14-YEAR-OLDS: RESULTS FROM A CROSS-SECTIONAL STUDY.

Bae T, Heiervang ER, Stormark KM, et al.

Youth mental health problems is the leading cause of disability worldwide and a major public health concern. Prevalence rates are needed for planning preventive interventions and health care services. We here report Norwegian prevalence estimates for youth mental disorders based on findings from the Bergen Child Study cohort. A web-based psychiatric interview; the Development and Well-Being Assessment, was completed by parents and teachers of 2,043 10-14-year-olds from the city of Bergen, Norway. Post-stratification weights were used to account for selective participation related to parental educational in the estimation of prevalence rates. Prevalence rates are presented for the whole sample and stratified by gender and age. The overall population weighted estimate suggests that 6.93% (95% CI 5.06-9.41) of the children met DSM-IV diagnostic criteria for one or more psychiatric disorders. There were no robust indications of age- or gender-related differences in the prevalence. 11.4% of the children fulfilled criteria for more than one diagnosis. The most common comorbid conditions were ADHD and disruptive disorders. The prevalence of psychiatric disorders was relatively low among Norwegian 10-14-year-olds, compared to published worldwide prevalence estimates. This is in line with estimates from prior studies from the Nordic countries. These findings raise important questions about the origins of different prevalence rates for psychiatric disorders between societies. The findings also illustrate the importance of locally driven epidemiological studies for planning preventative efforts and appropriately scaling mental health services to meet the need of the population

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Prim Care. 2021 Sep;48:475-91.
ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.
Fawns T.
The treatment of attention-deficit/hyperactivity disorder can be a very rewarding and challenging task. The management of this condition has impact on a child's performance in school in both academics and extracurriculars, and therefore, can be a determinant of what they are able to achieve and become. Treatment can also impact the child's self-image and ability to successfully interact with their peers. Adequate control of the disorder can break down barriers to successful development of a child's potential and ability to play a role in the work force someday

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Prim Care Companion CNS Disord. 2020 Sep;22.
METHYLPHENIDATE AMELIORATES WORSENING DISTRACTIBILITY SYMPTOMS OF MISOPHONIA IN AN ADOLESCENT MALE.
Osuagwu FC, Osuagwu VC, Machoka AM.

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Prim Care Companion CNS Disord. 2021 Jun;23.
COMORBID PSYCHIATRIC ASPECTS OF BAINBRIDGE-ROPERS SYNDROME.
Ikekwere JC, Osuagwu FC, LePlatte D, et al.
Objective: Bainbridge-Ropers syndrome (BRPS) is a neurodevelopmental genetic disorder associated with mutations in the additional sex combs-like ASXL3 gene on chromosome 18q12.1. The objective of this study is to describe the comorbid psychiatric aspects of BRPS.
Methods: A retrospective review was conducted of the electronic medical records of patients diagnosed with BRPS from 2013 to 2020 at an academic medical center. Results were deidentified and presented as frequencies and percentages.
Results: Seven cases (5 White males and 2 White females) of BRPS were identified. The mean age at the time of referral was 12 years, while the mean age at diagnosis of BRPS was 7 years. Comorbid psychiatric symptoms and diagnoses associated with BRPS included global developmental delay: 6 (86%), sleep impairment: 5 (71%), autism spectrum disorder: 3 (43%), speech impairment: 2 (29%), disruptive behavior: 4 (57%), attention-deficit/hyperactivity disorder: 3 (43%), self-injurious behavior: 3 (43%), aggression: 4 (57%), and seizures: 3 (43%). All 7 patients (100%) had multiple DSM-5 diagnoses.
Conclusions: These data highlight the need for awareness of the psychiatric comorbidity of BRPS. The findings also underscore the need for further research and emphasize the importance of multidisciplinary collaboration in the prompt assessment, diagnosis, and management of patients presenting with BRPS

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Prim Care Companion CNS Disord. 2021 May;23.
TRANSCRANIAL MAGNETIC STIMULATION FOR ADOLESCENTS WITH ADHD.
Patel RK, Saeed H, Mekala HM, et al.

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Probl Radiac Med Radiobiol. 2020 Dec;25:516-30.
PSYCHOLOGICAL STATE AND TYPOLOGICAL PERSONALITY FEATURES OF CHILDREN RESIDENTS OF RADIOACTIVELY CONTAMINATED TERRITORIES IN THE REMOTE PERIOD OF CHORNOBYL CATASTROPHE.
Poznysh VA, Stepanova EI, Kolpakov IE, et al.
OBJECTIVE: To evaluate the psycho-emotional state of children-residents of radioactively contaminated territoriesand to characterize the typological features of their personality in the remote period of the Chornobyl catastrophe.
MATERIALS AND METHODS: Psycho-emotional status and typological personality traits were determined in 96 childrenaged 12 to 17 years, who resided in radioactively contaminated territories with a soil contamination density of 137Csabove 185 kBq/m-2, and were admitted for examination and treatment in the

pediatric departments of the NRCRMclinic. Psycho-emotional state of children was determined using the test «non-existent animal», which was assessedin points on symptom complexes: anxiety, aggression and neuro-mental exhaustion. The questionnaire of A. Bassand A. Darkey was used to discriminate various aspects of the aggression symptom complex. In all children, the content of incorporated 137Cs was determined using a whole body counter.

RESULTS: The results of the evaluation of the psycho-emotional state of children - residents of radioactively contaminated territories in the remote period of the Chornobyl catastrophe according to the test Â«non-existent animalÂ»showed, that the state of anxiety was registered in all 96 children (100 %); state of aggression - in 60 children (62.5 %); exhaustion - in 57 children (59.37 %). Depending on the prevalence of the one or another symptom complexes, or their combination, 5 groups of observations were formed and the personality traits of children characteristic for each group were determined. In the largest group I with the predominance of anxiety symptom complex (45,83 % of the total sample) were noted: stable tendency to perceive many life-threatening situations and environment, pessimistic assessment of one's own life perspective, constant high level of anxiety. Girls were in majorityin this group. For group II, which showed a combination of high rates of two symptom complexes - anxiety andaggression (18.75 % of the total sample), the characteristic personality traits were a constant high level of emotional tension, a tendency to perceive the environment with distrust and a sense of guilt that arouses. In group IIIof children (14.58 % of the total sample), the symptom complex of aggression with feelings of alienation, isolationand hostile attitude towards the environment prevailed. Group IV of children (16.67 % of the total sample), with thecombination of signs of exhaustion and anxiety, had poor ability to concentrate, memory and attention deficit disorders, decreased learning ability, constant fatigue and irritability, apathy, inactivity, and inertia. Group V (only 4.17 %of the total sample) was characterized by low (less than 2 points) indices of all three symptom complexes. Girls weremuch more prone to anxiety, boys were more aggressive, sometimes accompanied by anxiety. Symptom complex ofexhaustion was determined with the same frequency in both boys and girls.

CONCLUSION: Assessment of psycho-emotional sphere of children - residents of radioactively contaminated territories in the remote period of the Chornobyl catastrophe according to the «non-existent animal» test revealed in of100 % of children the presence of anxiety signs, in the vast majority - the state of aggression and exhaustion. Therewere no probable associations between the content of incorporated 137Cs (in the range from 111 to 7024 Bq) and thepeculiarities of the psycho-emotional state of children

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Progress in Brain Research. 2021;264:91-116.

TRANSCRANIAL DIRECT CURRENT STIMULATION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A META-ANALYSIS OF CLINICAL EFFICACY OUTCOMES.

Brauer H, Breitling-Ziegler C, Moliadze V, et al.

Background: Evidence for the application of transcranial direct current stimulation (tDCS) in the clinical care of attention-deficit/hyperactivity disorder (ADHD) is limited. Therefore, we aimed to summarize study results using meta-analyses of measures of the cardinal symptoms of ADHD.

Methods: We conducted a systematic literature search (PubMed/pubpsych/PsychInfo/WOS) until 01/05/2020 for randomized controlled trials (RCTs) evaluating tDCS vs. control condition in patients with ADHD. A random effects meta-analysis of symptom-related outcomes was performed separately for data on the immediate effect and follow-up. Subgroup- and metaregression analyses for patient characteristics and tDCS parameters were included.

Results: Meta-analyzing 13 studies (n = 308, age = 23.7-¦ 13.3), including 20 study arms, tDCS had an immediate effect on overall symptom severity, inattention, and impulsivity, but not on hyperactivity. Results were significant in children and adolescents (8 studies, n = 133, age = 12.4 -¦ 3.0). Follow-up data (3 days 4 weeks after stimulation) suggested an ongoing beneficial effect regarding overall symptom severity and a delayed effect on hyperactivity.

Discussion: TDCS seems to be a promising method to treat clinical symptoms in ADHD with long-lasting effects. Still, more research considering the individual neuropsychological and anatomical dispositions of the subjects is needed to optimize tDCS protocols and efficacy. Safety issues of tDCS treatment in children and adolescents are addressed

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Progress in Brain Research. 2021;264:363-86.

TRANSCRANIAL DIRECT-CURRENT STIMULATION AND PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) FINDINGS FROM AN INTERVIEW ETHICS STUDY WITH CHILDREN, ADOLESCENTS, AND THEIR PARENTS.

Sierawska A, Prehn-Kristensen A, Brauer H, et al.

Introduction: Transcranial direct current stimulation (tDCS) is a brain stimulation technique for an alternative or complementary treatment for various neurological disorders, including pediatric ADHD. However, little is known about the experiences of participants undergoing tDCS treatments in clinical trials. Exploration of their views on the matter is an important contribution to the societal debate on ethical issues of tDCS, allowing for a responsible translation into clinical practice and timely identification of potential challenges.
Methods: in-depth interviews study with children with ADHD undertaking tDCS and their parents (n = 32).
Results: Children reported overall good experiences with the stimulation, although they found participation in the clinical study very tiring and time consuming. Their responses to the actual effects of the stimulation were mixed. Parents were very keen for their children to participate in the study as they saw it as a promising and safe alternative to medication. Even though many of them understood the techniques, they often did not see the link between the (current) lack of side effects and an absence of longitudinal studies. Unlike children, interviewed parents were cautious about using tDCS for non-medical/enhancement purposes.
Discussion: There is a need for more transparent information about the state of the art of tDCS, its function and what it actually might be able to offer. It is especially important in order to prevent unrealistic hopes and to make sure that future pediatric patients and their carers are more aware of the potential side-effects and long-term effects of tDCS

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Psicothema. 2021 Feb;33:139-45.

PSYCHOMETRIC PROPERTIES AND NORMATIVE INFORMATION ON THE CHILD AND ADOLESCENT BEHAVIOR INVENTORY WITH RATINGS FOR SPANISH CHILDREN FROM PARENTS AND TEACHERS.

Burns GL, Servera M, Becker SP.

BACKGROUND: Psychometric properties and initial normative information are provided for the sluggish cognitive tempo, attention-deficit/hyperactivity disorder-inattention, attention-deficit/hyperactivity disorder-hyperactivity/impulsivity, oppositional defiant disorder, callous-unemotional behavior (limited prosocial emotions specifier), anxiety, depression, social impairment, and academic impairment scales of the Spanish Child and Adolescent Behavior Inventory.
METHOD: Mothers, fathers, and teachers of 2,142 third to sixth grade Spanish children (49.49% girls; ages 8-13) from randomly selected schools on the Balearic Islands completed the Child and Adolescent Behavior Inventory.
RESULTS: Scores from the scales demonstrated reliability (internal consistency and inter-rater), structural validity, and convergent/discriminant validity with attention-deficit/hyperactivity disorder and learning disorder diagnoses for boys and girls separately for each source. Normative information (T-scores) is provided for the nine scales separately for boys and girls, with test information functions supporting use of the symptom scales for screening purposes.
CONCLUSIONS: Although more comprehensive Spanish norms are still needed, the initial normative information on the scales should be useful to inform the clinical care of individual Spanish children, with the positive psychometric properties of the scores also supporting the use of the scale for research. Copies of the Spanish Child and Adolescent Behavior Inventory and norms are available for free to clinicians and researchers

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Psychiatriki. 2020 Oct;31:332-40.

DISENTANGLING PEDIATRIC BIPOLAR DISORDER AND ATTENTION DEFICIT-HYPERACTIVITY DISORDER: A NEUROPSYCHOLOGICAL APPROACH.

Zaravinos-Tsakos F, Kolaitis G.

The clinical and diagnostic debate circulating pediatric bipolar disorder (PBD) has been highlighted as one of the most controversial themes in child psychiatry. With atypical symptomatic expression, constituting its predominant diagnostic discrepancy, PBD is manifested through prolonged manic episodes and affective

storms, lacking the symptomatic cycling and episodic nature presented in adult BD. Apart from its unique clinical presentation, the substantial symptomatic overlap with attention deficit hyperactivity disorder (ADHD) indicate an important diagnostic challenge in PBD. Specifically, both disorders share core characteristics such as irritability, hyperactivity, excessive talking and distractibility. Against this background of findings on the overlapping symptomatology between PBD and ADHD, current research guidelines highlight the need of exploring non-symptomatic markers as potential clinical phenotypes. Especially in disorders with distinctive biologic underpinnings, both clinicians and researchers have shown increased interest in establishing neuropsychological profiles. Recent neuropsychological studies indicated the distinct nature of neurocognitive deficits in PBD, describing impairments in various cognitive skills during acute episodes phases, while this severe deterioration of cognitive deficits appears to persist even during euthymic states. Regarding neuropsychological assessment in AHD, recent findings suggested dysfunctions in the domains of working memory, verbal memory and response inhibition. Furthermore, neuroimaging studies are fast becoming a key instrument to establish distinct neuropsychological profiles for PBD and ADHD. A large number of neuroimaging studies have indicated abnormalities in limbic, cortical and subcortical brain systems, while meta-analytic findings of voxel based morphometric studies highlight abnormalities in dorsolateral and lateral orbitofrontal-temporal areas in PBD. In recent neuroimaging findings with focus on neurocognitive performance during an emotional Stroop task, patients diagnosed with ADHD indicated activation on higher cortical centres associated with processing speed and significantly decreased role of sustained attention. Furthermore, these findings suggest emotional regulation and inhibitory control are moderately intercorrelated, adding more complexity to the theme of neurocognitive deficits in ADHD. These observations on the neurobiological mechanisms of cognitive impairments in PBD appear to provide robust evidence on a potential specific neuropsychological profile of PBD, the relationship between mood states and neuropsychological functioning, and the link between emotion generation and regulation in children with PBD

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Psychiatry Res. 2021 Jul;301:113985.

ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND PSYCHOLOGICAL DISTRESS, HAZARDOUS DRINKING, AND PROBLEM GAMBLING: A POPULATION-BASED STUDY.

McDonald AJ, Cook S, Turner NE, et al.

Recognition of ADHD in the adult population is relatively recent. Epidemiological research examining the mental health impact of ADHD in adulthood is thus limited. The objective of this study was to examine whether adult ADHD symptoms are associated with psychological distress, hazardous drinking, and problem gambling, after controlling for traumatic brain injury and sociodemographic characteristics. We analyzed data from a population-based survey administered in 2015 and 2016 to adults aged 18 years and over in Ontario, Canada (N = 3,817). Logistic regression was used to construct unadjusted and multivariable models for each of the three focal relationships. In the unadjusted models, ADHD symptoms were significantly related to psychological distress (OR = 9.3; 95% CI:6.1, 14.0) and hazardous drinking (OR = 2.1; 95% CI: 1.3, 3.4), but not to problem gambling (OR = 1.5; 0.5, 4.3). After adjustment, ADHD symptoms were significantly related to psychological distress (OR = 7.1; 95% CI: 4.6, 11.1), but not hazardous drinking (OR = 1.4; 95% CI: 0.8, 2.5) or problem gambling (OR = 0.6; 95% CI: 0.2, 2.5). This study further highlights the importance of clinicians assessing for concomitant ADHD and psychological distress in adults

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Psychol Med. 2021 Jan;51:290-99.

COORDINATION DIFFICULTIES, IQ AND PSYCHOPATHOLOGY IN CHILDREN WITH HIGH-RISK COPY NUMBER VARIANTS.

Cunningham AC, Hall J, Owen MJ, et al.

BACKGROUND: The prevalence and impact of motor coordination difficulties in children with copy number variants associated with neurodevelopmental disorders (ND-CNVs) remains unknown. This study aims to advance understanding of motor coordination difficulties in children with ND-CNVs and establish relationships between intelligence quotient (IQ) and psychopathology.

METHODS: 169 children with an ND-CNV (67% male, median age = 8.88 years, range 6.02-14.81) and 72 closest-in-age unaffected siblings (controls; 55% male, median age = 10.41 years, s.d. = 3.04, range 5.89-

14.75) were assessed with the Developmental Coordination Disorder Questionnaire, alongside psychiatric interviews and standardised assessments of IQ.
RESULTS: The children with ND-CNVs had poorer coordination ability (b = 28.98, p < 0.001) and 91% of children with an ND-CNV screened positive for suspected developmental coordination disorder, compared to 19% of controls (OR = 42.53, p < 0.001). There was no difference in coordination ability between ND-CNV genotypes (F = 1.47, p = 0.184). Poorer coordination in children with ND-CNV was associated with more attention deficit hyperactivity disorder (ADHD) (Î² = -0.18, p = 0.021) and autism spectrum disorder trait (Î² = -0.46, p < 0.001) symptoms, along with lower full-scale (ÃŸ = 0.21, p = 0.011), performance (Î² = -0.20, p = 0.015) and verbal IQ (Î² = 0.17, p = 0.036). Mediation analysis indicated that coordination ability was a full mediator of anxiety symptoms (69% mediated, p = 0.012), and a partial mediator of ADHD (51%, p = 0.001) and autism spectrum disorder trait symptoms (66%, p < 0.001) as well as full scale IQ (40%, p = 0.002), performance IQ (40%, p = 0.005) and verbal IQ (38%, p = 0.006) scores.
CONCLUSIONS: The findings indicate that poor motor coordination is highly prevalent and closely linked to risk of mental health disorder and lower intellectual function in children with ND-CNVs. Future research should explore whether early interventions for poor coordination ability could ameliorate neurodevelopmental risk

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Psychol Med. 2021 Jan;51:329-39.

SHARED ALTERATIONS IN RESTING-STATE BRAIN CONNECTIVITY IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THEIR UNAFFECTED FIRST-DEGREE RELATIVES.

Pironti VA, Vatansever D, Sahakian BJ.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a developmental condition that often persists into adulthood with extensive negative consequences on quality of life. Despite emerging evidence indicating the genetic basis of ADHD, investigations into the familial expression of latent neurocognitive traits remain limited.
METHODS: In a group of adult ADHD probands (n = 20), their unaffected first-degree relatives (n = 20) and typically developing control participants (n = 20), we assessed endophenotypic alterations in the default mode network (DMN) connectivity during resting-state functional magnetic resonance imaging in relation to cognitive performance and clinical symptoms. In an external validation step, we also examined the dimensional nature of this neurocognitive trait in a sample of unrelated healthy young adults (n = 100) from the Human Connectome Project (HCP).
RESULTS: The results illustrated reduced anti-correlations between the posterior cingulate cortex/precuneus and right middle frontal gyrus that was shared between adult ADHD probands and their first-degree relatives, but not with healthy controls. The observed connectivity alterations were linked to higher ADHD symptoms that was mediated by performance in a sustained attention task. Moreover, this brain-based neurocognitive trait dimensionally explained ADHD symptom variability in the HCP sample.
CONCLUSIONS: Alterations in the default mode connectivity may represent a dimensional endophenotype of ADHD, hence a significant aspect of the neuropathophysiology of this disorder. As such, brain network organisation can potentially be employed as an important neurocognitive trait to enhance statistical power of genetic studies in ADHD and as a surrogate efficacy endpoint in the development of novel pharmaceuticals

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Psychoneuroendocrinology. 2021;134.

GESTATIONAL DIABETES MELLITUS, AUTISTIC TRAITS AND ADHD SYMPTOMS IN TODDLERS: PLACENTAL INFLAMMATORY AND OXIDATIVE STRESS CYTOKINES DO NOT PLAY AN INTERMEDIARY ROLE.

Zhu B, Deng F, Yan S, et al.

Objective: To evaluate whether gestational diabetes mellitus (GDM) is associated with increased risks of autistic traits and attention deficit/hyperactivity disorder (ADHD) among offspring and whether placental inflammatory and oxidative stress cytokines play an intermediary role.
Methods: Based on a prospective cohort study from China, namely, the Ma'anshan Birth Cohort study (MABC), 3260 mother-child pairs were included. Autistic traits and ADHD symptoms among children were assessed at 18 months and 36 months, respectively. The mRNA expression levels of fourteen placental

cytokines were determined using PCR. Logistic regression analysis was used to examine the associations between GDM and the risks of autistic traits or ADHD symptoms. Mediation analysis was used to assess the potential mediation effects of certain placental inflammatory factors.
Results: Of the 3260 children, 419 (12.85%) were exposed to GDM. The prevalence rates of autistic traits and ADHD symptoms were 13.86% and 6.4%, respectively. A 48.6% increased risk of autistic traits was observed among offspring born to mothers with GDM [odds ratio (OR) = 1.49, 95% confidence interval (95%CI): 1.11ΓÇô2.00)], while no significant association was found in terms of ADHD symptoms. There were significant positive associations between GDM and IL-10 expression and between HIF1-+¦ and CRP mRNA expression and a significant negative association between GDM and CD206 mRNA expression. The expression of MCP-1 mRNA was negatively associated with the risk of autistic traits [adjusted OR = 0.73 (95%CI: 0.73-0.55)]. The levels of TNF-+¦ were positively associated with the risk of ADHD symptoms [OR = 2.11 (95%CI: 1.39-3.21)], while GRP78 was inversely associated with it [OR = 0.64 (95%CI: 0.44-0.94)]. However, none of the 14 placental cytokines was involved as a key mediator.
Conclusion: Our findings suggest that GDM may act as a risk factor for autistic traits in offspring, while the biological mechanisms may not involve the 14 placental cytokines studied. No significant association between GDM and ADHD symptoms was observed

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Res Child Adolesc Psychopathol. 2021 Nov;49:1403-17.

THE EFFECTS OF CHOICE ON THE READING COMPREHENSION AND ENJOYMENT OF CHILDREN WITH SEVERE INATTENTION AND NO ATTENTIONAL DIFFICULTIES.

Kakoulidou M, Le Cornu KF, Filippi R, et al.

It has been proposed that enhancing motivation supports the learning of children with Attention Deficit Hyperactivity Disorder (ADHD). Less is known if inattentive children with no ADHD diagnosis may similarly benefit, when being motivated to engage in an academic task. Using a repeated-measures design, this study investigated the effects of text choice as an intrinsic motivator on the reading comprehension and enjoyment of Year 4 children attending mainstream primary schools (N=92; aged 8-9 years; 48 boys); comparing those with no attentional difficulties and severe inattention. We hypothesized that 1) choice would increase reading comprehension and enjoyment 2) choice would increase the reading comprehension and enjoyment of children both with severe inattention and no attentional difficulties 3) choice effects would be significantly greater for children with severe inattention than those with no attentional difficulties. Children participated in a reading intervention that included a Choice (experimental) and a No Choice (control) condition. Child inattention was measured via a Virtual Reality Continuous Performance Task (Omission errors, Reaction Time Variability) and Teacher Ratings. Choice significantly increased reading comprehension, but not enjoyment compared with no choice. Choice improved the reading comprehension of children with both severe inattention and no attentional difficulties. Choice did not benefit the reading of severely inattentive children more than that of children with no attentional difficulties. These findings underline the educational benefits of choice for young readers both with severe inattention and no attentional difficulties, which are further discussed drawing on existing theory and research

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Res Child Adolesc Psychopathol. 2021 Feb;49:197-210.

PRESCHOOL NEUROPSYCHOLOGICAL PREDICTORS OF SCHOOL-AGED SLUGGISH COGNITIVE TEMPO AND INATTENTIVE BEHAVIORS.

Becker SP, Dvorsky MR, Tamm L, et al.

Sluggish cognitive tempo (SCT) is characterized by excessive daydreaming, slowed thinking, and mental confusion and 'fogginess'. A growing body of research supports the empirical differentiation of sluggish cognitive tempo (SCT) from the inattentive (IN) behaviors that characterize attention-deficit/hyperactivity disorder (ADHD). Further SCT and IN are uniquely associated with clinical correlates across academic, social, and emotional domains; however, there is limited understanding of how neuropsychological functioning contributes to SCT and/or IN behaviors. The two broad domains of neuropsychological functioning that have been most frequently examined in relation to SCT behaviors are processing speed and executive functions (EF). The present study tested whether EF and processing speed measured when

children were on average age five years were predictive of teacher-rated IN and SCT behaviors in 1(st) - 3(rd) grades. Participants included 1,022 children from the Family Life Project, an ongoing prospective longitudinal study of child development in low-income, non-metropolitan communities. EF and processing speed uniquely made independent contributions to the prediction of IN and SCT. In secondary analyses that focused on specific facets of EF and processing speed, inhibitory control and working memory abilities predicted lower IN but not SCT behaviors, whereas slower processing speed significantly predicted both greater SCT and IN behaviors. These results are discussed as they inform developmental models of SCT and IN

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Res Child Adolesc Psychopathol. 2021 May;49:643-56.

CHILDREN'S ADHD SYMPTOMS AND FRIENDSHIP PATTERNS ACROSS A SCHOOL YEAR.

Lee Y, Mikami AY, Owens JS.

Symptoms of attention-deficit/hyperactivity disorder (ADHD) in elementary school-age children are associated with poor relationships with classroom peers, as indicated by poor social preference, low peer support, and peer victimization. Less is known about how friendship patterns relate to ADHD symptoms, or how friendships may buffer risk for negative peer experiences. Participants were 558 children in 34 classrooms (grades K-5). At the beginning (fall) and end (spring) of an academic year, children completed (a) sociometric interviews to index friendship patterns and social preference, and (b) self-report questionnaires about their support and victimization experiences from classmates. In fall, higher teacher-reported ADHD symptoms were associated with children having more classmates with no friendship ties (non-friends) and who the child nominated but did not receive a nomination in return (unreciprocated friends), and with having fewer classmates with mutual friendship ties (reciprocated friends) and who nominated the child but the child did not nominate in return (unchosen friends). Higher fall ADHD symptoms predicted more non-friend classmates, poorer social preference, and more victimization in the spring, after accounting for the same variables in fall. However, having many reciprocated friends (and to a lesser extent, many unchosen friends) in fall buffered against the trajectory between fall ADHD symptoms and poor peer functioning in spring. By contrast, having many unreciprocated friends in fall exacerbated the trajectory between fall ADHD symptoms and poor peer functioning in spring. Thus, elevated ADHD symptoms are associated with poorer friendship patterns, but reciprocated friendship may protect against negative classroom peer experiences over time

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Res Child Adolesc Psychopathol. 2021 Sep;49:1165-78.

CONDITIONAL LEARNING DEFICITS IN CHILDREN WITH ADHD CAN BE REDUCED THROUGH REWARD OPTIMIZATION AND RESPONSE-SPECIFIC REINFORCEMENT.

De MH, Tripp G, Beckers T, et al.

When children with ADHD are presented with behavioral choices, they struggle more than Typically Developing [TD] children to take into account contextual information necessary for making adaptive choices. The challenge presented by this type of behavioral decision making can be operationalized as a Conditional Discrimination Learning [CDL] task. We previously showed that CDL is impaired in children with ADHD. The present study explores whether this impairment can be remediated by increasing reward for correct responding or by reinforcing correct conditional choice behavior with situationally specific outcomes (Differential Outcomes). An arbitrary Delayed Matching-To-Sample [aDMTS] procedure was used, in which children had to learn to select the correct response given the sample stimulus presented (CDL). We compared children with ADHD (N=45) and TD children (N=49) on a baseline aDMTS task and sequentially adapted the aDMTS task so that correct choice behavior was rewarded with a more potent reinforcer (reward manipulation) or with sample-specific (and hence response-specific) reinforcers (Differential Outcomes manipulation). At baseline, children with ADHD performed significantly worse than TD children. Both manipulations (reward optimization and Differential Outcomes) improved performance in the ADHD group, resulting in a similar level of performance to the TD group. Increasing the reward value or the response-specificity of reinforcement enhances Conditional Discrimination Learning in children with ADHD. These

behavioral techniques may be effective in promoting the learning of adaptive behavioral choices in children with ADHD

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Res Dev Disabil. 2021;119.

INATTENTION, HYPERACTIVITY/IMPULSIVITY, AND MATHEMATICS: EXPLORING GENDER DIFFERENCES IN A NONCLINICAL SAMPLE.

Kuzmina Y, Ivanova A, Kanonirs G.

In this study, we considered two subscales of attention problem (AP) behaviour, inattentiveness and hyperactivity/impulsivity, as latent traits, extreme values of which indicate attention deficit hyperactivity disorder (ADHD). We examined gender differences in these traits in a community sample of Russian schoolchildren and estimated the extent to which the association of AP behaviour and math achievement varied for boys and girls. The data from a three-wave longitudinal study of math achievement of 958 children (49 % girls) were used, and growth in math achievement was estimated. The levels of inattentiveness and hyperactivity/impulsivity of each child were measured based on teachersΓÇÖ responses using the Behaviour Rating Scale (BRS). The results demonstrated that inattentiveness had a negative association with math achievement, while hyperactivity/impulsivity was positively associated with math achievement when inattentiveness was controlled for. Inattentiveness was negatively associated with math achievement in both boys and girls. However, the size of this association decreased over time for boys, so the gap between boys with high inattentiveness and low inattentiveness decreased from grade 1 to grade 2. Meanwhile, for girls, the association between inattentiveness and math remained stable, so the gap between girls with high inattentiveness and girls with low inattentiveness did not change

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Rev Psiquiatr Clin. 2021;48:155-61.

VOLUNTARY AND AUTOMATIC ORIENTING OF ATTENTION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mariani MMC, Lellis VRR, Novaes RACB, et al.

Objective: Voluntary and automatic orienting of attention enable proper processing of environmental information. Few studies have assessed how this process varies during development in children with attention deficit hyperactivity disorder (ADHD).

Methods: This study analyzed voluntary and automatic orienting in 30 children with ADHD and 30 age and sex matched controls (Control group-CG). Two experiments assessed voluntary and automatic orienting by recording reaction times (RT) to conditions in relation to temporal interval, spatial position, cue validity and age. The RT medians calculated for each condition and participant were analyzed using ANOVA to compare ADHD and CG.

Results: Children with ADHD exhibited globally higher RT than the CG group. They also showed prejudices during the reorienting process and demonstrated adequate voluntary orienting for shorter intervals. In automatic task, there was no group interaction, expressing early facilitation, but not inhibition of return.

Conclusion: These results identify correlations of ADHD and the children's age in relation to voluntary and automatic orienting of attention

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Rev Paul Pediatr. 2022;40.

CLINICAL CHARACTERISTICS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: ASSOCIATION WITH QUALITY OF LIFE AND BEHAVIORAL ASPECTS.

de Souza Oliveira M, Marinho MFD, Lemos SMA.

Objective: To identify associations between clinical characteristics of children with attention-deficit/hyperactivity disorder (ADHD) and their sociodemographic aspects, quality of life, and results from the strengths and difficulties questionnaire.

Methods: This is an observational analytical cross-sectional study with a non-probabilistic sample consisting of 72 children diagnosed with ADHD, aged 6 to 13 years, treated at 2 neuropediatric outpatient clinics. The instruments used were the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity

Disorder Swanson, Nolan, and Pelham, version IV (MTA-SNAP-IV), the Strengths and Difficulties Questionnaire (SDQ), the Brazilian Economic Classification Criteria (CCEB), and the Quality of Life Assessment Scale for Children and Adolescents (AUQEI). We performed descriptive, bivariate, and multivariate analyses, considering a 5% significance level.
Results: SDQ results were associated with abnormal MTA-SNAP-IV results (inattentive/hyperactive/combined). A 1-point increment in the SDQ score increased by 36.5% the likelihood of the child having an abnormal MTA-SNAP-IV classification. Regarding AUQEI, 30.6% of participants perceived their quality of life as poor and 69.4% as good.
Conclusions: A higher SDQ score increased the child's chance of having an abnormal MTA-SNAP-IV result

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Scand J Psychol. 2021 Jun;62:301-11.
RETROSPECTIVE SYMPTOMS AND LEARNING DIFFICULTIES PREDICTING ADHD IN ADULTS: DIFFERENCES BETWEEN PRISON INMATES AND THE CLINICAL POPULATION.
Rodra-guez C, Garca-a T, Areces D, et al.
People who suffer from ADHD in their childhood are more likely to be involved in criminal acts in late adolescence and adulthood. This study analyses the association between retrospective ADHD symptoms and associated problems (somatic and learning difficulties), and current symptoms in a sample of adults from imprisoned and clinical populations. Four hundred and fifty-seven participants, aged between 17 and 69 years, were divided into four groups: ADHD prison group without clinical history of symptoms (n=61), prison group (n=162), ADHD clinical group (n=176) and clinical group (n=58). The ADHD-IV scale and Wender Utah Rating Scale (WURS) were administered to the four groups and demonstrated high rates of persistence of ADHD symptoms into adulthood. ADHD groups reported significantly higher impairment both during childhood (symptoms, somatic and learning difficulties) and at present, with the ADHD clinical group being the most severely impaired. Finally, current symptoms of ADHD, along with childhood ADHD symptoms and learning difficulties, significantly predicted current impairments, but only in the clinical group. These findings represent some initial steps into the identification of predictors of ADHD symptomatology in adulthood in order to elucidate its etiopathogenesis and better identify high-risk groups for targeted prevention

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Sci Rep. 2021 May;11:9604.
QUANTIFIED ASSESSMENT OF HYPERACTIVITY IN ADHD YOUTH USING IR-UWB RADAR.
Lee WH, Kim JI, Kwon AM, et al.
Research on the quantification of hyperactivity in youth with attention-deficit/hyperactivity disorder (ADHD) has been limited and inconsistent. The purpose of this study was to test the discriminative value of impulse-radio ultra-wideband (IR-UWB) radar for monitoring hyperactive individuals with ADHD and healthy controls (HCs). A total of 10 ADHD patients and 15 HCs underwent hyperactivity assessment using IR-UWB radar during a 22-min continuous performance test. We applied functional ANOVA to compare the mean functions of activity level between the 2 groups. We found that the mean function of activity over time was significantly different and that the activity level of the ADHD group slightly increased over time with high dispersion after approximately 7 min, which means that the difference in activity level between the two groups became evident at this period. Further studies with larger sample sizes and longer test times are warranted to investigate the effect of age, sex, and ADHD subtype on activity level function

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Sleep Med. 2021;87:174-82.
ASSOCIATIONS BETWEEN SLEEP, DAYTIME SLEEPINESS AND FUNCTIONAL OUTCOMES IN ADOLESCENTS WITH ADHD.
Loram G, Silk T, Ling M, et al.
Objective/background: Adolescents with attention-deficit/hyperactivity disorder (ADHD) experience greater difficulties in the domains of sleep, daytime sleepiness, and functioning compared to their peers. However, the relationship between these domains has not been fully elucidated. This study aimed to examine the relationship between sleep problems (including daytime sleepiness), ADHD severity, and functional

outcomes (irritability, sluggish cognitive tempo, homework difficulties, and substance use) in a sample of adolescents with ADHD.
Patients/methods: Eighty-two adolescents (13ΓÇô17 years) and their families participated in the study. Sleep was measured by both adolescent and parent-report. Adolescent irritability and sluggish cognitive tempo were reported by both adolescents and parents, while other variables were reported by a single reporter (homework difficulties parent; ADHD severity parent; substance use adolescent). Analyses controlled for demographic factors and internalising and externalising comorbidities.
Results: A weak relationship was found between adolescent-reported sleep problems and daytime sleepiness, which became non-significant in adjusted analyses (β = -0.19, p = 0.115). In adjusted analyses, there was an association between adolescent-reported sleep problems and adolescent-reported irritability (β = -0.27, p = 0.023) as well as between adolescent-reported daytime sleepiness and parent-reported sluggish cognitive tempo (β = 0.28, p = 0.033). In adjusted analyses, parent-reported adolescent sleep problems were associated with ADHD severity (β = 0.54, p = <0.001), parent-reported sluggish cognitive tempo (β = 0.64, p = <0.001), both reporters of irritability (parent-report: β = 0.32, p = 0.004; adolescent-report: β = 0.29, p = 0.022), and homework problems (β = 0.37, p = 0.003). Parent-reported daytime sleepiness was associated with parent-reported sluggish cognitive tempo (β = 0.34, p = 0.024).
Conclusions: This study demonstrates the importance of a holistic assessment of adolescents with ADHD, not only focusing on symptomatology but also on sleep problems and functional outcomes. The importance of multi-informant assessment of sleep problems is also reinforced

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Soc Cogn Affect Neurosci. 2021 Sep;16:1100-10.

EARLY MATERNAL CARE AND AMYGDALA HABITUATION TO EMOTIONAL STIMULI IN ADULTHOOD.

Holz NE, HÃ¤ge A, Plichta MM, et al.

Evidence suggests that maternal care constitutes a protective factor for psychopathology which may be conditional on the level of family adversity. Given that psychopathology is frequently linked with social deficits and the amygdala with social functioning, we investigated the impact of early maternal care on amygdala function under high vs low familial risk for psychopathology. Amygdala activity and habituation during an emotional face-matching paradigm was analyzed in participants of an epidemiological cohort study followed since birth (=172, 25 years). Early mother-infant interaction was assessed during a standardized nursing and play setting at the age of 3 months. Information on familial risk during the offspring's childhood and on the participants' lifetime psychopathology was obtained with diagnostic interviews. An interaction between maternal stimulation and familial risk was found on amygdala habituation but not on activation, with higher maternal stimulation predicting stronger amygdala habituation in the familial risk group only. Furthermore, amygdala habituation correlated inversely with Attention Deficit Hyperactivity Disorder (ADHD) diagnoses. The findings underline the long-term importance of early maternal care on the offspring's socioemotional neurodevelopment and of interventions targeting maternal sensitivity early in life, particularly by increasing maternal interactive behavior in those with familial risk

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Soc Psychiatry Psychiatr Epidemiol. 2021 Nov;56:2063-72.

INCIDENCE AND COMORBIDITIES OF DISRUPTIVE BEHAVIOR DISORDERS DIAGNOSED IN FINNISH SPECIALIST PSYCHIATRIC SERVICES.

Uotila J, Gyllenberg D, Korhonen L, et al.

PURPOSE: Disruptive behavior disorders (DBD), including oppositional defiant disorder (ODD) and conduct disorder (CD), are some of the most common psychiatric conditions in childhood. Despite this, there has been limited research on DBDs. We examined the incidence, comorbidity and gender differences of DBDs diagnosed by specialist services.
METHOD: This was a nationwide register study of 570,815 children and adolescents born in 1996-2005. The 7050 individuals diagnosed with DBD by specialist healthcare services were matched to 26,804 controls.
RESULTS: By the age of 15, the cumulative incidence of diagnosed DBDs was 3.5% for boys and 1.4% for girls. The yearly incidence rate increased for girls after 13Â years of age, while the incidence for boys was relatively stable between 8 and 15 years of age. When we compared subjects born between 1996-1998 and

1999-2001, we found that by the age of 12, the cumulative incidence per 100 people had increased from 0.56 to 0.68 among girls and from 2.3 to 2.6 among boys. This indicated a minor increase in treated incidence. The parents of children diagnosed with DBDs had lower educational levels than the parents of controls. Children with DBD were also more likely to have been diagnosed with other psychiatric disorders.
CONCLUSION: Although DBDs were 3.5 times more common among boys during the whole follow-up period, the yearly incidence during adolescence was fairly similar between boys and girls. DBD existed alongside various psychiatric disorders at a relatively young age and only a minor increase in treated incidence was found during childhood

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Soc Psychiatry Psychiatr Epidemiol. 2021 Nov;56:2053-62.
PREVALENCE AND COMORBIDITY OF BORDERLINE PERSONALITY TRAITS IN THE QUEBEC GENERAL POPULATION AGED 12-14 YEARS.
Guil JM, Zavaglia E, Berthiaume C, et al.
PURPOSE: The early identification of borderline personality traits (BPT) in adolescents helps to prevent their progression. Data are available for the clinical population, but little has been published on the general population, especially regarding age and sex distribution in adolescence. Even less is known about the comorbidity of BPT with other mental disorders.
METHODS: We estimated the prevalence of BPT, by sex, age, and comorbidity, in a sample of adolescents aged 12-14Â years (n=799) from the Quebec Mental Health Survey. A complex sampling design was used to ensure representativeness. BPT was assessed with the abbreviated-diagnostic interview for borderlines-revised, with the adolescent as an informant. Reliability coefficients were above 0.80. Several levels of severity were explored using an independent criterion, defined by impairment according to the Columbia impairment scale.
RESULTS: The overall prevalence of BPT was 6.3%. Prevalence estimates for the most impaired were 3.2% for the entire sample and 1.3% for 12-year-olds. Prevalence increased significantly with age for most impairment levels but did not differ significantly between the sexes. In adolescents, BPT displayed moderate-to-strong comorbidity with anxiety (AD) and insomnia disorders, and very strong comorbidity with depressive (DD), attention deficit hyperactivity (ADHD), and oppositional defiant/conduct disorders (ODD/CD).
CONCLUSION: We, therefore, make two clinical recommendations for child psychiatry practice: (1) with respect to the lower rate of male adolescents attending BPT Health Programs, increase BPT screening in male adolescents; (2) evaluate BPT when children with ADHD or ODD/CD develop AD or DD during adolescence

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Soc Sci Med. 2021;291.
MEDICALIZATION AND MANHOOD: IS AN ADHD DIAGNOSIS EMERGING FOR ALLEGEDLY TROUBLESOME BOYS IN ACCRA, GHANA?
***Braer C, Agyekum HA*.**
Although mental health diagnoses and treatments are spreading across the globe, most medicalization research originates from the Global North, where diagnosis and treatment are well institutionalized. In this article, we examine the earliest possible emergence of ADHD diagnosis and treatment in the context of Ghanaian boys transition towards manhood. Based on ethnographic fieldwork among boys from different class backgrounds in Accra in 2017, we identify how interactional troubles arising at the tricky transition to manhood provide a fertile or inhibiting context for medicalization. Torn between norms of obedience, autonomy and striving for societal achievements, boys face obstacles on the road towards manhood that are not yet medicalized. We demonstrate that boys and adults use specific idioms (in Ghanaian local language Twi) to describe issues around overactivity and inattention, but do not refer to medical categories. Instead, we witness an emerging shift towards psychological counselling, potentially supported by global mental health actions, and Pentecostalism. This psychologizing might constitute an intermediate step towards medicalization of troubling interactions. However, the colonial stigma of psychiatric labels and the limited reach of psycho-medical institutions in Ghana make medicalization unlikely. At the same time, there is a possibility for medicalization at the intersection of interactional problems, inequality, the global spread of

psychiatry and transition to manhood. Medical labels and potentially ADHD might shift the blame from family to disease. The incipient introduction of diagnosis and treatment might engender a creolized notion of ADHD with disrespect being a core problem

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Sociol Health Illn. 2021 May;43:844-58.

MORE SCIENTIFIC, MORE ETHICAL: THE ADHD CONTROVERSY AND BOUNDARY-WORK IN TAIWAN.

Tseng FT.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most controversial childhood psychiatric condition. With the globalisation of its diagnosis and treatment, Taiwan has followed other medically advanced countries in meeting the challenge of medicalising children's problematic behaviours and encountering the resistance discourses on ADHD. To contribute to the extant literature, this study employs the social worlds framework to decipher the relational dynamics amongst these competing discourses on ADHD, namely the mainstream psychiatry, the critiques of overdiagnosis and the antipsychiatric protest, and to suggest the links between these domestic advocacies and the relevant debates abroad. In addition, the concept of boundary-work is used to analyse the strategies through which these collective actors pursue legitimacy for their respective claims. Based on the existing research of scientific and ethical boundary-work, this study argues that when it comes to clinical practices fraught with uncertainties, these two seemingly distinct forms of boundary-work may become mutually supportive in order to act as arbiters of disputes. Despite the disparity of power amongst these social worlds in this case study with seemingly predictable outcomes of the dispute, representing their heterogeneous narratives and the process of discursive struggle helps to destabilise the seemingly naturalised conceptualisation of biomedical ADHD

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Span J Psychol. 2021 Feb;24:e12.

WHAT PREDICTS LIFE SATISFACTION IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)? A STUDY FROM PARENT AND CHILD/ADOLESCENT PERSPECTIVES.

Garca-a T, et al.

The aim of this study was to analyze life satisfaction in a sample of 70 children and adolescents (M = 12.21, SD = 2.85) with Attention-Deficit/Hyperactivity Disorder (ADHD), according to parents' and children's/adolescents' reports. In addition, we examined the influence of a series of child/adolescent variables (ADHD presentation, and Conduct Disorder (CD) symptoms, age, gender, and pharmacological support status) on their levels of life satisfaction. Results indicated moderate correlations between children's/adolescents' and parents' perceptions of life satisfaction ($r = .40$; $p < .01$), with school being the area with the lowest levels of satisfaction. Also, 44.3% of the sample of parents reported that ADHD drastically interferes negatively in this context. Examining the effects of child/adolescent variables, only the variables age and CD symptoms generated statistically significant differences, showing that as children/adolescents grow up and/or present associate symptoms of CD, perceptions of life satisfaction tend to be more negative. These variables explained 34.5% of the variance of a composite score of life satisfaction, demonstrating a negative effect over the dependent variable. These results might have important implications for diagnosis and intervention in ADHD, as they highlight the relevance of considering life satisfaction as an important aspect to consider in both processes. Further studies must look more deeply into the mechanisms that explain these findings

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Subst Abus. 2021;42:13-32.

BEYOND THE TIP OF THE ICEBERG: A NARRATIVE REVIEW TO IDENTIFY RESEARCH GAPS ON COMORBID PSYCHIATRIC DISORDERS IN ADOLESCENTS WITH METHAMPHETAMINE USE DISORDER OR CHRONIC METHAMPHETAMINE USE.

Kuitunen-Paul S, Roessner V, Basedow LA, et al.

Methamphetamine use disorder (MUD) frequently begins in adolescence, often accompanied by other psychiatric or mental disorders. Up to now, no comprehensive review about MUD and comorbid disorders in adolescents is available. We thus aimed to review the literature on comorbid mental disorders and MUD in adolescents in order to identify future research topics. Method: A PubMed search was conducted in July

2019. Relevant comorbidities were defined as attention-deficit disorder with/without hyperactivity, anxiety disorders, depression, eating disorders, post-traumatic stress disorder, psychosis, borderline personality disorder, conduct disorder and antisocial personality disorder, as well as other substance use disorders. For each comorbidity, we summarized prevalence rates, findings on comorbidity mechanisms, and recommended treatment options, if applicable. Results: Few articles focused on MUD in adolescents. Prevalence rates differed largely between comorbid disorders, with tobacco use disorder, conduct disorder, post-traumatic stress disorder, anxiety disorders, and attention-deficit disorders being the most prevalent comorbidities while eating disorders were rare. Examined onset patterns and comorbidity mechanisms indicated three groups of comorbidities: preexisting disorders self-medicated with methamphetamine, disorders induced by chronic methamphetamine use, and disorders arising due to risk factors shared with MUD. Reviewed comorbidities were frequently associated with worse treatment outcomes. Conclusions: The limited evidence is in stark contrast to the presumably high prevalence and relevance of comorbid mental disorders in adolescents with MUD. Suggestions for future research topics, informed by adult findings, include genetic vulnerabilities, biological changes, and consequences of different use patterns. Surprisingly few MUD treatment programs explicitly integrate comorbid mental disorder modules

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Trials. 2021 Oct;22:752.

ORGANIZATIONAL SKILLS TRAINING FOR CHILDREN WITH ADHD: STUDY PROTOCOL FOR A RANDOMIZED, CONTROLLED TRIAL.

Bikic A, Dalsgaard S, Olsen KD, et al.

BACKGROUND: Problems with sustained attention, impulsivity, and hyperactivity are the most prominent symptoms of attention-deficit hyperactivity disorder (ADHD), but many children with this diagnosis also present with poor organizational skills that are important in relation to school. These problems tend to increase from childhood to adolescence and are often not well managed by medication. Organizational skills training (OST) is a range of behavioral interventions that specifically target organizational skills deficits. Evidence supports the effect of OST on improving organizational skills, inattention, and academic performance in children with ADHD. Because previous clinical trials included mostly children above the age of 8 years, this trial includes children in the age range 6-13 years to expand the knowledge on the effects of OST in younger children. Previous OST research has also shown improvement on inattention in parent ratings; we will investigate if a change in inattention can be confirmed with neurocognitive tests. Finally, little is known about predictors of treatment response in OST.

OBJECTIVES: The primary objective is to investigate if OST has positive effects on organizational skills in children with ADHD. The primary outcome measurement is the parent-rated Children's Organizational Skills Scale (COSS), collected before and at the end of the 10 week intervention. Secondary and exploratory outcomes include inattention ratings, family and school functioning, and cognitive functions measured before the intervention period, immediately after, and at 6 month follow-up. Additional objectives are to investigate both neurocognitive outcomes and age as predictors of treatment response.

METHODS: This is a randomized clinical superiority trial investigating the effect of OST vs a treatment-as-usual (TAU) control group for children with ADHD in the age range of 6-13 years. All participants (n=142) receive TAU. OST is administered in a group format of 10 weekly sessions. Adverse events are monitored by study clinicians during weekly therapy sessions and all assessments. Data analyses will be conducted using mixed linear regression models with random intercepts for patients, adjusted for the stratification variables and the baseline value.

PERSPECTIVES: This study will provide important new knowledge and expand on existing research in the field of non-pharmacological treatment of children with ADHD. OST can potentially have a significant impact on the lives of children with ADHD by helping them learn how to cope with their present deficits and to become more independent and self-reliant. It is also important to investigate predictors of treatment response in order to optimize OST.

TRIAL REGISTRATION: ClinicalTrials.gov NCT03160378 . Registered on May 19, 2017

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Turk Psikiyatri Derg. 2021;32:109-17.

THE RELATIONSHIP BETWEEN ALEXITHYMIA AND IMPULSIVENESS IN ADULT ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Kiraz S, et al.

OBJECTIVE: It has been emphasised recently that emotion regulation problems may be the core symptoms of attention deficit hyperactivity disorder (ADHD). In this study, we aimed to determine the incidence of alexithymia, the relationship between alexithymia and impulsiveness, the severity of ADHD, depression and anxiety semptoms in adult ADHD.

METHOD: All participants were assessed with the Structured Clinical Interview For DSM IV Axis I Disorders (SCID-I); and completed the Toronto Alexithymia Scale (TAS), the Impulsive Behavior Scale (UPPS), the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), Adult Attention Deficit and Hyperactivity Disorder Self Reporting Scale (ASRS) and the Wender Utah Rating Scale (WURS). The ADHD patients were also assessed with the Diagnostic Interview for ADHD (DIVA) for DSM-5 criteria.

RESULTS: The study included 101 ADHD patients with a mean age of 23.06 ± 4.24 years with 47.5% females, and 100 healthy control individuals with a mean age of 22.76 ± 5.68 years with 50% female participants. Alexithymia incidence was 41.5% in the ADHD group. The increase in the levels of impulsiveness, depression and anxiety correlated with the severity of ADHD symptoms; and impulsiveness predicted alexithymia in the ADHD group.

CONCLUSION: Alexithymia incidence was higher in the ADHD group. When ADHD and control participants were combined, alexithymic individuals was more associated with impulsivity with frequent display of anxiety symptoms

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Zhonghua Er Ke Za Zhi. 2021 Nov;59:981-84.

RESEARCH PROGRESS IN DEFAULT-MODE NETWORK BRAIN FUNCTIONAL MAGNETIC RESONANCE IMAGING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zhang H, Yang BR.

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Zhonghua Er Ke Za Zhi. 2021 Nov;59:912-15.

INTERPRETATION OF AMERICAN SOCIETY FOR DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS CLINICAL PRACTICE GUIDELINE FOR THE ASSESSMENT AND TREATMENT OF CHILDREN AND ADOLESCENTS WITH COMPLEX ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jin XM, Li TY, Chen L, et al.

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Restless Legs Syndrome in Children and Adolescents

Lourdes M. DelRosso, MD, MEd[a], Maria Paola Mogavero, MD[b], Argelinda Baroni, MD[c], Oliviero Bruni, MD[d], Raffaele Ferri, MD[e,*]

KEYWORDS

• Restless legs syndrome • Anxiety • Depression • ADHD • ODD • Sleep

KEY POINTS

- Restless legs syndrome (RLS) is a common and often underdiagnosed sleep disorder in children and adolescents.
- Children with psychiatric conditions may be at higher risk of RLS, especially children with attention-deficit/hyperactivity disorder.
- Many psychotropic medications, including antidepressants, sedating antihistamines, and antipsychotics, are associated with increased RLS or restless sleep.
- Both nonpharmacologic and pharmacologic therapies can be used in children with RLS.

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS), or Willis-Ekbom disease, is a neurologic disorder initially described by Sir Thomas Willis in 1685 and further defined by Ekbom in 1944; however, pediatric RLS was not described until 1994. Diagnostic criteria for pediatric-onset RLS, introduced in 2003 and updated in 2013, outline specific considerations for diagnosis in children and allow the use of age-related descriptive terms and words.[1] The recency of its recognition and limited education in sleep medicine by most clinicians have resulted in RLS still generally overlooked. This is true particularly in children who usually present with complaints related to bedtime refusal or insomnia, rather than with classic RLS symptoms. Additionally, children with RLS have been found to have an increased risk of comorbidities, in particular attention-deficit/hyperactivity disorder (ADHD). This article discusses clinical features of RLS, its treatment, and the association between RLS and ADHD and other comorbid psychiatric conditions.

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childpsych.theclinics.com

CLINICAL FEATURES

RLS is a clinical diagnosis and polysomnogram is not required for the diagnosis, although it can be useful in specific situations. The primary feature of RLS is the urge to move the legs, with or without accompanying leg sensations. If sensations are present, they invariably involve the legs, although the arms and other body parts sometimes are affected. Symptoms occur in the evening, when patients are settling for sleep and are relieved by movement. The discomfort associated with RLS can engender bedtime refusal and delayed sleep onset, which might be mistaken for behavioral insomnia in children.

RLS is relatively common in pediatrics, with an estimated prevalence of 2% to 4% in school-aged children and adolescents.[2] It often is misdiagnosed and generally is ignored by most pediatricians and general practitioners because of the mild and intermittent nature of the symptoms at younger ages or the inability of young children to characterize the sensations or discomfort in the legs. RLS is, however, usually progressive and can cause significant functional impairment.

A majority of children with RLS also report daytime leg discomfort. This differs from the typical increase during the evening or at night of adults and may be linked to the number of hours children spend sitting during the school day.[3]

The *International Classification of Sleep Disorders – Third Edition* (*ICSD-3*), states that "for children, the description of these symptoms should be in the child's own words." The interview questions should be phrased using words developmentally appropriate for the child. Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age. As in adults, a significant impact on sleep, mood, cognition, and function is found. Impairment is manifest, however, more often in behavioral and educational domains.

Differentiating pediatric RLS from other conditions, or mimics, can be complicated.[4] Some of the common mimics of pediatric RLS are positional discomfort, sore leg muscles, ligament sprain/tendon strain, positional ischemia (numbness), dermatitis, bruises, growing pains, leg cramps, arthritis, peripheral neuropathy, radiculopathy, myelopathy, myopathy, fibromyalgia, and sickle cell disease.[5]

Patient Evaluation Overview

RLS is difficult to diagnose in children. The formal evaluation of children with RLS starts with a comprehensive history and physical examination. The sleep history must include a thorough bedtime routine, with particular attention to symptoms that occur while trying to fall asleep. Sensory symptoms are difficult for children to explain, so simple descriptions, such as a funny feeling, pain, hurting, tickling, bugs, spiders, ants, and goose bumps in the legs, can be clues alerting the clinician. Children may draw pins, needles, tiny sand particles, bugs, or a saw over their legs when asked to depict their symptoms. Walters and colleagues[6] initially described the presenting symptoms of children with RLS, which included, similarly to adults, nocturnal predominance of leg paresthesia or discomfort, and relief with movement. In younger children, other symptoms, such as delayed sleep onset, bedtime struggles, and parental concern of restlessness, were included as symptoms of pediatric RLS. In qualitative interviews, children expressed their symptoms as "have to move," "need to kick," "hurts," "bugs crawling," "weird feelings," and "tingling."[7] In this study, 48% of children expressed having similar feelings in their arms in addition to their legs, and 67% described experiencing the same symptoms during the day.[7] RLS-related pain in children typically occurs from both knees down and especially involves the calves, although symmetric or asymmetric thigh pain also may occur.

Family history is of utmost importance. Most early-onset cases (by definition with onset before age 35) are familial; approximately 40% to 92% of children with RLS have affected family members.[8] Several medical conditions, however, are associated with RLS symptoms. Causes of secondary RLS include peripheral neuropathy and uremia. In patients who are thought to have secondary RLS, screening for renal disease, thyroid dysfunction, vitamin B_{12}, and folic acid deficiency (peripheral neuropathy) should be considered.[9]

Periodic limb movements (PLMs) occur in approximately two-thirds of children with RLS and are considered an objective motor finding in RLS and supportive of an RLS diagnosis.[10] PLMs are brief extremity jerks that can be accompanied by transient arousals from sleep that are identified and measured by polysomnography. Often, a diagnosis of PLM disorder (PLMD) precedes the diagnosis of RLS in children under 6 years of age who do not yet have sufficiently well-developed language skills to describe the sensory component of RLS.[11] For this reason, although a sleep study is not indicated for RLS, a PLM during sleep (PLMS) index greater than 5 per hour in polysomnography could aid in the diagnosis.[6]

Finally, daytime symptoms are important to evaluate RLS. Children present with cognitive and academic difficulties in approximately half of cases and mood changes, irritability, or sadness in 58% of cases.[7]

Differential Diagnoses

Differential diagnoses should include mimics of RLS. Growing pains can occur intermittently in the evening and have a peak prevalence at 4 years to 6 years of age. Growing pains can be confused with RLS, but the urge to move the legs and the relief by movement differentiates RLS.[5] Furthermore, growing pains always are described as painful, whereas childhood RLS is considered painful only in 45% of cases.[12] In painful nocturnal leg cramps, there is no urge to move the legs and they do not necessarily occur in the evening prior to sleep.[13] Skin inspection during physical examination can rule out eczema. Examination and palpation of the legs also can exclude bruises, ligament tear, and tendon or muscle pain.

Offending Medications

Several classes of medications and common drugs can unmask or aggravate RLS, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, metoclopramide, diphenhydramine, nicotine, caffeine, and alcohol.[9] For this reason, treating children with psychiatric disorders and RLS can be tricky. Objectively, it also has been shown that antidepressants or antipsychotics can cause an increase in PLMS, as a proxy for RLS.[14] Commonly used antidepressants, such as venlafaxine,[15] mirtazapine,[16] and tricyclic antidepressants,[17] can lead to an increase in PLMS. By contrast, drugs, such as levetiracetam, perampanel, or gabapentin, reduce PLMS[18,19]; valproic acid or carbamazepine have no effect on PLMS.[20,21] Considering the frequent association between PLMS and RLS in children[22] and the their presence since adolescence,[23,24] the choice of antidepressants for treating pediatric psychiatric disorders should seek to avoid possible drug-induced onset or worsening of PLMS.

PRESENTATION IN CHILDREN WITH PSYCHIATRIC COMORBIDITIES

Children with RLS have a higher incidence of ADHD, oppositional defiant disorder, anxiety disorders, and depression.[25] A retrospective study of 374 children with RLS found that 64% had 1 or more comorbid psychiatric conditions. ADHD was found in 25%, mood disturbances in 29%, and anxiety in 11.5% of children.[26] Work on children

with PLMS by DelRosso and colleagues[14] demonstrated that 21.6% also have a mood disorder/anxiety and 10% have ADHD. Unfortunately, there are scarce data on the link of pediatric depression and anxiety with RLS. The most commonly studied association is the one between ADHD and RLS although the directionality between the 2 conditions is unclear. Therefore, the remainder of this article discusses the link between ADHD and RLS in children.

Additionally, gender differences and possible iatrogenic factors might complicate the issue. A retrospective study showed that RLS was associated with ADHD in boys and mood disorders in girls and that there was a greater number of antidepressants prescribed in the same year of the diagnosis of RLS, possibly indicating a worsening of preexisting pathology by psychotropics.[26]

Both RLS and elevated PLMS are common in children with ADHD.[27] For instance, 93% of children with RLS and ADHD reported sleep problems whereas this concern was seen in only 56% of children without ADHD, even if the high comorbidity may be due to recruitment bias because the clinic at which the study was conducted specializes in ADHD and RLS. A study of 129 children (aged 6–17 years) with PLMS index greater than 5 per hour found that 91% were diagnosed with ADHD.[28] Other studies have shown that 26% to 64% of children with ADHD meet criteria for PLMD. Furthermore, an elevated PLMS index correlates with inattention/hyperactivity scores.[27,29] There is increased morbidity when the 2 conditions co-occur; children with PLMD and ADHD have more enuresis, nightmares, and difficulty initiating sleep than children with PLMD alone. ADHD, RLS, and PLMD have been postulated to result from reduced dopamine activity, potentially related to low iron stores, leading to the suggestion that improving ferritin levels also may improve ADHD symptoms.[27,29]

Pullen and colleagues[26] evaluated 374 children with RLS and found that 25% met criteria for ADHD; 29% had either a transient mood disturbance (eg, adjustment disorder) or a recurrent mood disturbance (ie, major depressive disorder or bipolar disorder); 11.5% had an anxiety disorder; and 11% had behavioral disturbances. Mood disturbances and anxiety disorders were more prevalent in girls and ADHD and behavioral disorders were more prevalent in boys. The study concluded that two-thirds of children with RLS had at least 1 psychiatric comorbidity, with 35% having more than 1. Picchietti and Stevens[25] studied 18 children with RLS and found that 13 had ADHD, 4 had oppositional defiant disorder, and 6 were diagnosed with anxiety and 5 with depression. Three children had both anxiety and depression. In all cases of anxiety and depression, the sleep disturbance occurred before the psychiatric diagnosis but the definite RLS diagnosis was given after the psychiatric condition was diagnosed, illustrating the common delay in RLS diagnosis. Oner and colleagues[30] studied 87 children with ADHD and found that 33% met criteria for RLS, and children with ADHD and RLS had lower ferritin levels than children without RLS. The impact of RLS on psychiatric comorbidities, however, has not been reported. The study also demonstrated that children and adolescents with RLS often present first for psychiatric evaluation rather than for sleep medicine evaluation. This dual relationship suggests both sleep-related symptoms and ADHD should be evaluated simultaneously. **Table 1** summarizes studies showing the increased prevalence of RLS in children with ADHD and the increased prevalence of ADHD symptoms in children with RLS.

TREATMENT

Treating pediatric RLS is important, because the associated sleep disturbances can lead to significant developmental, behavioral, and cardiovascular morbidities as well as impact on family well-being. **Table 2** summarizes the treatment options of RLS in

Table 1
Studies in children with attention-deficit/hyperactivity disorder and restless legs syndrome

Authors, Year of Publication	Method	Age (Mean [SD]), or Range	Sample Size	Findings
Liu et al,[31] 2019	AHQ	14.5 y (1.4 y)	11,831	RLS (OR 1.47; 95% CI, 1.02–2.11) was associated with subsequent symptoms of ADHD.
Castano-De la Mota et al,[32] 2017	SDSC questionnaire	6–18 y	73	RLS prevalence of 6.8% in children with ADHD
Kwon et al,[33] 2014	Questionnaire	10.8 y (2.3 y)	56	Family history of RLS (12.5%); symptoms of RLS in 24 patients (42.9%); probable or definite RLS (7.2%)
Pullen et al,[26] 2011	Diagnostic criteria	0–18 y	374	25% (94/374) of RLS patients met criteria for ADHD
Silvestri et al,[34] 2009	SDSC, Conners, video polysomnography	8.9 y (2.7 y)	45	RLS in 11.9%. IRLS severity scale average 18.6 (SD 8.6)
Picchietti and Stevens,[25] 2008	*DSM-IV, ICSD-3* criteria	0.2–17 y	18	ADHD was diagnosed in 13/18 children with RLS.
Oner et al,[30] 2007	Conners, RLS criteria	9.4 y (2.5 y)	87	33.3% of children with ADHD had RLS. Children with ADHD and RLS had lower ferritin levels.

Abbreviations: AHQ, Adolescent Health Questionnaire; Conners, Conners Parent Rating Scale; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); SDSC, Sleep Disturbance Scale for Children.

children with psychiatric comorbidities while **Fig. 1** displays a recommended algorithm for their evaluation and management.

Nonpharmacologic Treatment Options

All children and parents should be educated on elements of sleep hygiene, including consistent bedtime routines, avoidance of electronics at bedtime/evening, and avoidance of caffeinated products. Caffeine consumption can exacerbate symptoms of RLS. Children should avoid not only coffee but also any other substances containing caffeine, including iced tea or chocolates.[35]

Other interventions include leg movements to alleviate the symptoms of RLS. These may include exercise in the afternoon or brief walks a few hours prior to bedtime.

Table 2
Treatment options of restless legs syndrome in children with psychiatric comorbidities

Intervention Modality	Recommendation	Concerning Side Effect
Antidepressant medication assessment	Treat underlying psychiatric condition. Consider using dopaminergic antidepressants (bupropion) when RLS present.	Worsening psychiatric symptoms if changing medications
Other medication assessment	Limit antihistaminic or other medications that can exacerbate RLS when possible.	
Avoid caffeine	Avoid chocolates, tea, coffee.	
Lifestyle modification	Exercise, massage, heating/cooling pads	
If ferritin <50 ng/mL	Oral iron supplementation (1–6 mg/kg/d) to a maximum of 65 mg/d	Constipation, teeth staining
If ferritin >50 ng/mL (off-label)	Clonazepam, 0.1–1 mg, at bedtime Gabapentin, 50–100 mg, at bedtime Clonidine, 0.05–0.1 mg, at bedtime Pramipexole, 0.03–0.25 mg/d	Drowsiness, suicidal ideation Depression, suicidal ideation Hypotension, depression Psychosis, impulse control disorders

Similarly, stretching, rubbing, or massaging the legs may provide relief.[36] Incidentally, some children find relief using cool or heating pads or weighted blankets. Parents can try these interventions one at the time for a few days and keep a sleep diary to assess effectiveness.

Avoiding or discontinuing medications that could aggravate RLS, that is, SSRIs, tricyclic antidepressants, metoclopramide, diphenhydramine, nicotine, caffeine, and alcohol, also may help.[9]

Pharmacologic Treatments

There currently are no Food and Drug Administration (FDA)-approved medications for RLS in children, and clinical guidelines and recommendations are sparse. Furthermore, the International Restless Legs Syndrome Study Group has published guidelines on treatment of RLS using iron supplementation in children, stating that evidence to recommend iron supplementation for children with RLS remains insufficient.[37] Iron supplementation, nevertheless, remains the first-line therapy for children with RLS in clinical care.[9,38]

Iron therapy

Serum ferritin is the best indicator of early iron deficiency . Saturation of peripheral iron stores typically occurs at ferritin levels of 80 ng/mL to 100 ng/mL. Current evidence suggests that achieving and maintaining serum ferritin above 50 ng/mL can be beneficial for RLS, PLMS, and ADHD.[39] The dopaminergic theory of RLS further supports

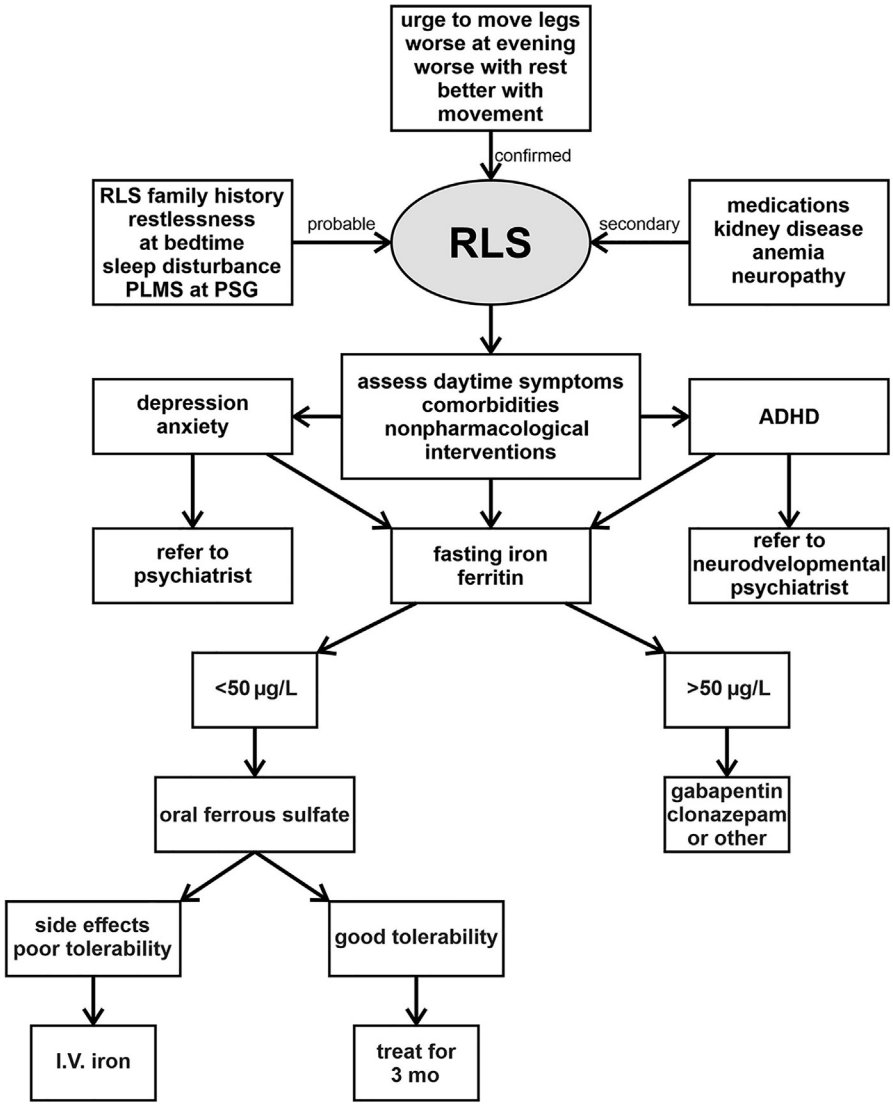

Fig. 1. Recommended algorithm for the evaluation and management of children with RLS and psychiatric comorbidities. I.V., intravenous.

the iron deficiency hypothesis, because iron is fundamental for the biosynthesis of dopamine and is necessary for tyrosine hydroxylation, which is the rate-limiting step for dopamine production.[40] The authors recommend checking fasting iron profile and ferritin levels prior to beginning oral iron supplementation. Iron is offered for patients with ferritin levels below 50 µg/Lng/mL, with dose ranges of 1 mg/kg/d to 6 mg/kg/d of ferrous sulfate at a dose of 50 mg to 65 mg of elemental iron.[9] To enhance absorption, iron ideally should be taken in the morning on an empty stomach with a source of vitamin C. It may take 3 months or more to improve iron levels and to demonstrate improvement of symptoms, based on a handful of studies.[35,41,42] In

addition to improving symptoms, iron therapy also may improve response to psychostimulant drugs,[43,44] an important consideration if correct management of iron status in children with RLS and psychiatric disorders allows the use of a lower antidepressant dose, with a lower probability of adverse effects. The most frequent adverse effects resulting from oral iron administration are constipation, nausea, and unpleasant taste[45]; these can reduce or prevent adherence. Moreover, not all patients respond to oral iron therapy; most responders show an improvement in ferritin levels after 2 months to 3 months of supplementation, with further improvement over time, whereas nonresponders maintain a low ferritin level, despite adherence.[45] When oral iron administration is not successful due to adverse effects or poor absorption, intravenous iron supplementation might be an alternative. Intravenous iron has been shown effective and safe in adults with RLS and some data appear to prove to support its efficacy for pediatric RLS and PLMD patients who do not tolerate or do not respond to oral iron; the most common adverse events reported are difficulty in positioning the intravenous access with risk of extravasation, changes in blood pressure, skin discoloration, and transient hypophosphatemia. A careful selection of candidates is needed because of possible allergic reaction, and caution should be considered in children from families with hemochromatosis, recent infections, or malaria.[46] Although various intravenous iron preparations have been tried in adults (iron dextran, iron gluconate, iron sucrose, ferumoxytol, iron isomaltoside, and ferric carboxymaltose), a single study using iron sucrose 1.2 mg/kg to 6.6 mg/kg, infused over 2 hours in 16 children aged 2 years to 16 years, showed improvement in sleep symptoms in 62.5% of them.[46]

Iron and psychotropic agents

Treatment of pediatric RLS always should include nonpharmacologic interventions, elimination of factors that worsen or precipitate RLS such as elimination of caffeine, and assessment of ferritin levels.[3,47] Because there are no FDA-approved medications for the management of RLS in children, any pharmacologic option used is off-label. When symptoms persist after iron supplementation, combination therapy with a second medication may be considered. In a study of 25 children with RLS and 28 controls, clonazepam (0.1–1 mg) or pramipexole (0.03–0.25 mg) was added to oral iron supplementation in children with persistent symptoms after 2 months.[48] Clonazepam is a long-acting benzodiazepine shown to improve sleep consolidation in patients with RLS albeit without reducing the motor or sensory manifestations of RLS.[49,50] Clonidine (0.05–0.1 mg) is used commonly in children to improve symptoms of insomnia. Clonidine is an α_2-adrenergic agonist that improves sleep onset in children with RLS and has been given in combination with iron supplementation.[51] Gabapentin is used commonly in adults with RLS to improve sleep-onset latency.[52] A small cohort of children treated with gabapentin (50–100 mg at bedtime) for RLS showed resolution of symptoms.[35] Gabapentin also can be combined with iron supplementation in refractory cases. The use of dopaminergic agonists should be restricted to the purview of pediatric sleep specialists. Consideration of side effects, risks, and benefits of each medication needs to be discussed with the family. **Table 3** lists treatment studies on children with ADHD and RLS.

Evaluation of Outcome and Long-Term Recommendations

Children with RLS should be evaluated periodically. If oral iron supplementation is initiated, side effects should be assessed within a couple of weeks. Side effects can be the limiting factor in treatment success for oral iron. Rapid identification of problems, such as bad taste or constipation, can delineate a strategy to address the side effects,

Table 3
Studies with treatment options for children with attention-deficit/hyperactivity disorder and restless legs syndrome

Authors, Year of Publication	Medication, Dose	Age (Mean [SD]) or Range	Sample Size	Conclusions
Baykal and Karakurt,[53] 2017	Atomoxetine, 0.8 mg/kg/d	9 y	1	Resolution of RLS symptoms
England et al,[54] 2011	Carbidopa/Levo-dopa, 25/100 controlled-release	9.3 (1.3) y	29	Levo-dopa improved RLS symptoms on international RLS severity scale. ADHD symptoms were worse in the non-RLS group and did not improve after treatment (Conners Parent Rating Scale)
Gagliano et al,[18] 2011	Levetiracetam, 10–20 mg/kg/d, up to 50–60 mg/kg/d	5–12 y	7	All showed significant improvement in the international RLS severity scale, quality of sleep, and daytime function. Behavioral symptoms improved although not overall ADHD.
Konofal et al,[55] 2005	Ferrous sulfate, 80 mg Ropinirole, 0.25 mg	6 y	1	Conners Parent Rating Scale improved from 30 to 21 after 3 mo of ferrous sulfate. After ropinirole, Conners Parent Rating Scale, oppositional behavior, attention, and sleep improved.

(*continued on next page*)

Table 3
(continued)

Authors, Year of Publication	Medication, Dose	Age (Mean [SD]) or Range	Sample Size	Conclusions
Walters et al,[39] 2000	L-dopa/carbidopa, CR 75/300–150/ 600 mg Pergolide, 0.4–1 mg daily	6–14 y	7	PLMS index improved from 72 to 15, the PLMS index decreased from 11.7 to 2.1. RLS symptoms improved. Conners Parent Rating Scale from 15.1 to 6.26. Significant improvement on oppositional defiant disorder scale and on Child Behavior Checklist

such as switching to a more palatable preparation or a sustained-release tablet and increasing fiber and liquid intake, among others. Discussion of alternative treatments should be done early to educate the family on potential risks, side effects, and alternatives to treatment. Studies on natural progression of RLS are lacking but, based on adult studies, a waxing and waning progression, with periods of exacerbation alternating with asymptomatic periods, can be expected. Education is key in identification of symptoms and prompt evaluation.

Treatment success can be assessed clinically by symptom relief. Questionnaires developed for symptom assessment have not been validated in children. If another sleep disorder, such as obstructive sleep apnea, is suspected or if symptoms are not improved, a sleep study may be indicated.

In summary, treatment of RLS should not be delayed in children with comorbid psychiatric conditions and both should be assessed and treated simultaneously to ensure improvement in quality of life and outcomes.

NEW DEVELOPMENTS

Recently, a new disorder has been proposed, restless sleep disorder (RSD).[40] Children with RSD do not have symptoms of RLS or leg movements on polysomnography but present with frequent movements and repositioning during sleep. The parent usually brings a child for evaluation with concerns of restless sleep and daytime symptoms which include, often, hyperactivity, daytime sleepiness, or behavioral problems. The proposed criteria include motor movements, involving large muscle groups, that occur during sleep and that persist all night and occur almost every night. The movements are evident on polysomnography and should be more than 5 per hour and cause clinically significant impairment in an area of functioning.[56] RSD has been shown to have a prevalence of 7.7% in patients referred to sleep centers and also is suspected to be associated with low iron stores in the brain.[57] Further studies are needed to assess the comorbidity of RSD with other neurodevelopmental, psychiatric, or neurologic conditions.

SUMMARY

RLS is a common and often overlooked disorder in children and adolescents. The relationship between RLS, ADHD, and psychiatric comorbidities is complex and bidirectional. Children with RLS have a significantly increased prevalence of symptoms of ADHD, anxiety, depression, and oppositional defiant disorder. But children diagnosed with ADHD also have an increased prevalence of RLS. This association calls for awareness of sleep disorders, in particular RLS, in children with ADHD and psychiatric disorders. Furthermore, commonly used psychotropic medications can exacerbate the symptoms of RLS. Patients with RLS present with difficulty with sleep onset, nocturnal awakenings, and daytime symptoms, such as behavioral problems. These symptoms can be masked by the presence of a comorbid conditions. Children often are referred to psychiatric evaluation before they are suspected of having RLS, and child psychiatrists should become familiar with clinical assessment and iron replacement therapy for RLS. The authors recommend concurrent evaluations, screening, and prompt treatment of RLS in children with ADHD or psychiatric diagnoses. The treatment of RLS improves both nighttime and daytime symptoms. Treatment options include behavioral interventions, iron supplementation, and combination therapy. For refractory cases of RLS, a referral to a pediatric sleep specialist is indicated.

Areas of future research include the impact of RLS treatment on symptoms of depression or anxiety in children and further assessment of RSD in the presence of comorbid ADHD or other psychiatric diagnoses. More studies are needed on pharmacologic treatment of RLS in children.

CLINICS CARE POINTS

- Screening of RLS and sleep disorders is recommended for all children referred for psychiatric evaluation.
- RLS often is associated with ADHD, anxiety, and depression.
- A diagnosis of RLS often is delayed in children with RLS and psychiatric comorbidities.
- Sleep problems, such as difficulty with sleep onset, are common in children with RLS and ADHD.
- Initial evaluation of children with RLS includes a thorough sleep history and physical examination.
- Fasting ferritin and iron profile should be obtained in all children with RLS.
- Iron supplementation is the first-line treatment in children with RLS.
- Nonpharmacologic treatment options include stretching exercises, cool or warm compresses, and weighted blankets.
- Common adverse effects of oral iron can limit adherence to treatment and need to be assessed early to find alternative treatments.
- There currently are no FDA-approved drugs for treating pediatric RLS; gabapentin and clonazepam often are used off-label as second-line treatment options.
- Concurrent evaluation and treatment of RLS and psychiatric comorbidities, especially ADHD, is recommended.

DISCLOSURE

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ORIGINAL ARTICLE

Attention Deficits Influence the Development of Motor Abnormalities in High Functioning Autism

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Abstract
Early attentional dysfunction is one of the most consistent findings in autism spectrum disorder (ASD), including the high functioning autism (HFA). There are no studies that assess how the atypical attentional processes affect the motor functioning in HFA. In this study, we evaluated attentional and motor functioning in a sample of 15 drug-naive patients with HFA and 15 healthy children (HC), and possible link between attentional dysfunction and motor impairment in HFA. Compared to HC, HFA group was seriously impaired in a considerable number of attentional processes and showed a greater number of motor abnormalities. Significant correlations between attention deficits and motor abnormalities were observed in HFA group. These preliminary findings suggest that deficit of attentional processes can be implied in motor abnormalities in HFA.

Keywords Autism · HFA · Attention and NSS · Selective attention · Attention deficits

Introduction

Attentional Functioning in Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a severe neurodevelopmental disorder diagnosed on the basis of persistent deficits in social communication and social interaction in different contexts and patterns of behavior or interests markedly restricted and repetitive [1]. As the symptoms of disorder fall on a continuum of severity, ASD is often divided into two forms: the first one with mental retardation and the second one with cognitive functioning average or above average, called high functioning autism or HFA [1]. In addition to the core symptoms of the disorder, attentional dysfunction is one of the most consistently reported deficits in patients with ASD, including subjects with HFA. Indeed, attentional abnormalities have been associated with the disorder since its first description [2]. Several studies show that patients with ASD exhibit early and pervasive abnormalities of attention [3–6]. Atypical attentional function has been shown in infants at risk for ASD and may be one of the earliest characteristics that distinguish infants who would later receive an ASD diagnosis [3, 4]. Most of the studies on attentional functioning in ASD are based on the Posner and Peterson conceptualization of attention as composite system. This system consists of three specialized neurofunctional networks, which are responsible for a distinct set of attention processes: the alerting, orienting and executive control networks [7]. Based on this model, abnormal function of each attentional network has been demonstrated in patients with ASD. Researches on alertness and arousal in ASD have been inconsistent: patients with ASD exhibit intact tonic [8] and phasic [9] components of alerting, yet demonstrate atypical arousal [10] and reduced sensitivity to novel information [11]. According to the study conducted by Dawson and colleagues, patients with ASD have difficulties orienting to

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both social and non-social information within their environment [12]. According to studies conducted by other authors, individuals with ASD have difficulties disengaging [13] and shifting visual attention [14] and show atypical activation of the orienting network [15]. Further studies confirm that patients with ASD show significant impairments in disengaging visual attention [3, 16]. Finally, studies on executive control abilities in ASD suggest intact inhibitory processing [17, 18], but impaired cognitive flexibility [19, 20]. Together, these findings indicate that individuals with ASD exhibit lifelong abnormalities in the adaptive allocation of visual attention.

Motor Functioning in Autism Spectrum Disorder

Motor impairment has been widely reported in patients with ASD, including subjects with HFA. Several studies have found deficits in many aspects of motor function, including coordination, gait and motor preparation in children and in adults with ASD. Motor dysfunction may lead to great difficulty for subjects with ASD in negotiating their physical environment, fine motor control (e.g. writing and tying shoes) and social play (e.g. riding a bike, throwing a ball and participating in team sports) [21]. In a study of motor control, children with ASD showed impaired performance on a wide variety of measures of motor examination, as compared to a control group of same-age subjects; in that study patients with ASD showed greater difficulty with balance and gait, slower speed and more dysrhythmia with timed movements of hands and feet and greater overflow movements during performance of timed movements and stressed gait maneuvers [22]. According to previous studies, we found that children with Asperger syndrome (included in ASD) and HFA experience motor impairment and a variety of neurological soft signs (NSS) [23, 24]. Neurological Soft Signs (NSS) are subtle motor, sensory and integrative abnormalities that cannot be related to impairment of a specific brain region and result in considerable sociopsychological dysfunction [25]. Although NSS are commonly observed in children with typical development and reflect the immaturity of the central nervous system, their persistence into later childhood and adolescence suggests motor dysfunction and could be a "marker" of atypical neurodevelopment [26]. NSS are mainly represented by overflow movements (OM) and dysrhythmia. OM are defined as co-movements of body parts not specifically needed to efficiently complete a motor task [26]. There are a number of different forms of OM: associated movements, contralateral motor irradiation and mirror movements. Associated movements refer to involuntary movement in non-homologous muscles, either contralaterally or ipsilaterally [27]. Contralateral motor irradiation and mirror movements are involuntary movements that occur in the homologous muscles contralateral to voluntary movements [28]. Dysrhythmia is defined as an improper timing and/or rhythm of movement otherwise normal [29]. OM seem to be related to a delay or defect of maturation within the intra-cortical and inter-cortical systems that support automatic inhibition [30], while dysrhythmia appears to be caused by cerebellar dysfunction [31]. Dysrhythmia and slowness of timed movements of hands and feet seem to be the most prominent motor abnormalities in children with ASD, including subjects with Asperger syndrome and HFA [22–24, 32] and to reflect functional deficits of the frontostriatal system, cerebellum and basal ganglia [23, 24, 31, 32].

What This Paper Adds

Starting from the conceptualization of attention devised by Posner and Petersen [7], Van Zomeren and Brouwer delineated a multidimensional model of attention, including tonic and phasic alertness, vigilance/sustained attention, selective attention, divided attention and strategy/flexibility [33]. While tonic alertness refers to a relatively stable level of attention which changes slowly according to diurnal physiological variations of the organism, phasic alertness is the ability to enhance the activation level following a stimulus of high priority. Selective attention is defined as the ability to focus attention in the face of distracting or competing stimuli. Divided attention requires a simultaneous response to multiple tasks or multiple task demands. The ability to sustain attention enables a subject to direct attention to one or more sources of information over a relatively long and unbroken period of time [33]. This multidimensional model also encompasses the distinction between aspects of selectivity and intensity made by Kahneman [34] and the concept of a supervisory attentional control devised by Shallice [35]. To our knowledge, studies on attentional functioning in ASD based on this multidimensional model are not available. Therefore, we have chosen to assess several components of attention, as suggested by the multicomponent model of Van Zomeren and Brouwer, in a drug-naive sample of children with HFA as well as in healthy peers. We have evaluated motor functioning by the Physical and Neurological Assessment of Subtle Signs (PANESS) [36] in patients with HFA and compared them to healthy subjects. The role of atypical attentional networks in the emergence of autism has been widely described (Keehn et al. [37] for a review) as well as the influence of attentional processes on motor functioning in normal school-age children [38–40]. To our knowledge there are no studies that investigated the co-occurrence of atypical attentional processes and NSS in clinical populations with HFA. The present study strives to fill the gap by analyzing the relationship between attentional functioning and motor impairment in subjects with HFA.

Method

Participants

The study included 30 participants divided into a clinical group and a control group: 15 patients with HFA (13 boys, 2 girl) and 15 healthy controls (12 boys, 3 girl) aged 7–16 years with an IQ ≥ 85. The subjects in the clinical group were consecutive referrals of the Unit of Child Neurology and Psychiatry of Tor Vergata University of Rome, Italy. In accordance with the DSM-5 criteria [1], the diagnosis of HFA was based on clinical assessment, observation of children and interview with parents, which were carried out by an experienced child psychiatrist. The Autism Diagnostic Inventory-Revised (ADI-R) [41] and the Autism Diagnostic Observation System (ADOS) [42] were used to make the diagnosis of HFA. The long version of the Conners' Parents Rating Scale-Revised (CPRS-R) and the Conners' Teachers Rating Scale-Revised (CTRS-R) [43] and the interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) [44] were used to exclude the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and other psychiatric comorbidities in all patients with HFA. The healthy children were recruited in schools and selected from a pool of subjects who participated voluntarily in the study. None of them had a history of neurological or psychiatric disease or learning disability. The long version of the Conners' Parents Rating Scale-Revised (CPRS-R) and the Conners' Teachers Rating Scale-Revised (CTRS-R) [43] and the interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) [44] were used to exclude the diagnosis of ADHD and other psychiatric disorders in all healthy participants. All subjects included in the study had a normal IQ as measured with the Wechsler Intelligence Scale for Children-III (WISC-III) [45]. At the time of the study, no participants were taking any medication known to affect the central nervous system. Before the testing and in accordance with the Helsinki Declaration, every parent or legal guardian of the subjects included in the study undersigned a written informed consent.

Evaluation of Attentional Functioning

All participants were tested with four computerized tasks measuring different aspects of attention. The tests of attention used were developed and validated for the assessment of attentional deficits in children and adults with cerebral lesions [46, 47]. Test procedures were presented on a computer screen. Instructions were given orally by an examiner who was not blinded to the group membership. Albeit the participants' clinical status was not fully blinded to the examiner, the computerized test battery administration (i.e., Test of Attentional Performance (TAP; Zimmermann and Fimm [47])), that has typically high objectivity in terms of administration and scoring, minimized the effect of any putative bias in the examiner's assessment.

Participants were instructed to perform the computerized tasks as quickly as possible maintaining a high level of accuracy. In order to familiarize the participants with the tasks, two brief sequences of about five practice trials preceded each test. Tests were performed only after participants had completed the practice trials without errors. All the participants were able to perform the actual task without additional training. There was no difference between HFA and healthy participants in the number of practice trials needed to understand the tasks.

Participants were assessed individually in a quiet room and the examiner was present during the entire assessment.

In the *alertness task*, reaction time is examined under two conditions. The first condition represents a simple reaction time measurement, in which a cross appears on the monitor at randomly varying intervals and to which the subject has to respond as quickly as possible by pressing a key, providing a measure of intrinsic alertness. In the second condition, reaction time is measured in response to a critical stimulus preceded by a cue stimulus presented as warning tone ("phasic arousal" or temporal orientation of attentional focus). Therefore, in the alertness task participants were asked to respond by pressing a button when a visual stimulus appeared on a computer screen. In the first 20 trials, the stimulus appeared on the screen without prior warning (tonic alertness task), while during the second 20 trials, a warning tone preceded the appearance of the stimulus (phasic alertness task). The time span between the warning tone and the appearance of the stimulus was random [48]. Measures of tonic and phasic alertness are calculated on the basis of the reaction time of the participant. In addition, the variability of reaction time and number of omission errors are measured.

The *incompatibility task* tests the interference tendency in terms of stimulus-reaction incompatibility. For this test, arrows that are directed to the left or the right are presented on the left or right side of a fixation point. Depending on the direction of the arrow, the tested person is requested to respond with the right or left hand irrespective of the side on which the arrow is presented. Therefore, in the incompatibility task, arrows pointing to the left or the right were presented briefly on the left or right side of a fixation point in the center of the computer screen. The participants were requested to press a response button as quickly as possible on the side indicated by the direction of the arrow, independent

of the position of the arrow. If the position of the arrow and its orientation accorded (e.g. arrow on the left side of the fixation point pointing to the left side), the trial was classified as a compatible trial while trials in which presentation and orientation were not in accordance (e.g. arrow on the left side of the fixation point pointing to the right side) were classified as incompatible trials. The sequence of trials was random, with about half of the trials compatible and half incompatible [48]. Reaction time, variability of reaction time and number of commission errors are calculated, providing a measure of selective attention as the capacity to reject irrelevant information.

The *divided attention task* requires participants to process in parallel a visual and an auditory task presented by a computer. In the visual task, a series of matrices was presented in the center of the computer screen. Each matrix, consisting of a regular array of sixteen dots and crosses (4×4), was displayed for 2000 ms. The participant was asked to press the response button as quickly as possible whenever the crosses formed the corners of a square (visual target). In the acoustic task, the participant was requested to listen to a continuous sequence of alternating high and low sounds and to press the response button as quickly as possible when irregularities of the sequence occurred (acoustic target) [48]. Reaction time for correct responses, variability of reaction time and number of omission errors (lack of response to target stimuli) and number of commission errors (responses to non-target stimuli) are calculated as a measure of divided attention.

In the *sustained attention task*, a sequence of stimuli is presented on the monitor. The stimuli vary in a range of feature dimensions: color, shape, size and filling. A target stimulus occurs whenever it corresponds in one or the other of two predetermined stimulus dimensions with the preceding stimulus (e.g. the same shape but with different color, size and filling). Different levels of difficulty may be selected (e.g. reaction only to "shape" or reaction to "colour and shape"). In order to adapt the difficulty of the task to the performance level of the subjects, reaction only to "shape" was chosen [48]. Reaction time for correct responses, variability of reaction time, number of omission errors (lack of response to target stimuli) and number of commission errors (responses to non-target stimuli) are calculated as a measure of sustained attention.

Assessment of Neurological Soft Signs

For the assessment of motor functioning, the *Physical and Neurological Assessment of Subtle Signs* (PANESS) [36] was applied. These evaluations were performed by a child neurologist who underwent training for the reliable application of the PANESS. The examiner was blind to the child's diagnostic status at the time of assessment and during scoring. The PANESS has been found to have adequate test–retest reliability [49], inter-rater reliability, internal consistency [50] and sensitivity to age-related changes [26] in more current and diverse cohorts. The PANESS measures salient components of motor function, including lateral preference, gaits, balance, motor persistence, coordination, overflow, dysrhythmia and timed movements. Three primary outcome variables were obtained: (1) *total overflow movements* included the total number of abnormal movements for age observed during stressed gaits (i.e. walking on heels, toes or sides of feet), tandem gaits (walking in tandem forward and backward, touching heels to toes) and during timed movements; (2) *total dysrhythmia* included total number of times in which the children failed to maintain a steady rhythm throughout the task; (3) *total speed of timed activities* of hands/feet included three repetitive movements and three sequenced movements which were performed bilaterally: toe tapping, alternating heel-toe tapping, repetitive hand patting, hand pronation/supination, repetitive finger tapping and finger sequencing.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 21. Group difference on the gender variable was assessed with the χ^2 test. Independent t-tests were used to assess differences between HFA participants and HC in terms of age, IQ and presence of soft motor signs. Differences between the two groups on the attention functioning were also tested through independent t-tests comparisons. Specifically, we first computed the mean reaction times (RTs), the mean variability of reaction times and the mean number of errors for each subject for each of the four attention tasks: (a) Alertness (tonic vs phasic) (b) Selective attention (c) Divided attention (visual vs auditory) and (d) Sustained attention. Then, the performance scores of HFA and HC groups were compared using unpaired two-sample t-tests. A t statistic corrected for the non-homogeneity of variance was computed when Levene's test for equality of variances reached significance.

Cohen's *d* was used to calculate the effect size for differences between paired observations [51]. Following Cohen's (1988) guidelines for interpreting effect sizes, small effects ($d \geq 0.20$), medium effects ($d \geq 0.50$) and large effects ($d \geq 0.8$) were distinguished [52]. In order to account for the small sample size ($n = 15$), we also run non-parametric Mann–Whitney U test and find similar results to those discussed here. This non-parametric analysis is described in the Supplementary Material. The level of statistical significance used for all the analyses was defined as $p < 0.05$.

Finally, to determine the significance of the correlations between soft motor signs and variables of attentional

functioning, correlational analyses and Fisher's r to z transformation were performed.

Results

Demographic and Neurological Characteristics

Demographic and neurological characteristics of HFA and HC are illustrated in Table 1. In our study patients and healthy controls did not differ in terms of age, gender and IQ (Table 1, Panel A). Instead, we found significant differences between the HFA and control groups with regard to total overflow movements, total dysrhythmia and total speed of timed activities (Table 1, Panel B).

Attentional Functioning

Performance scores of HFA and HC on the four attention tasks are reported in Table 2.

Alertness

Comparison between the HFA and control groups using unpaired two-sample t-tests revealed no significant differences with regard to reaction time and number of omission errors in the tonic alertness task; however, we found that variability of reaction time was greater in the HFA group than healthy controls. The performance on the phasic alertness task did not differ significantly between the two groups (Table 2, Panel A).

Selective Attention

There were no significant differences between the HFA and control groups with regard to reaction times and the number of omission errors in the incompatibility task, but we found significant difference in the variability of reaction time between the two groups within the same task. Again, we found that HFA showed greater variability in RTs than healthy participants (Table 2, Panel B).

Divided Attention

In the auditory task we found significant difference between the HFA and control groups with regard to variability of reaction time and number of omission errors, but not with regard to reaction time. Specifically, HFA participants showed greater variability of reaction times and committed a higher number of missing responses than HC participants. Similarly, in the visual task, we found that children with HFA showed greater variability of reaction times and more omission errors than HC. Finally, we found that, in the overall performance, HFA patients were less accurate than HC (Table 2, Panel C).

Sustained Attention

In the sustained attention task, the HFA group did not differ from the control group in reaction time and variability of reaction time, but the patients with HFA showed a greater number of both omission and commission errors when compared to the healthy controls (Table 2, Panel D).

Table 1 Demographic and neurological characteristics of 15 participants with HFA and 15 healthy control subjects

A. Demographical variables					
Variable	HFA (n = 15) Mean (SD)	Controls (n = 15) Mean (SD)	*t*	*df*	*p*
Age	10.53 (2.1)	11.6 (2.77)	− 1.188	28	0.245
IQ	104.07 (12.38)	100.87 (8.93)	0.812	28	0.424
	N (%)	N (%)	χ^2	*df*	*p*
Gender (male)	13 (87)	12 (80)	0.24	1	0.624
B. Motor assessment using PANESS					
Variable	HFA (n = 15) Mean (SD)	Controls (n = 15) Mean (SD)	*t*	*df*	*p*
Total overflow movements	3.53 (1.24)	1.73 (1.95)	3.019	23.84	**< 0.01**
Total dysrhythmia	11.60 (1.55)	1.80 (1.74)	16.29	28	**< 0.01**
Total speed of timed activities	202.27 (39.17)	157.07 (14.19)	4.202	28	**< 0.01**

d.f degrees of freedom, *SD* standard deviation

Significant p values are indicated in bold

Table 2 Performance on attention tasks of 15 participants with HFA and 15 healthy control subjects

Variable	HFA (n = 15) Mean (SD)	Controls (n = 15) Mean (SD)	*t*	*df*	*p*	*d*
A. Alertness						
Tonic alertness						
Mean RTs	349.07 (102.08)	312.13 (101.48)	0.994	28	0.329	0.36
Variability of RTs in msec	94.47 (59.38)	51.20 (40.70)	2.328	28	**0.027**	0.85
Number of omission errors	0.20 (0.41)	0.07 (0.26)	1.058	23.46	0.301	0.38
Phasic alertness						
Mean RTs	314.00 (101.93)	281.47 (83.96)	0.954	28	0.348	0.35
Variability of RTs in msec	72.53 (69.42)	39.13 (19.12)	1.797	28	0.083	0.65
Number of omission errors	0.07 (0.26)	0.07 (0.26)	< 0.001	28	1.00	0.00
B. Selective attention						
Mean RTs	571.53 (97.47)	568.60 (124.99)	0.49	28	0.962	0.02
Variability of RTs in msec	139.60 (44.01)	99.27 (30.86)	2.906	28	**0.007**	1.06
Number of omission errors	2.53 (4.63)	0.27 (0.59)	1.882	14.461	0.080	0.68
C. Divided attention						
Auditory task						
Mean RTs	788.20 (303.19)	652.87 (83.25)	1.667	16.099	0.115	0.61
Variability of RTs in msec	290.53 (190.61)	141.07 (56.96)	2.910	16.480	**0.010**	1.06
Number of omission errors	1.87 (1.24)	0.53 (0.52)	3.829	18.672	**0.001**	1.41
Visual task						
Mean RTs	982.20 (169.66)	902.00 (124.75)	1.475	28	0.151	0.54
Variability of RTs in msec	391.67 (146.91)	243.93 (111.95)	3.098	28	**0.004**	1.13
Number of omission errors	3.87 (2.72)	1.53 (1.35)	2.972	20.543	**0.007**	1.09
Total number of errors	31.93 (43.12)	3.27 (4.20)	2.563	14.266	**0.022**	0.93
D. Sustained attention						
Mean RTs	678.93 (218.81)	666.40 (133.64)	0.189	28	0.851	0.07
Variability of RTs in msec	216.93 (106.65)	167.87 (79.05)	1.431	28	0.163	0.52
Number of omission errors	20.67 (13.13)	3.80 (4.19)	4.739	16.829	**< 0.001**	1.73
Number of commission errors	52.13 (41.64)	5.40 (6.03)	4.302	14.587	**0.001**	1.57

d.f degrees of freedom, *SD* standard deviation, *RT* reaction times

Significant p values are indicated in bold

Correlations Between Attentional and Motor Performances Within the Clinical Group

Bivariate correlations between soft motor signs and performance on the four attention tasks are reported in Table 3.

Regarding alertness, the analysis showed a significant positive correlation between the total number of omission errors in the tonic alertness task and greater measure of overflow movements and dysrhythmia (Table 3, Panel A).

Regarding selective attention, a significant correlation was found between the variability of reaction time and total speed of timed activities (Table 3, Panel B).

Regarding divided attention, the analysis revealed a significant positive correlation between the variability of reaction time and overflow movements in the visual task. Moreover, the total number of errors in the overall performance (i.e., considering the visual and auditory tasks together) correlated positively with the total overflow movements and dysrhythmia (Table 3, Panel C).

Regarding sustained attention, we found that variability of reaction times was associated with higher measure of dysrhythmia in HFA children. Furthermore, the analysis revealed that low accuracy (i.e., measured in terms of omission) was associated with higher overflow movements (Table 3, Panel D).

No other correlations reached statistical significance.

Discussion

The neuropsychological theories of autism suggest contributions of attentional deficits to the development of social communication problems [53, 54]. Moreover, in ASD procedural learning mechanisms, important for acquisition of motor skills, may also contribute to impaired development

Table 3 Bivariate correlation between soft motor sign and attentional functioning in 15 patients with HFA and 15 healthy control subjects

Variables	HFA (n = 15)		
	Total overflow movements	Total dysrhythmia	Total speed of timed activities
A. Alertness			
Tonic alertness			
Mean RTs	0.296 (0.284)*	0.056 (0.843)	0.381 (0.161)
Variability of RTs in msec	0.089 (0.752)	0.062 (0.827)	− 0.245 (0.379)
Number of omission errors	**0.583 (0.023)**	**0.544 (0.036)**	− 0.193 (0.490)
Phasic Alertness			
Mean RTs	0.379 (0.163)	0.341 (0.213)	0.166 (0.553)
Variability of RTs in msec	0.133 (0.636)	0.258 (0.354)	0.020 (0.944)
Number of omission errors	0.161 (0.566)	0.291 (0.293)	− 0.372 (0.172)
B. Selective attention			
Mean RTs	0.167 (0.551)	− 0.073 (0.797)	0.324 (0.239)
Variability of RTs in msec	0.082 (0.772)	− 0.185 (0.510)	**0.555 (0.032)**
Number of omission errors	− 0.078 (0.783)	0.283 (0.307)	0.127 (0.651)
C. Divided attention			
Auditory task			
Mean RTs	− 0.035 (0.900)	0.146 (0.605)	0.052 (0.854)
Variability of RTs in msec	0.197 (0.481)	0.280 (0.312)	0.048 (0.864)
Number of omission errors	0.290 (0.295)	0.159 (0.572)	0.179 (0.524)
Visual task			
Mean RTs	− 0.428 (0.112)	− 0.453 (0.090)	0.113 (0.689)
Variability of RTs in msec	**0.534 (0.040)**	0.358 (0.190)	0.293 (0.289)
Number of omission errors	− 0.134 (0.634)	− 0.262 (0.345)	0.159 (0.572)
Total number of errors	**0.583 (0.023)**	**0.605 (0.017)**	0.067 (0.814)
D. Sustained attention			
Mean RTs	0.195 (0.485)	0.235 (0.399)	0.277 (0.317)
Variability of RTs in msec	0.353 (0.197)	**0.644 (0.010)**	− 0.102 (0.717)
Number of omission errors	**0.613 (0.015)**	0.160 (0.569)	0.267 (0.336)
Number of commission errors	0.334 (0.223)	0.154 (0.584)	− 0.154 (0.584)

*Spearman Rho sr (p value); Significant p values are indicated in bold

of communicative and social skills [55–57]. Therefore, the motor signs exhibited by individuals with ASD may serve as markers for deficits in parallel systems important for communication and socialization [55–57]. In this framework the careful consideration of attentional and motor impairments may provide valuable information about the neurobiological basis of ASD. Furthermore, the correlation analysis between attentional and motor functioning may help to clarify how the atypical attentional processes may be related to the motor signs in HFA. Therefore, the present study has had two main aims: the first one was to evaluate extensively attentional functioning and motor signs in a drug-naive sample of children with HFA compared to healthy children; the second one was to elucidate a potential relationship between attentional and motor performances in HFA. To the best of our knowledge, this is the first study in which attentional functioning was assessed according to the multidimensional model devised by Van Zomeren and Brouwer [33]. All participants were assessed with a computerized tests battery, which measures different aspects of attention, such as tonic and phasic alertness, selective attention, divided attention and sustained attention. Finally, a correlation analysis was conducted to evaluate the relationship between attention deficits and the salient components of motor function—as measured by PANESS—in HFA.

Attentional Dysfunction in HFA

The present study reveals that, compared to healthy sex- and age-matched children, patients with HFA were impaired in a considerable number of attentional processes, including alertness, selective attention, divided attention and sustained attention. While selective attention and divided attention are considered to be aspects of selectivity, alertness and sustained attention are expressions of intensity of attention [33]. Therefore, attentional dysfunction observed in our patients

involves both aspects of selectivity and intensity of attention. Compared to healthy subjects, children with HFA displayed an enhanced variability of reaction time in tasks of tonic alertness, in those of selective attention, as well as in the auditory and visual tasks of divided attention. The variability of reaction time is considered a measure of the attentional fluctuations in the subject's efficiency of processing during the course of a continuous task [33]. The present study showed that, in comparison to healthy peers, children with HFA displayed a significant impairment of accuracy in divided and sustained attention tasks, but not in those of alertness and selective attention. Indeed, a greater number of omission errors in divided attention task and a greater number of omission and commission errors in the sustained attention task were observed in the HFA group compared to the control group. While omission errors (lack of response to target stimuli) are considered as a measure of inattention, commission errors (responses to non-target stimuli) are a measure of impulsivity [58, 59]. The goal of this study is to demonstrate the presence of attentional dysfunction in individuals with HFA using for the first time the multidimensional model devised by Van Zomeren and Brouwer. The body of this research shows that ASD is characterized by attentional dysfunction of the alerting, orienting and executive control networks. Moreover, ASD may be characterized by dysmodulation of arousal (subjects with hyperarousal and subjects with hypoarousal) and impaired novelty processing, slowed attentional disengagement and shifting and poorer performance on complex executive control tasks [37]. Attentional processes are mediated by cerebral networks, including several cortical and subcortical brain regions. Alertness functions are supported by the locus coeruleus-norepinephrine system (LC-NE), which is the core arousal center. Through its projections to the thalamic nuclei and cerebral cortex, the LC-NE supports appropriate levels of alertness in order to maintain efficient information processing [60]. The anterior cingulate cortex and the right dorsolateral prefrontal frontal cortex maintains tonic alertness by modulating activity in the locus coeruleus via the reticular nucleus of the thalamus [61]. The alerting network is mediated by a right-lateralized ventral frontoparietal network, which is responsible for achieving and maintaining appropriate levels of alertness [62]. Selective attention is related to anterior cingulate gyrus, inferior frontal cortex (left hemisphere) and frontal-thalamic connections to the reticular nucleus of thalamus [63]. Divided attention is served by frontoparietal network [64, 65] and anterior cingulate gyrus [66]. Sustained attention is mediated by reticular and intralaminar thalamic nuclei and anterior cingulate gyrus [63].

According to the results of the present study, it may be hypothesized that a dysfunction of these cerebral networks is involved in early and lifelong abnormalities in efficiently modulating attentional processes in patients with ASD, including subjects with HFA.

Motor Impairment in HFA

The present study reveals that, in comparison to healthy sex- and age-matched children, patients with HFA performed worse on the Physical and Neurological Assessment of Subtle Signs (PANESS) [36], used to assess motor functioning. Indeed, the HFA group showed multiple motor abnormalities as compared to the control group. These abnormalities included a greater number of OM, a greater dysrhythmia and a greater motor slowness. These findings are consistent with results of previous investigations, that emphasize the presence of motor dysfunction in children with ASD. According to these studies, patients with HFA exhibit difficulty with motor preparation and execution, increased dysrhythmia and motor slowness of time activities, when compared to healthy children [22–24, 32]. These motor impairments could reflect functional deficits in the fronto-striatal circuits and cerebellum and dysfunction of basal ganglia [67, 68]. Functional magnetic resonance studies found that patients with ASD have greater variety in their functional maps and less distinct regional activation patterns than the healthy controls. Therefore, motor pathways are not properly organized in subjects with ASD, leading to difficulties in generating appropriate motor responses [69]. In particular some functional imaging studies showed an atypical activation on the premotor cortex [70] and the cerebellum [71–73], during motor execution and decreased connectivity of the motor execution network [73]. Cardinale and colleagues reported atypical rightward lateralization of multiple functional brain networks in subjects with ASD, including language, motor and visuospatial circuits [74]. This result was confirmed recently: indeed, in a study conducted by Floris and collaborators in 2016, children with ASD showed rightward lateralization in mean motor circuit connectivity compared to typically developing children and this was associated with poorer performance on all three PANESS measures [75]. Structural magnetic resonance studies revealed an increased brain volume in younger, but not older, children with ASD [76–78]. The increased volume has been principally attributed to larger white matter volumes, particularly in outer radiate regions [79]. Mostofsky and colleagues found a robust positive correlation between total PANESS score and left hemisphere primary motor and pre-motor white matter volume. According to the same authors, the correlation between motor performance and left motor cortex white matter volume distinguishes children with ASD from typically developing children and from those with ADHD. Therefore, the authors believed that an increased radiate white matter volume within the primary motor cortex may be a predictor of motor impairment in children with ASD [80]. It may be hypothesized that overgrowth

of localized cortical connections and undergrowth of more distant connections between cerebral cortical regions and subcortical structures [79, 81] result in impaired complex information processing and weak central coherence [82, 83] and also contribute to impaired motor sequence learning necessary for development of complex motor skills and social/communicative gestures [55–57, 84].

Neurological Soft Signs and Attentional Dysfunction in HFA

The influence of attentional processes on motor performance has already been studied in non-clinical populations [38–40]. Waber and colleagues analyzed the role of attentional processes in OM in normal school-age children. According to these authors, children who produced high levels of OM were more responsive to task-irrelevant cues (maintained low levels of attention), whereas those who produced low levels of OM were more responsive to task-relevant cues (maintained high levels of attention) [38]. The relationship between reduced attention and increased OM was strengthened by subsequent findings of a reduction but not elimination of OM when participants were asked to inhibit it [39]. Moreover, a study by Lazarus and Todor showed that children of all age groups reduced the magnitude of OM when receiving sensory feedback during the task [40]. The goal of the present study was to analyse the relationship between attentional processes and motor functioning in the clinical population with HFA. Using correlation analysis, we found significant correlations between disturbances of attentional functioning and motor abnormalities in children with HFA. Based on our results, deficit of alertness (in terms of increased number of omission errors) correlates significantly with increased OM and greater dysrhythmia. Dysfunction of selective attention (in terms of variability of reaction time) correlates significantly with greater motor slowness of time activities. Disturbance of divided attention (in terms of variability of reaction time in visual tasks and increased number of commission errors in both auditory and visual task) and impairment of sustained attention (in terms of increased number of omission errors) correlates with increased OM. Furthermore, disturbance of divided attention (in terms of increased number of errors in both auditory and visual task) and impairment of sustained attention (in terms of increased variability of reaction time) correlate significantly with greater dysrhythmia.

Since the reaction time, the variability of reaction time and the number of omission errors are considered a measure of inattention, our findings suggest that a link is present between attentional and motor functioning in children with HFA. Our results support the hypothesis that impairment of the core components of attention control—i.e., alertness, orienting, divided and sustained attention—plays a role in the pathophysiology of the NSS in clinical population with HFA. Indeed, several studies on motor learning showed that motor abnormalities in autism may be secondary to a deficit in executive functions, such as planning [32, 85] and learning skills [55], rather than general motor abilities. For instance, it has been showed that individual with autism have difficulty in learning the sequence of movements necessary to perform skilled motor tasks [55]. In addition, they exhibit deficits in the preparation of an action, whereas they have intact ability to execute action [32]. Consistent with these studies, our results may suggest that atypical motor functioning can be secondary to executive dysfunction possibly involving difficulty in disengaging the orienting of attention from a target object [86] or difficulty in selecting the proper movement for the action preparation. Intriguingly, as we revealed an association between atypical motor functioning and attention control through a correlational analysis, it is conceivable to hypothesize that attention deficits are indeed secondary to motor impairment. Several studies showed that individuals with autism place unusual reliance on proprioception when learning a novel movement pattern [87, 88], and exhibit difficulty to integrate visual spatial and temporal characteristics of a movement to guide and adjust motor tasks, like catching or throwing a ball [89]. Motor symptoms occur early in ontogeny and may precede the development of the core features of the disorder [90]. In this vein, atypical internal model of the action that place strong reliance on proprioception may lead to attentional deficits involving erroneous prediction of the sensory consequence of self-generated action, thus impairing skill development [87, 88]. Deeper examination of the relationships between impairment of the core components of attention control and motor abnormalities in autism may contribute to further define motor impairment specificity in children with HFA.

Conclusions

So far, attentional functioning studies in ASD were addressed to understanding the role of atypical attentional processes in the emergence of socio-communicative impairment typical of the disorder. To the best of our knowledge, this is the first study in which the correlation between attentional dysfunction and motor impairment was analyzed in a clinical population with HFA. Our findings suggest that impairment of the core components of attention control is related to abnormalities of salient characteristics of motor function in individuals with HFA. The first strength of our study is the inclusion of a well-defined group of drug-naive children with HFA, who were carefully screened for other comorbid psychiatric conditions. The second strength of our study is the inclusion of subjects with normal IQ. Indeed,

lower IQ appears to be related to increased NSS in children with HFA.

The interpretation of our findings is limited by the small sample size, and the study should be qualified as exploratory in nature. Further studies on a greater sample size will help to expand our knowledge about the role of higher order cognitive mechanisms, such as attentional processes, in motor functioning and to better understand the link between attentional dysfunction and NSS in individuals with HFA.

Summary

Attention deficits and motor impairment have been widely reported in patients with ASD, including individuals with HFA. In this study we evaluated the functioning of multiple components of attention (i.e., alertness, selective, divided and sustained attention) and motor sign in a sample of children with HFA compared to healthy children. Furthermore, we explored the putative relationship between attentional and motor performance in HFA. The results of our study revealed that patients with HFA exhibit impairments in several attention domains as well as motor performance in comparison with typically developing children. In addition, we found strong correlation between inattentional phenomena and neurological soft sign, suggesting that altered attentional processing may be related to abnormalities of salient components of motor function in HFA.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed Consent Informed consent was obtained from all individual participants included in the study

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Investigating the effects of COVID-19 lockdown on Italian children and adolescents with and without neurodevelopmental disorders: a cross-sectional study

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Abstract

We conducted a cross-sectional study to compare the impact of social distancing and lifestyle changes that occurred during Corona Virus Disease 2019 (COVID-19) lockdown on children and adolescents with and without Neurodevelopmental Disorders (NDDs). An online questionnaire was administered in order to investigate the effects of NDD condition, socio-demographic status, familiar/home environment and COVID-19 exposure on their lives during a two months period of social isolation. We used logistic regression, focusing on five endpoints (remote learning, lifestyle, stress/anxiety, sociality, scolding) to define the extent of these effects. Most questions were paired up to parents and children, to verify the occurrence of agreement. 8305 questionnaires were analyzed, 1362 of which completed by NDDs and 6943 by controls. Results showed that the presence of a NDD, compared to controls, had a significant impact on: *Remote Learning* (i.e. subjects with NDDs experienced more difficulties in attending online classes and studying), *Sociality* (i.e. subjects with NDDs missed their schoolmates less), *Scolding* (i.e. subjects with NDDs were scolded more often) and *Anxiety* (i.e. subjects with NDDs were perceived by their parents as more anxious). Substantial agreement between parents and children arose from questions concerning *Remote learning*, *Lifestyle* and *Scolding*. The current study actually points out that having a NDD gives account for a stronger influence on school performance and on behavioral and psychological aspects, during a two months lockdown. Such results may provide useful information to governments and school authorities on how carrying through supportive strategies for youth affected by NDDs.

Keywords COVID-19 · Neurodevelopmental Disorders · Tic · Autism Spectrum Disorder · ADHD · Specific Learning Disorders

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Introduction

The World Health Organization declared a public health emergency of international concern for the COVID-19 on 30th January 2020. Italy was one of the most affected countries at the beginning of 2020 and COVID-19 outbreak was particularly dramatic in Lombardy (a northern region of Italy). In February 2020, Italian government applied mandatory rules for its citizens to abide by and social isolation was adopted as the main measure to prevent the spread of the viral infection (WHO, 2020). The lockdown thus included home confinement, interdiction of outdoor activities and indefinite closure of schools, rehabilitation and educational centers and sport associations. Such measures resulted in upheaval for citizens' everyday life, and this was notable amongst families with school-aged children. Many parents

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had to shift to home-working, while they had to take care of their children because schools were closed. Childcare and homeschooling had to be managed without the usual supportive systems, such as school extra-services and therapists. Hence, parents often felt unprepared to carry out both home-working and child-caring successfully (Cluver et al., 2020). As for children, school closure was the most disruptive change in their routine. The school system quickly attempted to restore normality: alternative educational tools were introduced by developing distance learning solutions (United Nations, 2020). Both children and teachers tried to use the new educational models, but virtual communication was found to negatively affect the relationship between teachers and students previously created in the classroom, that is key to influencing student's motivation (Khalilzadeh & Khodi, 2018). During lockdown, many life changes impacted children's lives: school closure, lack of outdoor activities, aberrant dietary and sleeping habits. All these changes could promote distress and exacerbate any latent neuropsychiatric or psychological symptoms (Ghosh et al., 2020). Therefore, although children seemed to be the less affected by the virus, they were hit the hardest by the psychosocial consequences of social distancing (Golberstein et al., 2020). The negative consequences of the pandemic were certainly exacerbated when a pre-existent neuropsychiatric or psychological condition was present, such as in the case of Neurodevelopmental Disorders (NDDs). NDDs are a group of medical conditions that have their onset during childhood and are life-lasting; they result in functional limitations concerning neuropsychological, cognitive, and adaptive development. DSM-5 (American Psychiatric Association, 2013) considers neurodevelopmental disorders as a single cluster, which includes subjects affected by Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), Specific Learning Disabilities (SLD), Tourette Syndrome (TS/Tics), intellectual disability and language (communication) disorders. Individuals with ASD typically present abnormalities in understanding the intent of others, displaying diminished interactive eye contact and atypical use and understanding of gesture (Hyman et al., 2020). ADHD is associated with deficits across a range of cognitive domains (e.g., executive functions, working memory) (Posner et al., 2020) so that such patients have great difficulties in following instructions and understanding complex situations, such as the pandemic. SLD subjects are identified by impairments in automatizing learning processes, such as reading, writing and/or math (American Psychiatric Association, 2013). TS/Tics subjects are characterized by sudden, involuntary, purposeless, and partially controllable movements and vocalizations/noises (Arzimanoglou et al., 2018). Intellectual disability includes, instead, deficits in cognitive and adaptive functions, such as language, memory, logical-mathematical and visuo-cognitive skills and organization of activities of daily living (American Psychiatric Association, 2013). All these conditions have "domains of difficulty" in common, although they can be compromised within various ranges of severity: emotional and behavioral issues, family stress, impaired learning, communication, and social skills (Thapar et al., 2017). Frequently, a child may have co-occurring diagnoses because the neural correlates of NDDs often encompass diffuse brain injury (Van den Berg et al., 2018) with consequent functional impairment in multiple domains. Thus, a multidisciplinary therapeutic approach is often adopted to treat neurodevelopmental disorders (Arzimanoglou et al., 2018).

Our hospital care experience during lockdown confirmed the great disadvantage of children affected by NDD: very often, their parents asked for specialistic support, after having noticed a worsening in behavioral symptoms, a reduced compliance with online school and a progressive change in their everyday lives. To reduce this negative impact, some neuropsychiatric units in Italy have promptly developed useful strategies (telerehabilitation, tele-consultation, telemedicine) (Fazzi & Galli, 2020). However, a comprehensive response to these needs could not be completely guaranteed during periods of social isolation; assessment and treatment for children with these disorders require the cooperation of specialists, many of whom are based in different services, which may be impossible to reach. To envisage a targeted support for these children, it is important to define the specific areas of difficulty to deal with. First, the proposed remote learning solutions proved harder to accomplish for students affected by NDDs. In fact, shifting classes online led to a dearth of special educational assistance to children, for at least two reasons: (i) parents could not completely manage special educational needs, because they have no specific professional training; (ii) a lack of assistive technologies was sometimes present. The most obviously disadvantaged groups are those with intellectual disabilities and SLDs, which may be particularly affected in their school outcomes during distance learning. In addition, the difficulty in coping with complex situations in children with ADHD led them into more troubles with respect to their peers in complying with remote learning, even in adolescence. This was confirmed by their parents, who realized—by spending more time together—the hard difficulties in both managing and supporting them (Becker et al., 2020). A second area to investigate is the degree of change in lifestyle habits caused by forced home confinement, that could have negatively impacted psychological stability. As an example, in ADHD patients, a recent study reported a disruption in everyday life, with a greater use of digital devices and changes in sleeping habits (Sciberras et al., 2020). Third, it is likely that COVID-19 pandemic resulted in increased stress and anxiety, given the fact that individuals with NDDs are particularly susceptible to distress caused by physical distancing measures. In children with intellectual disability, given their reduced

adaptive functions, the COVID-19 pandemic exerted a psychological impact, including high levels of stress, anxiety, and depression, in both disabled children and their families. Patients with TS/Tics can be disadvantaged as well during a pandemic lockdown, a source of distress; in fact, the severity of tics is magnified under environmental and psychological pressures. A fourth critical consequence of lockdown was the decrease in social relationships, as social distancing was the first measure adopted to contain the spread of the virus. In children with intellectual disabilities, traumatic life events, like a pandemic, can intensify the feelings of social stigma and discrimination, already existing in these subjects. Sociality was disrupted in ADHD as well (Sciberras et al., 2020). In ASD subjects, the already occurring social difficulties are likely to be negatively impacted by the forced isolation due to the pandemic status. Finally, emotional and cognitive profiles of SLD subjects normally benefit from the cooperative relationships with classmates and teachers (Kiuru et al., 2020), that was greatly diminished by social distancing. In the end, a fifth area of difficulty faced during the COVID-19 lockdown was the potential deterioration of relationships also amongst family members, that were forced to spend all day together and to share resources. In this context, ADHD children might display increased behavioral problems (Cortese et al., 2020). Moreover, a recent study (Alhuzimi, 2021) reports how stress and lack of support in families with children affected by ASD can bring a deterioration in parental emotional wellbeing. On the other hand, familiar patterns of SLD children, especially those with dyslexia, are often anxiety-oriented and prone to conflict avoidance models (Bonifacci et al., 2014). Therefore, in this study we hypothesized that COVID-19 restrictions notably hurt NDDs subjects in different ways, since they usually depend on the support of caregivers and networks of services to maintain their emotional balance and mental health (Tajè et al., 2020). The aim of our study is to evaluate whether the COVID-19 restrictions had a greater impact in subjects with NDDs than in controls.

Objective and Significance of the Study

This study has the ambition to guide decision makers towards a more targeted treatment for children and adolescents with NDDs in crisis situations, such as the COVID-19 lockdown. The assessment of pedagogical or psychological needs would produce a refinement in the intervention efficacy. Indeed, we defined the different areas in which children and adolescents experienced difficulties during lockdown (i.e. *Remote Learning, Lifestyle, Anxiety, Social* and *Scolding*) as potential areas of intervention. Therefore, the primary aim of this study was to identify which factors (demographical, environmental or pathological) impacted the most on each area of difficulty, with a special focus on the role of the presence of a NDD condition. The secondary aim was to investigate if parents and children/adolescents had the same perception of the effect of the lockdown on children/adolescents' lives and whether this agreement changes for families having children with NDD. To reach these aims, we designed a questionnaire that was proposed at scale to students attending all grades of the school system, exploiting different data sources, such as hospitals and associations, but mainly the schools' network. The latter was available thanks to the cooperation with the local school office, which allowed to reach as many students as possible, being potentially representative of most of the population. Our results could be helpful to implement information about NDD vulnerability in lockdown and could ideally be used to improve virtual help tools, not only in a future pandemic scenario, but also in addition to the traditional health and didactic resources.

Methods

Participants

As we aimed at achieving a comprehensive view of the lockdown effect on the school-aged population, we included in the study children and adolescents living in the province of Varese, attending a grade comprised between the first year of primary school and the fifth year of high school, together with their parents. It must be considered that the Italian school system is divided into primary school (PS, five grades—from 6 to 10 years), middle school (MS, three grades—from 11 to 13 years) and high school (HS, five grades—from 14 to 19 years). To recruit a large and representative sample of parents and children, different sources were leveraged: 1) Child Neuropsychiatry Unit of Filippo Del Ponte Hospital in Varese; 2) advocacy associations for people with different NDDs: AIFA (Associazione Italiana Famiglie ADHD – Italian association of ADHD families), ANGSA (Associazione Nazionale Genitori Soggetti Autistici – National association of ASD parents) and AIST (Associazione Italiana Sindrome di Tourette – Italian association of Tourette syndrome); 3) websites of schools in the province of Varese. An online questionnaire was designed (see the following paragraph), and made available from April 30th to June 8th, 2020. Both children/adolescents and parents were asked to complete the questionnaire, after expressing an informed consent. They were informed that the participation at the study was confidential. Data were collected anonymously (no name, nor contact information were allowed), as per Google' privacy policy and treated for research purposes only. The voluntarily participation at the study was acknowledged with both a positive answer to a

direct question and the submission of the questionnaire, that was not recorded if the participant did not complete it fully. The study was approved by the Ethics Committee of ASST dei Sette Laghi di Varese (n.82 of 2020), in compliance with the Declaration of Helsinki.

The online questionnaire

The electronic survey was designed by a steering group of multidisciplinary scientists and academics (i.e. child neuropsychiatrists, psychologists and bioengineers) at the University of Insubria (principal investigator), following a structured review of the literature. The questionnaire included 38 single and multiple-choice questions. It started with a characterization section, that was addressed to parents only and investigated demographical and environmental factors. Besides the characterization of study participants, this section is useful to segment the population in different categories, that could have been impacted differently in different areas of difficulty. First, we hypothesize that the approach to the different aspects of life described by the endpoints could greatly vary according to age. Moreover, socioeconomic status could influence the availability of different instruments for virtual contacts or support and it is considered a crucial factor for development of cognitive functions, like attention, language and learning abilities (Schibli & D'Angiulli, 2013). Socioeconomic disadvantaged situations could also result in impossibility to attend remote classes (Agnelli Foundation, 2020), increased anxiety (Vazirani & Bhattacharjee, 2020) and violence against children (Cluver et al., 2020). The presence of siblings, instead, can affect the availability of resources and spaces for remote learning, but also have an impact on socialization (Szymańska, 2020). Family status (i.e. parents living together versus separate or single-parent families) can affect different psychological aspects and it is known that children of divorced parents may have social problems (Liu et al., 2000). The shift to homeworking was a never-experienced situation for many families and could impact life habits, but it could also be a chance for young children to be helped during remote classes. On the counterpart, having parents working in the healthcare field – that was the most exposed to the virus – could have increased children's anxiety (Skokauskas et al., 2020). The latter could have been caused also by having contacts with people positive to COVID-19. Finally, it was possible to conjecture that the availability of a private outdoor space, such as a terrace or a garden, might have been helpful in getting some relief from the isolation (Jackson et al., 2021). A summary of these questions and available answers can be found in Table 1.

Then, two corresponding set of questions were repeated, once addressed to parents and once addressed to children. These questions were selected to render the five areas of difficulties into the corresponding endpoints: *Remote Learning*

Table 1 Answers frequency divided by Controls and NDDs – stratifying variables

INDEPENDENT VARIABLES	CONTROLS	NDDs
Gender		
Male	3280	861
Female	3663	501
H-SES		
1	621	196
2	1442	329
3	1798	347
4	2324	372
5	758	118
Family Status		
Separate/single-parent	859	233
Parents living together	6084	1129
Siblings		
0	1675	309
1	4058	761
>1	1210	292
Outdoor		
No	701	160
Yes	6242	1202
Covid Family		
No	6648	1305
Yes	295	57
Covid Exposure		
No	6565	1268
Yes	378	94
School Grade		
PS	3318	455
MS	1790	442
HS	1835	465
School Class		
PS-grade 1	672	40
PS-grade 2	696	54
PS-grade 3	701	103
PS-grade 4	668	111
PS-grade 5	581	147
MS-grade 1	656	174
MS-grade 2	603	140
MS-grade 3	531	128
HS-grade 1	506	146
HS-grade 2	432	112
HS-grade 3	390	98
HS-grade 4	299	61
HS-grade 5	208	48
Remote Work		
None	3795	821
One	2328	423
Both	820	118
Healthcare Professional		
None	6157	1167

Table 1 (continued)

INDEPENDENT VARIABLES	CONTROLS	NDDs
One	654	160
Both	132	35

(i.e. difficulties in attending online lessons and doing homework), *Lifestyle* (i.e. changing in lifestyle habits concerning sleep, diet and use of electronic devices), *Anxiety* (i.e. COVID-like symptoms, asking for information and reassurances about virus), *Sociality* (i.e. feeling of missing peers and school) and *Scolding* (i.e. possible increase in domestic disputes). The summary of these questions and available answers can be found in Table 2.

Table 2 Answers frequency divided by Controls and NDDs – endpoint question

		PARENTS		CHILDREN	
		Controls	NDDs	Controls	NDDs
REMOTE LEARNING	HOMEWORK				
	Continues doing homeworks	5221	669	4947	670
	Stopped/has difficulties	1722	693	1996	692
	REMOTE CLASS				
	Attending regularly	5540	809	5275	788
	Not attending/having difficulties	1403	553	1668	574
LIFESTYLE	DIETARY STYLE				
	More vegetables/ unchanged	4067	741	3878	701
	Changed otherwise	2876	621	3065	661
	SLEEP HABITS				
	Unchanged	883	186	785	172
	Changed	6060	1176	6158	1190
	NIGHT WAKING				
	Absent/decreased	5896	1130	5852	1067
	Increased	1047	232	1091	212
	ELECTRONIC DEVICES				
	Unchanged/slightly changed	6263	1204	6292	1204
	Changed	680	158	651	158
ANXIETY	INFO COVID-19				
	Never/seldom	5833	1165	5913	1173
	Often/everyday	1110	197	1030	189
	SYMPTOMS				
	Never/seldom	6887	1343	6850	1334
	Often/every day	56	19	93	28
	REASSURANCES				
	Never/seldom	6700	1299	6773	1316
	Often/every day	243	63	170	46
	NEW PAIN				
	No	6455	1212		
	Yes	488	150		
SOCIALITY	ASKS FOR SCHOOL				
	Sometimes/often			5125	861
	Never			1818	501
	MISSES MATES				
	A bit/a lot			6748	1297
	No			195	65
SCOLDING	SCOLDING				
	As usual/less often	4667	923	4721	905
	More often	2276	437	2222	454

In total, 26 questions were directed to parents and 12 to children. When children were less then twelve years old, parents were suggested to help them in questionnaire administration; parental support for children under the age of 12 is also useful for children whose diagnosis could influence reading comprehension (e.g. learning or language disorders).

Data analysis

Statistical analysis was conducted using R (version 4.0.1). For all tests, significance was set at 5%. The answers of the characterization section (first part), answered by parents only, were used as independent variables. The answers were both ordinal and categorical. The latter were always 2-levels answers, therefore could be treated as binary variables.

Specifically:

- NDD: certified NDDs [2-levels: control (0); NDD (1)];
- Gender: [2-levels: male (0); female (1)];
- H-SES: socioeconomic status through Hollingshead index (Hollingshead, 1975), [5-levels: from very low to very high];
- Family status: [2-levels: parents living separated or single-parent family (0); parents living together (1)];
- Presence of siblings: [3-levels: none, one, more than one];
- Attended school: [3-levels: PS, MS, HS];
- Attended school class: [13-levels: from 1stgrade PS to 5thgrade HS];
- Presence of COVID-19 cases in the family: [2-levels:no (0), yes (1)];
- Exposure to COVID-19 cases outside the family: [2-levels:no (0), yes (1)];
- Presence of outdoor spaces at home: [2-levels:no (0), yes (1)];
- Parents working as healthcare professionals: [3-levels: none, one, both];
- Parents working from home: [3-levels: none, one, both].

The answers of the endpoints' sections were dichotomized to give them a positive (1) or negative (0) meaning, according to the effect we hypothesized on the endpoints itself. Then, for the endpoints formed by more than one question (*Remote Learning, Lifestyle, Anxiety, and Social*), the answers were transformed using Item Response Theory (IRT). Such transformation allows to represent a set of items as a unique latent trait, which measures a subject's attitude on a specific topic (the endpoint). Given the consistent attribution of the value 1 to positive answers, the IRT transformation produced an ordinal variable with high values corresponding to positive attitude on the endpoint. After IRT, if the granularity of the latent trait was above 5, the levels of the latent trait were additionally reduced to obtain a 3-point scale (low, medium, and high values). The 33rd and the 66th percentiles were chosen to distinguish between levels. The obtained endpoints are reported in Table 3. As for the primary objective, to assess the effect of different factors on the endpoints, logistic regression was adopted. For ordinal endpoints (*Remote Learning*; *Lifestyle*; *Anxiety*; *Sociality*), we applied an ordinal logistic regression, while we opted for a binary logistic regression for binary endpoints (*Scolding*). For both ordinal and logistic regressions, we first checked the assumptions of absence of multicollinearity between independent variables through the variance inflation factor (VIF), verifying that there was not multicollinearity in the dataset (VIF below 10) (Hair et al., 2010). For the ordinal logistic regression, we also verified the respect of proportional odds using the Brant Test. When a variable violated the assumption of proportional odds, it was removed from the set of independent variables for the ordinal logistic regression models. After that, ordinal logistic regression and binary logistic regression models have been fitted, considering ordinal and binary endpoints, respectively, as dependent variables. In a second step, we further selected the best subset of covariates through the Akaike Information Criterion AIC-based step forward and backward procedure. To conclude, all the non-significant variables were excluded and only the remaining ones were used to build the final model, and finally assess the influence of each independent variable on the endpoint. However, the NDD group was composed by different sub-types, that might differently affect the endpoint. With the aim of assessing the effect of specific NDD type on the endpoints, we considered only subjects who did not present a comorbidity with another NDD type, and performed a Kruskal–Wallis test, considering the ordinal endpoint as dependent variable, and the NDD type or control condition as independent variable. When significance was reached, Mann–Whitney U test with Bonferroni correction was leveraged as post hoc. Given the low sample size of the single NDD groups in respect to the controls, we computed the effect size with Cohen's d. Concerning the secondary objective, to test the agreement between parents and students, we computed the Fleiss Kappa on the binarized questions which composed the endpoints. Fleiss Kappa is an index of agreement adaptable in case of multiple raters. The agreement was computed for all subjects and separately for NDDs and Controls. To investigate between-group differences in agreement homogeneity (NDDs and Control) we also ran a homogeneity score test (Honda & Ohyama, 2020). To assess the potential influence of parents' presence during questionnaire completion for children younger than 12 years old, we applied the same homogeneity test between children and adolescents groups, using the second year of middle school as a cutoff.

Table 3 Questions considered to build the endpoint and meaning of the endpoint itself

ENDPOINT	ANSWERED BY	TYPE/GRANULARITY	ITEMS TO MESURE THE END-POINT	MEANING/DIRECTION
Remote Learning	Children	4-level ordinal	-Difficulties with remote classes -Difficulties with homework	-Was it difficult to follow remote school classes? -High values: low difficulties
	Parents			
Lifestyle	Children	3-level ordinal	-Dietary style -Sleep habits -Night waking -Exposure to electronic devices	-Did daily lifestyle change with lockdown? If so, to which extent and how? -High values: reduced change
	Parents			
Anxiety	Children	3-level ordinal	-Info about COVID-19 -COVID-19-like symptoms -Reassurances seeking about one's own health	-Did anxiety signs appeared or changed with COVID-19 pandemic? -High values: low anxiety
	Parents			
Sociality	Children	4-level ordinal	-Missing peers	-Has the lack of social relationships been perceived as negative? -High values: high feeling of missing peers
Scolding	Children	Binary	-Scolding increased	-Did children show difficulties in coping with COVID-19 lockdown, resulting in frequent scolding? -High values: rarely scolded
	Parents			

Results

8305 questionnaires were analyzed. Subjects' details are reported in Table 1 and in Fig. 1A, where students are arranged by gender, school grade and NDDs category or control group. Specifically, the sample comprised 4141 males and 4164 females. 45.4% of the respondents attended primary school (median age (inter quartile range): 9(2) years old), 26.9% attended middle school (13(2) years old), 27.7% (17(3) years old). The median socioeconomic status, in a range 1–5 (Hollingshead, 1975), was 3, with a 2-points symmetric inter quartile range. Students affected by NDDs were 1362 (861 males, 501 females); their distribution in NDDs type is reported in Fig. 1B. Specifically, 983 were affected by SLD, 313 by ADHD, 72 by TS/Tics,

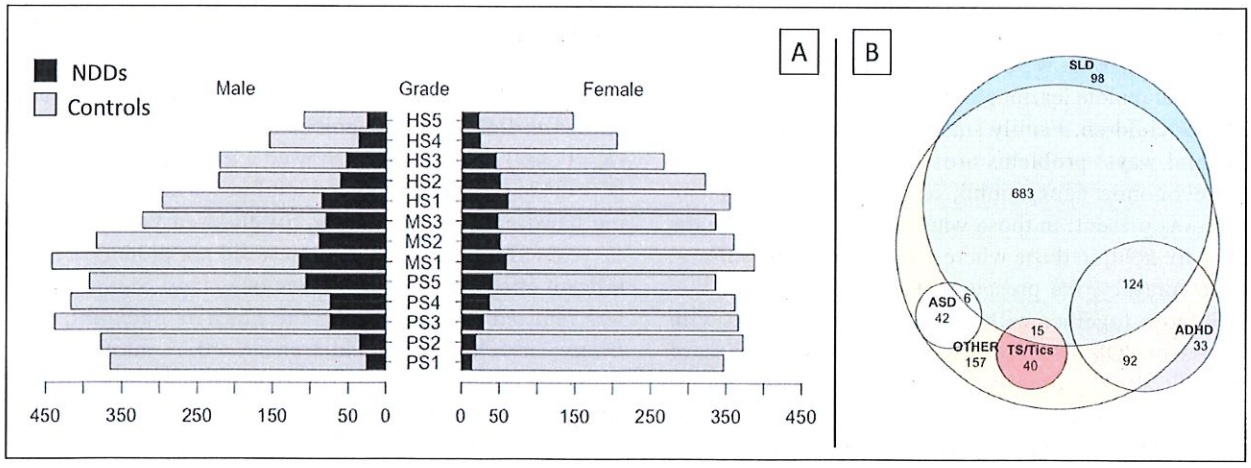

Fig. 1 Population description. A: pyramid plot of subjects' distribution among gender, school grade and NDDs/Control condition. B: Euler-Venn diagram of NDDs distribution. The overlapping parts represent comorbidities

48 by ASD, 1159 by other NDDs. The overlaps between areas represent the presence of a comorbidity between different NDD.

Answer distribution

Answer frequency is reported in Table 1 (A for characterization, and B for endpoints), divided by children and parents' questions, and stratified by NDDs or Controls condition. Thanks to the parents' help, we did not have missed answers in the children sample, even for children with NDD.

Logistic regression and post hoc

Results of the logistic regression are summarized in Table 4, whilst the post hoc tests are reported in Online Resource 1. In the post hoc, given the high degree of comorbidities between the OTHER condition and the remaining NDD types, to assess the effect of the single NDD on the endpoint, it was decided to disregard the comorbidity with the OTHER, and to delete only children who had comorbidities between the remaining NDD types. Therefore, the number of children in each NDD type was: 781 in SLD, 125 in ADHD, 46 in TS/Tics, 42 in ASD. In Table 4, for each model, the significant predictors are presented in order of t-value. The algebraic sign of the value represents the direction of the effect over the endpoints, given the coding of the independent variables previously described. The comment below each numerical result is intended to help interpretation. As shown, the presence of NDDs has a strong negative effect on the *Remote Learning* endpoint, for both students and parents, suggesting that the presence of NDDs made it more difficult for students to attend school remotely, compared to the control group. The post hoc analysis confirmed the result, as most of the comparisons between the control group and the specific NDDs groups showed a medium to large effect. Between-NDDs comparisons were never significant. The analysis reports that remote learning difficulties were starker, especially for children. Family status impacted this endpoint in several ways: problems arose in families with lower socio-economic background; in those where only one parent was present; in those where parents worked in the healthcare field; in those where there were many siblings. On the contrary, the presence of an outdoor space was a facilitator, together with not having any contact with people with COVID-19. A significant (negative) effect of NDDs was also reported for the *Sociality* endpoint, meaning that subjects with NDDs tended to be missing their peers less. On the contrary, children without siblings miss more their friends. As for the *Scolding* endpoint, children/adolescents with NDDs felt like they were scolded more often by their parents during the COVID-19 lockdown. This endpoint was affected from the attended school, as younger children were scolded more; from the family composition, as children with separated parents were scolded more; from the presence of an outdoor space, as those constrained at home were scolded more. Concerning the *Anxiety* endpoint, the analysis suggested that parents of NDDs children perceived their kids slightly more stressed and anxious compared to parents of controls. This was mainly due to the ASD group, which differed from the others with medium effect size (additional data are given in Online Resource 1). Children who had contacts with people positive to COVID-19 suffered more from anxiety, whilst an outdoor space had a beneficial effect. Regarding the *Lifestyle* endpoint, we did not find any difference between NDDs and controls, but we observed a higher change in lifestyle of adolescents; in those who came from a family with low socioeconomic status; to those where parents started working from home; and where an outdoor space was not available.

Child-parent agreement

Figure 2 reports the results for the agreement on each item, grouped by endpoint. Agreement thresholds are reported on the right. Substantial agreement ($0.6 < K < 0.8$, $p < 0.001$) arose from questions concerning *Remote Learning*, *Lifestyle*, and *Scolding*. In the *Anxiety* endpoint, a moderate agreement (0.58) was reached concerning the request of information about the virus. The feeling of COVID-like symptoms and the request for reassurances reached a fair level of agreement (0.30 and 0.37, respectively). The *Sociality* endpoint included questions directed to children only, therefore agreement could not be computed. In regard to homogeneity in agreement between NDDs and Controls, a significant group effect was found in questions related to the *Anxiety*, i.e. Symptoms ($p < 0.001$) as the NDD group obtained a greater value than controls ($p < 0.001$, $K = 0.393$, $K = 0.298$, respectively); in Reassurances ($p = 0.017$), a fair agreement was found in Controls ($K = 0.339$), whilst NDDs showed a moderate agreement ($K = 0.474$). As for the potential influence of parents' during questionnaire completion for children younger than 12 years old, the homogeneity test did not produce a significant effect in seven out of ten questions. Significance was reached in two items of the *Lifestyle* endpoint, i.e. *Dietary style* ($p = 0.013$, children's $K = 0.71$, adolescents' $K = 0.75$), *Night awakening* ($p = 0.044$, children's $K = 0.74$, adolescents' $K = 0.78$); and one item of the *Anxiety* endpoint, i.e. *Info Covid-19* ($p = 0.043$, children's $K = 0.65$, adolescents' $K = 0.62$). In these three questions, the agreement was always slightly higher between parents and adolescents, rather than between parents and children.

Table 4 Logistic regression results. For each model, the significant predictors are presented in order of t-value. The algebraic sign of the value represents the direction of the effect over the end-point

	CHILDREN					PARENTS				
	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value
REMOTE LEARNING	NDD	-0.967±0.058	-16.721	0.381	<0.0001	NDD	-1.191±0.059	-20.171	0.304	<0.0001
		The NDD condition negatively impacted Remote Learning					*The NDD condition negatively impacted Remote Learning*			
	School class	0.084±0.007	12.316	1.087	<0.0001	H-SES	0.161±0.020	7.920	1.175	<0.0001
		Older children had less difficulties in Remote Learning					*Children with high socio-economic status had less difficulties in Remote Learning*			
	H-SES	0.166±0.020	8.502	1.181	<0.0001	Siblings	-0.538±0.072	-7.431	0.584	<0.0001
		Children with high socio-economic status had less difficulties in Remote Learning					*Having more siblings negatively impacted Remote Learning*			
	Siblings	-0.495±0.069	-7.152	0.609	<0.0001	Family status	0.374±0.067	5.575	1.454	<0.0001
		Having more siblings negatively impacted Remote Learning					Having both parents was beneficial for Remote Learning			
	Outdoor	0.402±0.070	5.729	1.495	<0.0001	Outdoor	0.321±0.073	4.425	1.378	<0.0001
		Outdoor space availability was beneficial for Remote Learning					*Outdoor space availability was beneficial for Remote Learning*			
	Family status	0.284±0.065	4.365	1.329	<0.0001	School class	0.069±0.019	3.680	1.071	<0.001
		Having both parents was beneficial for Remote Learning					*Older children had less difficulties in Remote Learning*			
	Healthcare professionals	-0.290±0.116	-2.504	0.748	0.013	Healthcare professionals	-0.377±0.120	-3.153	0.686	0.002
		Having parents working in the healthcare negatively impacted Remote Learning					*Having parents working in the healthcare negatively impacted Remote Learning*			
	COVID-19 exposure	-0.233±0.099	-2.359	0.792	0.018	School	0.173±0.076	2.275	1.189	0.023
							Older students had less difficulties in Remote Learning			
		Having contacts with people affected by COVID-19 negatively impacted Remote Learning				COVID-19 exposure	-0.200±0.102	-1.971	0.818	0.049
							Having contacts with people positive to COVID-19 negatively impacted Remote Learning			

Table 4 (continued)

	CHILDREN					PARENTS				
	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value
LIFESTYLE	School class	-0.050±0.006	-7.974	0.951	<0.0001	School class	-0.057±0.006	-9.237	0.944	<0.0001
		Older children changed their Lifestyle more					Older children changed their *Lifestyle* more			
	Outdoor	0.378±0.072	5.271	1.459	<0.0001	Outdoor	0.454±0.070	6.462	1.575	<0.0001
		Outdoor space availability was associated with less changes in Lifestyle					*Outdoor space availability was associated with less changes in Lifestyle*			
	H-SES	0.079±0.022	3.680	1.082	<0.001	H-SES	0.111±0.018	6.010	1.117	<0.0001
		Children with high socio-economic status changed their *Lifestyle* less								
	Remote work	-0.169±0.071	-2.367	0.844	0.018		*Children with high socio-economic status changed their Lifestyle less*			
		Children change their Lifestyle more if parents performed remote working								
ANXIETY	COVID-19 family	-0.457±0.130	-3.527	0.633	<0.001	COVID-19 exposure	-0.776±0.186	-4.168	0.460	<0.0001
		Having cases of COVID-19 among family members was associated with more Anxiety					*Knowing people affected by COVID-19 was associated with more Anxiety*			
	Outdoor	0.253±0.091	2.774	1.288	0.006	Outdoor	0.439±0.156	2.811	1.551	0.005
		Outdoor space availability was associated with less Anxiety					*Outdoor space availability was associated with less Anxiety*			
	School	-0.214±0.097	-2.206	0.807	0.027	COVID-19 family	-0.577±0.217	-2.655	0.561	0.008
		Children attending higher school orders had more Anxiety					*Having cases of COVID-19 among family members was associated with more Anxiety*			
	School class	0.052±0.024	2.180	1.053	0.029	School class	0.039±0.017	2.346	1.040	0.019
							Older children had less Anxiety			
		Older children had less Anxiety				NDD	-0.306±0.140	-2.184	0.737	0.029
							Having a NDD was associated with more Anxiety			

Table 4 (continued)

	CHILDREN					PARENTS				
	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value	Ordered Significant Covariates	value ± standard error	t-value	OR	p-value
SOCIALITY	School class	-0.175±0.020	-8.772	0.839	<0.0001					
		Younger children missed more their peers								
	NDD	-0.393±0.063	-6.258	0.675	<0.0001					
		Children with NDD missed less their peers								
	Siblings	-0.267±0.076	-3.512	0.765	<0.001					
		Children who have siblings missed less their peers								
	Family status	0.222±0.071	3.154	1.249	0.002					
		Students who do not have both parents at home missed less their peers								
	School	0.229±0.078	2.870	1.257	0.004					
		Children attending higher school orders missed less their peers								
SCOLDING	School class	0.143±0.008	18.856	1.153	<0.0001	School class	0.195±0.008	24.537	1.215	<0.0001
		Older children were associated with less Scolding					*Older children were associated with less Scolding*			
	Sex	0.207±0.049	4.251	1.230	<0.0001	Sex	0.324±0.050	6.534	1.382	<0.0001
		Female were associated with less Scolding					*Female were associated with less Scolding*			
	COVID-19 exposure	-0.302±0.102	-2.979	0.739	0.003	Outdoor	0.226±0.078	2.886	1.254	0.004
		Children who had contacts with people affected by COVID-19 were associated with more Scolding					*Outdoor availability was associated with less Scolding*			
	NDD	-0.184±0.066	-2.796	0.832	0.005	Family status	0.16 ±0.073	2.245	1.178	0.025
		Children affected by NDDs were associated with more Scolding								
	Outdoor	0.174±0.078	2.243	1.190	0.025		*Children with both parents at home were associated with less Scolding*			
		Outdoor availability was associated with less Scolding								

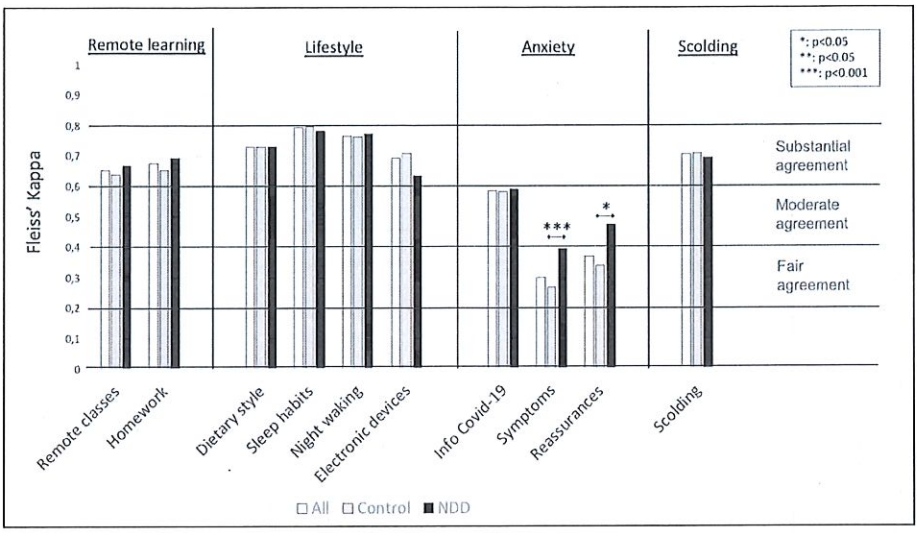

Fig. 2 Fleiss' Kappa for the agreement. Each bar represents the agreement on an item, considering all respondents together (white bars), Controls only (grey bars), or NDDs only (black bars), grouped by endpoint. Agreement thresholds are reported on the right. Asterisks indicate a significant group effect in agreement homogeneity

Discussion

In this study, the psycho-social impact of COVID-19 on children and adolescents with and without NDDs was investigated through an online questionnaire; the answers given by parents and children/adolescents were paired up—and then compared—in order to ensure reliable agreement. The aim of the study was to understand the effect of NDD condition, socio-demographic status, familiar and home environment and COVID-19 exposure on children/adolescent everyday lives. Such impact was evaluated considering five endpoints: *Remote Learning* difficulties, *Lifestyle* modifications, level of virus-related *Anxiety*, *Social* relationships and trend of familiar disputes—operationalized as *Scolding*. In what follows, we discuss the effect of independent variables on each dependent variable (AKA endpoint). We paid special attention on NDD effect, hypothesizing that COVID-19 lockdown should be even more complicated for these children; besides, we have discussed the other environmental variables with respect to the difficulties encountered by all children.

Remote learning

The COVID-19 pandemic has produced one of the largest breakdowns of education system in contemporary age. The United Nation has claimed that it has been a global crisis of teaching and learning. Closures of schools and educational structures have impacted 94% of the world's student population; the emergency has exacerbated preexisting disparities by reducing the learning opportunities for many vulnerable children (United Nations, 2020). Indeed, our analysis reveals a disadvantage in remote learning for children belonging to families with low socio-economic status. This finding is supported by a previous Italian study (Agnelli Foundation, 2020), which shows that even proper methods and technologies would make little sense in socio-culturally disadvantaged contexts. Moreover, we found that the presence of siblings had a negative effect on lessons and homework; it may be related to the fact that the only children usually receive larger amounts of feedbacks and attention from their parents and this is assumed to strengthen their self-confidence (Cao et al., 2021), improving their school performance as a result. Furthermore, availability of technology devices and quiet environments are supposed to be more difficult to find in large families and/or little homes, making attention harder to keep. In addition, children at their first years of school struggled more with remote learning than their older colleagues, for at least three reasons: (i) they probably are less confident with technology; (ii) there is an intrinsic difficulty in translating PS lessons into online sessions; (iii) most children could not pay attention as long as older students did. The psychological effect of COVID-19 is clear-cut: stress responses are more frequent in children of healthcare workers, because they probably realize their parents are putting themselves at risk to be infected by or to die of COVID-19 (Skokauskas et al., 2020). Regarding NDDs, our analysis suggests that the presence of such pathological condition had a strongly negative effect on the *Remote learning* endpoint, meaning that children with NDDs suited distance learning worse than controls. Our finding is supported by international studies, that show

difficulties in attending online lessons by children with special needs; they actually have to face barriers such as the absence of necessary equipment and internet access, but most of all they had no appropriate assistance to follow the online programs (United Nations, 2020). In point of fact, children with NDDs require individualized education plans and remote learning could not always be afforded to them. With the abrupt shift of caretaking responsibilities exclusively on the family unit, and without the support that schools typically provide, the burden was overwhelming for many parents (Tajè et al., 2020). In accordance with our results, another Italian study shows that, despite the efforts of the schools, during remote learning at least 1 out of every 4 disabled students got left behind (Agnelli Foundation, 2020). School typically offers to children some sense of freedom, through the opportunity of interaction with peers and teacher, besides providing learning contents; furthermore, it plays an edifying role in promoting physical activity, healthy and social habits (Ghosh et al., 2020). According to that, difficulties in attending remote learning, especially for children with NDD, causes much more than loss of learning opportunities.

Lifestyle

We found no significant difference in lifestyle changes during the lockdown in NDDs and control group; nevertheless, we found drastic changes in the lifestyles of both groups, especially in the adolescents, who were probably freer to change their daily routine than the younger. We investigated diets, sleeping habits and usage of electronic devices and detected changes of usual habits in all these areas. Concerning diets, our findings are supported by previous researches: Italians' food habits changed and the weight increased in 48.6% of the population (Di Renzo et al., 2020). We also observed changes in sleep routine: children/adolescents started going to sleep later and waking up later. The drawbacks of this time shift are the reduced exposure to sunlight and the increased time spent working in bed, resulting in potential troubles in falling asleep (Becker & Gregory, 2020). Noticeably, families where parents could work from home had a greater modification in habits, and it could be due to a generalized change in time organization. Moreover, we observed an augmented usage of electronic devices, for both entertainment and educational purposes. The use of internet has increased dramatically during the COVID-19 pandemic. For young people, internet is appealing and quick to access and may be an easy way to relieve stress, escaping from reality; on the other hand, excessive users will be more focused on Internet and less interested in real life. The WHO "COVID-19:24/7 parenting" guide recognizes that web usage is essential to adolescent's is sociability, but suggests that the content should be carefully monitored by parents (WHO et al., 2020).

Sociality

As social distancing seems to be effective in reducing the transmission of COVID-19, the *Sociality* endpoint was made up to understand how children reacted to the deprivation of their mates and school life. We found that older children missed their peers less and this could probably be due to the diffused use of media amongst adolescents during the last decade, regardless of COVID-19 lockdown. In addition, family environment appeared as fundamental for sociality; we found indeed that the presence of siblings reduced the lack of friends, confirming that siblings play a major role in human relationships and that children often perceive them as one of the most important people in life (Szymańska, 2020). Children of families with divorced parents missed their friends less, too; however, this could be discussed according to socialization problems and high restraint that may occur in such children (Liu et al., 2000), sometimes making them entangled in closer relationships with the single parent and/or developing internalizing attitudes (Cohen & Weitzman, 2016). Results eventually show a significant difference between NDDs and controls: children with NDDs stated they miss their peers a little. We could consider different features of NDDs to explain this finding. For example, children with ASD have, by definition, persistent deficits in social communication and social interaction across multiple contexts (American Psychiatric Association, 2013); this could explain their reduced interest in keeping relationships during the lockdown period. Moreover, it is known that patients with TS/TICS and ADHD frequently experience feelings of loneliness and peer rejection (Cox et al., 2019), being therefore accustomed to having less contact with peers regardless of the pandemic. On this topic, the American Psychological Association published practical advices for caregivers of children with disabilities during the time of COVID-19, suggesting to contact others virtually in order to cope with self-isolation (American Psychological Association, 2020).

Anxiety

The spread of the COVID-19 pandemic has led countries to adopt restrictions in order to safeguard the health of citizens; such restrictions may have negative psychological consequences as people are limited in their social and leisure activities, thus daily life stressors could be harder to bear with (Niziurski & Schaper, 2021). Therefore, understanding children's reactions and emotions is essential to properly address their needs. In our study, we found that the most important predictor of anxiety was having a direct contact with people affected by COVID-19. This group of children

requested more information about virus and needed more reassurance about their health. In fact, it is predictable that, during a global pandemic, children may develop feelings of sadness, anxiety, fear of death and of their parents' death, with a detrimental effect on their psychological well-being (Singh et al., 2020). Conversely, the availability of an outdoor space is a factor that can mitigate fear: the availability of outdoor spaces has been proven to have positive effects on stressors, improving physical well-being and quality of life, especially in cases of forced home confinement (Jackson et al., 2021). A significant difference between NDDs and control group was found for *Anxiety* endpoint as well. Parents of children with NDDs perceived their kids slightly more stressed and anxious compared to controls; children with NDDs did the same, reporting a high self-perception of stress and anxiety. The post hoc analysis showed that all NDDs but ASD are more anxious than controls. These results could be explained by recurrent comorbidities between most NDDs and anxiety disorders (D'Agati et al., 2019; Haft et al., 2019). It is clear that understanding the response to anxiety is a crucial step also to optimize policy implementation in a crisis; in a previous Indian study (Vazirani & Bhattacharjee, 2020) investigating the correlation between anxiety, health, economic conditions and lack of food during lock-down from COVID-19, it was found that understanding the response to anxiety is fundamental when pandemics create limitation in the individual's ability to mitigate the problem. Therefore, in order to prevent and face anxiety and fear in children, healthcare professionals spoke to them about COVID-19 and encouraged them to talk about their feelings (American Psychiatric Association, 2020), according to operational indications about clinical-assistance activities, drafted by the Italian Society of Infancy and Adolescence Neuropsychiatry (SINPIA, 2020).

Scolding

We asked parents and children about their perception of family dynamics during lockdown, to explore comprehensive distress level. In particular, we asked parents and kids how often they scolded or were scolded, respectively and we found a general increase of about 30% in family disputes. In fact, there is compelling evidence in literature on domestic violence increase in families during lockdown caused by health emergencies (Pereda & Dìaz-Faes, 2020). The diffuse economic crisis was an additional risk factor for domestic abuse and violence against children (Cluver et al., 2020). During the first Italian lockdown, that lasted about 2 months, families experienced high levels of distress and fear—emphasized by medias—that led to a challenge about their tolerance level and empathy. Similar to findings concerning *Anxiety*, we found that the presence of an outdoor space gives relief to familial tension, in accordance with the common belief that nature has positive impacts on children's health, including physical, mental and social dimensions (Tillmann et al., 2018). Our results show a significant difference between NDDs and control groups also in *Scolding* endpoint: children with NDDs stated they were scolded more often during lockdown. This could be explained with the increase of behavioral problems throughout home-confinement; the unexpected lifestyle changes during the lockdown—together with augmented parental stress and NDD's condition per se—could in fact break up the emotional and behavioral balance in children.

Child-parent agreement

In our study, we considered: (a) agreement between parents and children and (b) the effect of NDD condition on the agreement. We found substantial agreement between all parents and children (a) for the endpoints other than *Anxiety*, in which K index was slightly lower. It may be due to the fact that anxiety is internalizing by nature, so it could be difficult to investigate it objectively. ASD and TS groups mainly accounted for the lower agreement, confirming that, in ASD subjects, anxiety is a dominant presenting problem, even though some autistic dimensions—most of all the communication deficit—prevent children to overtly talk about their feelings (American Psychiatric Association, 2013). TS subjects are indeed known to have poor internalizing symptoms and predominant externalizing ones (Ghanizadeh & Mosallaei, 2009); their parents could not properly identify their real worries, their attention being focused on other behaviors, such as movements and vocalizations. A similar trend of agreement about anxiety was noted in previous studies on TS, too (Cavanna et al., 2013). The higher agreement detected in the NDD group with respect to controls (b) could be discussed referring to the larger amount of time spent together by children with special needs and their parents. Caregivers are thus emotionally closer to their kids, given the fact that they offer them constant support for everyday activities, probably becoming more empathic and familiar with their feeling (Hohlfeld et al., 2018). Additionally, we found that parents did not influence children (< 12 years old), when helping them in questionnaire completion. In fact, when an age effect emerged, agreement between adolescents and their parents was stronger than agreement between children and their parents. This possibly suggests a difficult self-perception in children or even a high parental apprehension, but not an acquiescence bias (Cabitza et al., 2019).

Limitations

It must be considered that children with NDDs usually cope harder with learning, anxiety, routine and sociality even before pandemic. Although questions were purposed to compare the pre-pandemic situation to the current one, it was not possible to depict a baseline situation (i.e. before COVID-19). In addition, even if the agreement homogeneity analysis supports that parents' influence on children fulfilment was minimal, some kind of influence may have occurred. Some students younger than 12 years old could have completed the questionnaires alone; on the other hand, those with reading problems, language or intellectual disabilities could have received help also at older ages. This complex situation makes it hard to properly assess the presence of the acquiescence bias in answers. Finally, we selected a set of independent variables driven by literature and experience, but it is possible that other factors have latently influenced the endpoints. As an example, other similar studies investigate if families live in an urban or rural context, but the substantial territorial homogeneity of the Varese province makes it less meaningful than having a garden, in combination with the socioeconomic status. Moreover, adding more independent variables would have reduced the power of the analysis.

Conclusions

The first Italian COVID-19 lockdown had a great impact on families. In this study, children and adolescents with NDDs showed a more significant impact in remote learning, behavioral and emotional aspects (i.e. they were scolded more and were anxious, they missed their peers less), compared to controls. Our results could provide useful information for local policy makers, school authorities, health services and families in order to implement the best support strategies for children and adolescents with NDDs in the event of a re-occurrence of a pandemic or a situation of environmental contamination and general restrictions. Regarding remote learning, it is essential to provide personalized solutions adapting to the needs and abilities of children and they should be specifically tailored to NDDs. In particular, a constant collaboration between families and teachers should be guaranteed eventually involving a 1:1 remote support from special aid teachers. Specific training for teachers could be promoted, aiming at a better didactical and psychological support. Mental health services for children and adolescents should ensure continuity of care using telemedicine tools to ensure the necessary support and avoid the risk of contagion from COVID-19. The ESSENCE European project (ESSENCE, 2020) addresses most of these needs, offering a telemonitoring and teleassistance platform to support children, both with and without specific difficulties. It acts as a facilitator for children and families to keep in touch with peers, teachers and, eventually, clinical services. Furthermore, the importance of encouraging the preservation of social and familiar relationships is clear, to prevent their worsening in relational impairment. Finally, special permission and safety measures should be accorded to let children play outdoor, with significant benefits on both their physical and mental health.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12144-021-02321-2.

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Data availability the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability not applicable.

Declarations

Conflicts of interest we declare no competing interests.

Ethics approval the protocol was approved by the Ethics Committee of ASST dei Sette Laghi di Varese (n.82 of 2020), in compliance with the Declaration of Helsinki.

Consent to participate study participants filled out informed consent before filling out questionnaires anonymously.

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DRD1 and *DRD2* Receptor Polymorphisms: Genetic Neuromodulation of the Dopaminergic System as a Risk Factor for ASD, ADHD and ASD/ADHD Overlap

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The dopaminergic system (DS) is one of the most important neuromodulator systems involved in complex functions that are compromised in both autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), conditions that frequently occur in overlap. This evidence suggests that both disorders might have common neurobiological pathways involving the DS. Therefore, the aim of this study was to examine the *DRD1* and *DRD2* dopamine receptor single nucleotide polymorphisms (SNPs) as potential risk factors for ASD, ADHD, and ASD/ADHD overlap. Genetic data were obtained from four groups: 75 ASD patients, 75 ADHD patients, 30 patients with ASD/ADHD overlap, and 75 healthy controls. All participants were between 2 and 17 years old. We compared the genotypic and allelic frequency of 18 SNPs among all of the study groups. Moreover, in the case of statistically significant differences, odds ratios (OR) were obtained to evaluate if the presence of SNPs might be a risk factor of developing a specific clinical phenotype. This study found that *DRD1* and *DRD2* receptors SNPs might be considered as potential risk factors for ASD and ADHD. However, only *DRD2-12* (*rs7131465*) was significantly associated with a higher risk for the ASD/ADHD overlap. These data support the hypothesis of the genetic neuromodulation of the DS in the neurobiology of these conditions.

Keywords: autism spectrum disorder, ADHD, ASD/ADHD overlap, dopaminergic system, dopamine receptors, polymorphisms, neuromodulation, neurobiology

INTRODUCTION

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), as well as bipolar disorder or schizophrenia, are neuropsychiatric disorders characterized by strong genetic bases (Sullivan et al., 2012; Woodbury-Smith and Scherer, 2018; Rylaarsdam and Guemez-Gamboa, 2019; Grimm et al., 2020). The dopaminergic system (DS) is involved in the regulation and the neuromodulation of some central nervous system (CNS) functions, such as social skills, the perception and the reward mechanisms for social activities, and attention and motor functions (Pavăl, 2017; Klein et al., 2019; Madadi Asl et al., 2019). Moreover, over the last two decades, several studies underlined that alterations in DS contribute to both ASD and ADHD (Iversen and Iversen, 2007; Cousins et al., 2009; Del Campo et al., 2011; Dichter et al., 2012; Owen et al., 2017).

These alterations may be related to different consequences: a selective deficit of dopamine (DA), and genetic mutations to the genes involved in synaptic homeostasis, as DA receptors, membrane transporters, or the enzymes designated to DA degradation or reuptake.

Genome-wide association studies (GWAS) significantly contributed to the identification of several genome variants known as single nucleotide polymorphisms (SNPs) associated with neuropsychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, 2019; Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee et al., 2013). These genomic variations may remain silent, without functional implications. In other cases, SNPs can give rise to missense or non-sense mutations, gene expression, or splicing alterations. When a DS receptor region is involved, SNPs can cause increase or reduction, until the absence, of receptor protein. Alternatively, binding potential or binding affinity of receptor proteins for the ligand can also be modified (Sullivan et al., 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee et al., 2013).

Given the multitude of gene variants and possible mechanisms, several studies investigated the correlation between the SNPs involving the DS and ASD or ADHD.

Attention deficit/hyperactivity disorder is a neurodevelopmental disorder (NDD) characterized by a persistent pattern ofattention deficit, hyperactivity, and impulsivity; it is one of the most common NDDs with a complex etiology and a strong genetic component (Nigg, 2013; Matthews et al., 2014; Demontis et al., 2019; Grimm et al., 2020). The clinical symptomatology of ADHD is linked to a series of alterations of functions regulated by the DS in the CNS. Furthermore, functional neuroimaging evidence has offered results about dopaminergic dysfunction in patients with ADHD, supporting the possible role of catecholaminergic dysregulation in the neurobiology of the disorder (Nigg, 2013).

As in ADHD, the DS is also involved in the ethology of ASD (Pavăl, 2017; Madadi Asl et al., 2019). ASD is a disorder characterized by two main core symptoms: a social communication and interaction deficit and the presence of repetitive and restricted interests and behaviors. Most of the functions disrupted in ASD are regulated by the DS. For example, the prefrontal cortex and the mesocorticolimbic circuit are both involved in executive functions and social cognition, while a nigro-striatal pathway alteration might explain the motor symptoms of ASD (Pavăl, 2017).

Recent studies have already identified hundreds of ASD-related gene variant encoding for synaptic proteins, transcription factors, epigenetic modulators and molecules involved in intracellular signaling (Castellanos and Tannock, 2002; Wise, 2004; Yin and Knowlton, 2006; Balleine et al., 2007; Hettinger et al., 2012). The DS plays a role in motor functions, reward and motivation which are altered in ASD. Patients with ASD display inappropriate social behavior (Mayes et al., 2011; Neale et al., 2012; Lamanna et al., 2017). Furthermore, some genetic studies have identified several SNPs or gene mutations related to the DS in patients with ASD (Craig et al., 2015, 2016).

Autism spectrum disorder and ADHD share common clinical features related to the impairment of several functions, such as attention skills, executive functions, and motor and social skills (American Psychiatric Association, 2013; Craig et al., 2015, 2016; Antshel and Russo, 2019; Gudmundsson et al., 2019). The overlap between ASD and ADHD is the clinical condition in which the two disorders are comorbid and the respective symptoms occur in the same patient. Since the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ADHD is no longer an exclusion criteria for an ASD diagnosis and vice versa (American Psychiatric Association, 2013).

According to a recent review, the prevalence of ASD/ADHD overlap has increased over the years, and these disorders seem to share genetic heritability and some clinical features (Antshel and Russo, 2019). Other studies aimed to identify possible risk factors for these condition (Craig et al., 2015, 2016; Lamanna et al., 2017; Gudmundsson et al., 2019), but its neurobiology is still unclear.

Therefore, the purpose of this study was to provide new results that might confirm and support the involvement of DS in the pathogenesis of ASD, ADHD, and their overlap, focusing on dopaminergic receptor SNPs as possible genetic risk factors for these conditions.

MATERIALS AND METHODS

Participants

For the study, patients diagnosed with ASD, ADHD, and ASD/ADHD overlap were recruited at the Childhood and Adolescence Neuropsychiatry Unit, University of Bari Aldo Moro, from 2015 to 2019.

The inclusion criteria were patients diagnosed with ASD, ADHD, and ASD/ADHD overlap, and aged between 2 and 17 years. The diagnoses were made according to the diagnostic criteria of the DSM-5 (American Psychiatric Association, 2013). We decided to consider ASD/ADHD overlap as an individual group in order to identify dopamine receptor SNPs as possible genetic risk factors of this distinct clinical disorder. The clinical diagnostic procedures included a full medical history interview, a neurological examination, and the administration of standardized protocols. We recruited 75 patients with ASD, 75

patients with ADHD and 30 patients with ASD/ADHD overlap. All patients included in the study were Caucasian.

The exclusion criteria were patients suffering from ASD and ADHD attributable to known genetic syndromes or other medical conditions (e.g., ASD-like symptoms might occur in fragile X syndrome; ADHD-like symptoms might be caused by drug intoxication or fetal alcohol syndrome).

For comparison and risk assessment of genotypes, 75 subjects aged between 2 and 17 years that had surgery and without any neurodevelopmental disorders were recruited at the Pediatric Surgery Unit, Giovanni XXIII Hospital, Bari, as controls.

The study was approved by the Local Ethical Committee (protocol number 592/12) and for all participants, informed consent was collected from their parents.

Genotyping

The choice of polymorphisms was influenced by several factors. *DRD1* and some *DRD2* SNPs involved in this study were already known in the literature. Furthermore, using http://www.ncbi.nlm.nih.gov/nuccore/209977039?report=genbank&to=72685, we searched for all polymorphisms of the *DRD2* gene that are currently identified.

Since the methylation profiles of regions containing CpG islands could influence the levels of gene expression, using the CpGplot program of the EMBOSS package (available at https://www.ebi.ac.uk/Tools/seqstats/emboss_cpgplot/) we identified two regions within the introns of the *DRD2* gene that are unusually enriched with CpG dinucleotides; the first extends from nucleotide 4,634 up to nucleotide 5,660 (therefore longer than 1 kb), and the second extends from nucleotide 5,740 up to 5,953 (214 base pair long).

In these regions, we selected SNPs having an allelic frequency not less than 10% (0.1) in principle and, among these, only those that could be discriminated using the restriction fragment length polymorphism (RFLP) technique were considered.

This technique involves the use of restriction enzymes that recognize and cut specific DNA sequences. The enzymatic cutting is usually carried out in correspondence with the polymorphic sequence, allowing the recognition of the nucleotide variation.

The search for restriction enzymes to be used was conducted using the programs available on the New England Biolabs website[1]. The first program used was NEBcutter®[2], which allows the identification of restriction enzymes able to discriminate the polymorphic sequence. We then moved on to the Primer3 program (see 0.4.0) (available at http://bioinfo.ut.ee/primer3-0.4.0/primer3/) to design amplification primers for the restriction sites and, finally, the REBsites program[3] was used to predict the length of the fragments obtained after the restriction enzyme cutting. The genotyping of the recruited subjects was carried out using venous blood samples from patients and controls. To isolate the leukocytes of the study subjects, a sample was taken in tubes containing sodium citrate. A total of 10 ml of peripheral blood was mixed in a 1:1 ratio with Emagel (Piramal Healthcare, Northumberland, United Kingdom) heparinized (5 U.I. of heparin per ml of Emagel). The obtained solution was placed on a rotor for 10 min at the end of which the red cells were left to settle. The supernatant thus obtained was centrifuged at 1,600 rpm for 10 min. The pellet was re-suspended in 5 ml of 1X PBS and centrifuged at 1,600 rpm for 10 min. To remove the present cells, an osmotic shock was applied: the pellet was then re-suspended in 1 ml of 0.2% NaCl and vortexed for 1 min. Subsequently, 1 ml of 1.6% NaCl was added and the suspension was then centrifuged at 1,200 rpm for 10 min. Where necessary, the osmotic shock was repeated. The pellet was finally re-suspended in 1 ml of physiological solution and the leukocytes were counted in the Burker chamber. After cell counting, 10×10^6 cell aliquots were used to extract DNA using DNAzol® Reagent (Life Technologies, Carlsbad, CA, United States).

The DNA concentration was measured by spectrophotometer and the solution was diluted with H2O RNasi and DNasi free (SIGMA) to obtain a final value of 100 ng/μl. Each polymorphic region was amplified using 100 ng DNA, 5 μl 10X PCR buffer, 3 μl 25 mM MgCl2, 2 μl 10 mM dNTPs mix, 0.5 μl AmpliTaq Gold 5 U/μl (Life Technologies, Carlsbad, CA, United States) and 1 μl of specific primer (IDT Inc., Coralville, IA, United States). The thermal protocol used was the same for all reactions, with an annealing temperature of 57°C and several cycles equal to 40. **Table 1** shows the 18 polymorphisms selected for the study, their related gene and expected PCR amplicon size. Individual amplicons electrophoretic runs are displayed in **Figure 1**.

Restriction Fragment Length Polymorphism

All of the endonucleases used were purchased from Thermo Scientific (Carlo Erba reagents, Cornaredo, Italy) except for the enzyme *Cac*8I, which was purchased from New England Biolabs (Ipswich, MA, United States). Then, 10 μl of amplified obtained from the PCR reaction was used for enzymatic cutting. The digestion mix was prepared using 2 μl of specific digestion buffer and 1 U of the enzyme in a total volume of 20 μl. The reaction was carried out for 1 h in a thermostatic bath by varying the temperature depending on the enzyme used, as specified in **Supplementary Table 1**.

The information about each polymorphism is obtainable from the NCBI database; db SNPs with the relative expected digestion fragments predicted by the REBsite software are described in detail in the **Supplementary Material**.

An example of genotyping, regarding *DRD1-B* (*rs4532*) polymorphism, is shown in **Figure 2**.

Statistical Analyses

To determine the relationship between *DRD* SNPs under study and the risk of childhood ADHD, ASD and ASD/ADHD overlap phenotypes, both genotypic and allelic frequencies related to each SNP were compared among the groups reported above and the group of subjects unaffected by any neuropsychiatric pathology (control group) by the Chi-squared test or the Fisher's Exact test, where appropriate, (empirical *P*-value).

[1] https://www.neb.com/

[2] http://tools.neb.com/NEBcutter2/

[3] http://tools.neb.com/REBsites/index.php

TABLE 1 | List of analyzed polymorphisms of *DRD1* and *DRD2* genes and of the primer sequences with the expected amplicon size.

Gene (rsID)	SNP primer sequences	Expected amplicon size (bp)
DRD 1-A (rs686)	*FOR: 5′-GTGTGTTGGAAAGCAGCAGA-3′* *REV: 5′-CCATCACACAAAACGGTCAG-3′*	*166*
DRD 1-B (rs4532)	*FOR: 5′-GGCAGAGGTGTTCAGAGTCC-3′* *REV: 5′-CGGTCCTCTCATGGAATGTT-3′*	*187*
DRD 1-C (rs265973)	*FOR: 5′-GCATGCCAATTTGCTCTTG-3′* *REV: 5′-GGATTAAAGAGGATCCAGTCCA-3′*	*100*
DRD 1-D (rs265975)	*FOR: 5′-CCTCTCATGTCCCTCTCCAA-3′* *REV: 5′-GAGCAAGGACAACAGGAAGC-3′*	232
DRD 2-A (rs1076560)	*FOR:5′-GACAAGTTCCCAGGCATCAG-3′* *REV:5′-GGCAGAACAGAAGTGGGGTA-3′*	213
DRD 2-B (rs1800497)	*FOR:5′- AAATTTCCATCTCGGCTCCT-3′* *REV:5′-GAGGAGCACCTTCCTGAGTG-3′*	293
DRD 2-C (rs1079597)	*FOR: 5′-TTTCCCTTCTGTGGGATGAG-3′* *REV: 5′-GGAGGTTGCAATAGGCAAGA-3′*	274
DRD 2-E (rs7118900)	*FOR: 5′- CGCAGTAGGAGAGGGCATAG-3′* *REV: 5′-ATGGGAGCTTCAAAGGGAAG-3′*	*348*
DRD 2-1 (rs144851051)	*FOR: 5′- CTCAGCCTCCCAAGTAGCTG-3′* *REV: 5′- GCTGTCCACATGCTGAAGAA-3′*	*346*
DRD 2-2 (rs11608185)	*FOR: 5′-GTGTGCATGGCTGTGTCC-3′* *REV: 5′- GCTGCTGTGAGGGTTATATAGGA-3′*	396
DRD 2-7 (rs35352421)	*FOR: 5′-CCTGCACCCCAGATTCAG-3′* *REV: 5′- CTGTTTCCTCTCTGCCAACC-3′*	375
DRD 2-8 (rs2245805)	*FOR: 5′-CTCCTAGGCATCCAACCAAA-3′* *REV: 5′- GTGGCTCCCAAGTACTGGTC-3′*	373
DRD 2-10 (rs67800399 merged into rs2734832)	*FOR: 5′- TCAGGTCATTTTGGAAGTTGC-3′* *REV: 5′-AGGGAAGGGGTTGTTGAAAG-3′*	249
DRD 2-11 (rs1962262)	*FOR: 5′-CCTCAGCCTCCCAAGTATCT-3′* *REV: 5′-TCTTGGTAACCCTGGGAGTC-3′*	240
DRD 2-12 (rs7131465)	*FOR: 5′-GCCTGTAATCCCAGCACTCT-3′* *REV: 5′-AAGGGAAAACATGGCAAATG-3′*	366
DRD 2-15 (rs61902807)	*FOR: 5′-CCTCTAAGCACCAGACAGAGC-3′* *REV: 5′-ACCTCAAGAGCCACCGAAA-3′*	250
DRD 2-16 (rs10789943)	*FOR: 5′-TAGCCTCCTCGCCACTTAGA-3′* *REV: 5′-CGAAAGTTCAGGACCAAGGA-3′*	362
DRD 2-17 (rs10789944)	*FOR: 5′-TAGCCTCCTCGCCACTTAGA-3′* *REV: 5′-CTCTCCCCCATCCTTAGCTT-3′*	300

DRD, Dopamine Receptor; FOR, forward primer; REV, reverse primer; bp, base-pair.

Further the genotypic association analysis under the dominant and recessive models of inheritance were performed.

The differences were considered statistically significant if the *P*-value was < 0.05.

For the latter, the odds ratio (OR) and the 95% confidence interval (95% CI) were then calculated to assess the risk of expressing or not expressing the pathological phenotype for the group under examination compared to the reference group, based on the presence of the minor allele.

A multiple testing correction (false discovery rate) was performed to guard against the potential for false positive associations (corrected *P*-value). Data were analyzed with R version 4.0.2.

RESULTS

We recruited 75 patients with ASD, 75 patients with ADHD and 30 patients with ASD/ADHD overlap. Demographic features are summarized in **Table 2**, while allele frequencies distribution, regarding 18 analyzed SNPs, is shown in **Table 3**.

Among *D1* and *D2* receptor genes, Chi-squared test identified six and seven SNPs, respectively, in genotypic and allelic distribution, characterized by a statistically significant difference both in the case–control comparison and between the pathological groups, with empirical *P*-values < 0.05 (**Tables 4**, **5**).

About *D1* receptor polymorphisms, the SNP *rs4532* appeared to be associated with a greater risk for ASD (OR = 1.8; 95%IC = 1.115–2.912; empirical *P*-value = 0.02).

The most relevant results came from the analysis of D2 receptor polymorphisms. Indeed, *rs2245805* and *rs7131465* appeared to be associated with the increased risk of developing ASD/ADHD overlap compared to the other clinical phenotypes.

The presence of the minor allele in *rs144851051* and *rs2734832* seems to promote the development of a singular clinical disease, that is ADHD vs. controls for *rs144851051* (OR = 2.6; 95%IC = 1.0054–7.073; empirical *P*-value = 0.04) and ADHD

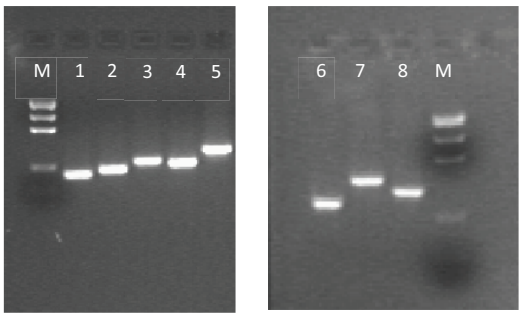

FIGURE 1 | Example of gel electrophoresis pattern of PCR amplicons about some analyzed *DRD* SNPs with their size. M, Precision Molecular Mass Ruler, Bio-Rad Laboratories, Inc., (size of DNA fragments: 1000, 700, 500, 200, 100 bp). PCR amplicons: 1, *DRD 1-A* (166 bp); 2, *DRD 1-B* (187 bp); 3, *DRD 1-D* (232 bp); 4, *DRD 2-A* (213 bp); 5, *DRD 2-B* (293 bp); 6, *DRD 2-15* (250 bp); 7, *DRD 2-16* (362 bp); 8, *DRD 2-17* (300 bp).

or ASD vs. overlap for *rs2734832* (OR = 1.9; 95%IC = 1.0564–3.5671; empirical *P*-value = 0.03 and OR = 2.1; 95%IC = 1.1196–3.7949; empirical *P*-value = 0.02, respectively).

By contrast, *rs11608185* and *rs61902807* could be protective factors for the development of the overlap condition.

However, the false discovery rate method dramatically reduced the number of significantly different SNPs and only *rs7131465* (*DRD2-12*), both in genotypic and allelic distribution, remained after the correction.

The presence of the minor allele in SNP *rs7131465*, located in the 5′-terminal untranslated region (5′ UTR) of the *DRD2* gene, seems to be a strong risk factor of developing ASD/ADHD overlap vs. a singular clinical disease, that is ASD or ADHD (OR = 2.7; 95%CI = 1.4701–5.024; corrected *P*-value = 0.003 and OR = 2.8; 95%CI = 1.5581–5.3447; corrected *P*-value = 0.003, respectively).

Actual results are impacted by the reduced sample size of overlap group and low statistical power of the comparison groups. To solve a similar situation, Ma et al. (2021) merged their data to form a single aggregated clinical group to be compared against a single aggregated control one. The advantage of this method is enlarging the comparison group size and thus increasing statistical power.

On our side, an enlarged ADHD or ASD group, including ADHD/ASD overlap, would lead to the loss of distinctive feature and prediction of specific risk for overlap patients.

To support our findings about rs7131465 SNP, we took a different approach that is dominant and recessive models of inheritance (**Table 6**; Liu et al., 2021; Ma et al., 2021).

The group with the C*/C* homozygous minor allele or the A/C* heterozygous genotypes of *rs7131465* showed an increased risk of overlap comparing to healthy controls (OR = 3.25, 95% CI = 1.11–11.91, empirical *P*-value = 0.04), ASD (OR = 4.84, 95% CI = 1.68–17.61, empirical *P*-value = 0.007) or ADHD (OR = 5.69, 95% CI = 1.198–20.69, empirical *P*-value = 0.003) in a dominant model, but not a recessive model. The last two of them survived the multiple testing correction and remained statistically significant, i.e., overlap vs. ASD (corrected *P*-value = 0.021), overlap vs. ADHD (corrected *P*-value = 0.017).

No significant difference in the genotype distribution of *rs7131465* in children with ASD or ADHD and healthy controls was observed, both in recessive or dominant model.

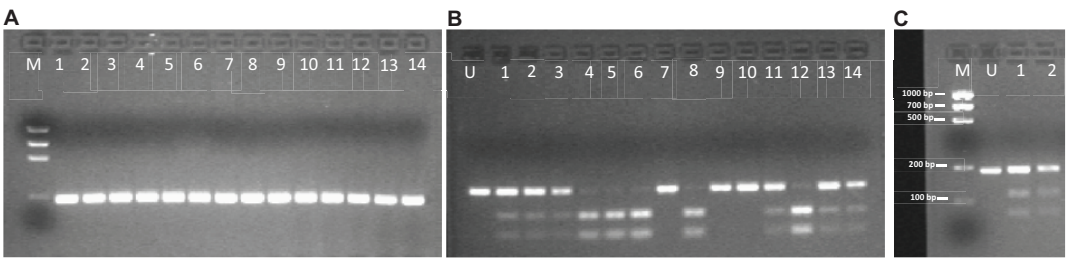

FIGURE 2 | Gel Electrophoresis pattern about *DRD 1-B* SNP (*rs4532*). **(A)** Electrophoretic gel of 14 patients *DRD 1-B* amplicons (187 bp). **(B)** *Bpu*10I enzyme digestion pattern on the same 14 patients PCR amplicons. Restriction site is on T allele. Single 187-bp electrophoresis band denotes a C/C homozygous genotype; 116-bp and 71-bp banding pattern is for a T/T homozygous genotype; the presence of three bands of 187-bp, 116-bp and 71-bp is for C/T heterozygous genotype. **(C)** Molecular length (bp) of restriction fragments derived from *rs4532 digestion by Bpu*10I. M, DNA Molecular Weight Marker (Precision Molecular Mass Ruler, Bio-Rad Laboratories, Inc.); U, undigested PCR amplicon (187 bp).

TABLE 2 | Demographic features of the study groups.

Participants		ADHD	ASD	ADHD/ASD overlap	Controls
Number		75	75	30	75
Average age, (years)		10.36	10.57	11.57	12.23
Gender	Male (%)	83	85	76.6	75
	Female (%)	17	15	23.4	25

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

TABLE 3 | Allele frequencies distribution of SNPs in study groups.

Gene	db SNP (rsID)	Minor/major allele	Minor allele frequency			
			ADHD ($n = 75$)	ASD ($n = 75$)	Overlap ($n = 30$)	Controls ($n = 75$)
DRD 1	*DRD 1-A (rs686)*	*G/A*	0.346	0.386	0.383	0.293
	DRD 1-B (rs4532)	*C/T*	0.346	0.420	0.383	0.286
	DRD 1-C (rs265973)	*T/C*	0.427	0.467	0.433	0.460
	DRD 1-D (rs265975)	*T/C*	0.327	0.346	0.317	0.427
	DRD 2-A (rs1076560)	*A/C*	0.14	0.14	0.150	0.16
	DRD 2-B (rs1800497)	*T/C*	0.17	0.16	0.150	0.21
	DRD 2-C (rs1079597)	*A/G*	0.11	0.12	0.150	0.16
	DRD 2-E (rs7118900)	*A/G*	0.14	0.17	0.167	0.21
	DRD 2-1 (rs144851051)	*T/C*	*0.1*	*0.05*	*0.050*	*0.04*
	DRD 2-2 (rs11608185)	*C/T*	*0.66*	*0.67*	*0.500*	*0.61*
DRD 2	*DRD 2-7 (rs35352421)*	*T/G*	*0.93*	*0.93*	*0.950*	*0.96*
	DRD 2-8 (rs2245805)	*A/C*	*0.23*	*0.21*	*0.350*	*0.23*
	DRD 2-10 (rs67800399 merged into rs2734832)	*C/A*	*0.34*	*0.33*	*0.500*	*0.39*
	DRD 2-11 (rs1962262)	*T/C*	0.11	0.12	0.176	0.16
	DRD 2-12 (rs7131465)	*C/A*	0.33	0.34	0.567	0.43
	DRD 2-15 (rs61902807)	*C/T*	0.40	0.45	0.333	0.47
	DRD 2-16 (rs10789943)	*A/G*	0.15	0.19	0.133	0.13
	DRD 2-17 (rs10789944)	*A/C*	0.16	0.19	0.133	0.14

SNP, single nucleotide polymorphism; ADHD: attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

DISCUSSION

In this study, we aimed to investigate if specific *DRD1* and *DRD2* receptor polymorphisms might be considered as potential genetic risk factors for ASD, ADHD, and ASD/ADHD overlap.

Our study found that two specific polymorphisms of the *D2* receptor, *rs2245805* and *rs7131465,* respectively, *DRD2-8* and *DRD2-12*, might be associated with ASD/ADHD overlap when compared with ASD, ADHD, and control groups. However, only the SNP *rs7131465* (*DRD-12*) showed a statistically significant higher risk for the ASD/ADHD overlap.

TABLE 4 | Results of the comparative analysis of genotype distribution of the SNPs among the study groups.

Polymorphism (rsID)	Compared groups	Empirical *P*-value*	Corrected *P*-value for false discovery rate
DRD 2-8 (rs2245805)	Overlap vs. ASD	0.05	0.20
DRD 2-10 (rs2734832)	Overlap vs. ASD	0.04	0.15
	Overlap vs. ADHD	0.05	0.15
DRD 2-12 (rs7131465)	Overlap vs. ASD	0.005	0.015
	Overlap vs. ADHD	0.003	0.015
DRD 1-B (rs4532)	ASD vs. CTR	0.04	0.12
DRD 1-D (rs265975)	ADHD vs. CTR	0.04	0.12
DRD 2-2 (rs11608185)	Overlap vs. ADHD	0.05	0.15

**Empirical P-value: result of Chi-squared test.*
SNPs, single nucleotide polymorphisms; ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

DRD2-12 is within the intronic region between exon 1 and exon 2 of 5′ UTR. This intronic region is large 50,391 base pair and *rs7131465* is located near the beginning of exon 2. Currently, no study has been conducted that examined the effect of this polymorphism. Since UTRs are the regulatory elements of genes, acting as controllers of translation and RNA decay, as well as targets for RNA interference (RNAi) and playing a central role in post-transcriptional regulation, it should be no surprise that polymorphisms in 5′ UTRs have been linked to many human, mainly oncological and neurological, diseases (Halvorsen et al., 2010). These SNPs can promote tumorigenesis by increasing c-Myc expression (Chappell et al., 2000), translation inhibition (Cazzola and Skoda, 2000), and transcription activity (Fan et al., 2013). 5′ UTR alterations was also involved in neurological disease such as spinocerebellar ataxia type 1 (Rachna et al., 2020), Parkinson's disease (Rubino et al., 2020), bipolar disorder type I (Alizadeh et al., 2019) and Alzheimer's disease (Lahiri et al., 2003).

To the best of our knowledge, no previous studies were carried out to investigate genetic polymorphisms of ASD/ADHD overlap. This is probably related to the fact that the nosographical recognition of the comorbidity between the two disorders occurred only after the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders in 2013.

However, from the results of the present study, it is hypothesized that dopaminergic neuromodulation may also be involved in the pathogenesis of the overlap, probably with different genetic risk aspects compared to those of ASD and ADHD. Even if these two disorders share a common clinical

TABLE 5 | Results of the comparative analysis of allelic distribution of the SNPs among the study groups with the corresponding OR values.

Polymorphism (rsID)	Compared groups	Empirical *P*-value*	Corrected *P*-value for false discovery rate	OR (95% CI)
DRD 2-1 (rs144851051)	ADHD vs. CTR	0.04	0.21	2.6 (1.0054–7.073)
DRD 2-8 (rs2245805)	Overlap vs. CTR	0.04	0.08	1.9 (1.0317–3.7817)
	Overlap vs. ASD	0.02	0.08	2.1 (1.1095–4.1077)
	Overlap vs. ADHD	0.04	0.08	1.9 (1.0317–3.7817)
DRD 2-10 (rs2734832)	ASD vs. Overlap	0.02	0.09	2.1 (1.1196–3.7949)
	ADHD vs. Overlap	0.03	0.09	1.9 (1.0564–3.5671)
DRD 2-12 (rs7131465)	Overlap vs. CTR	0.04	0.32	1.8 (1.0255–3.451)
	Overlap vs. ASD	0.001	0.003	2.7 (1.4701–5.024)
	Overlap vs. ADHD	0.001	0.003	2.8 (1.5581–5.3447)
DRD 1-B (rs4532)	ASD vs. CTR	0.02	0.12	1.8 (1.115–2.912)
DRD 2-2 (rs11608185)	Overlap vs. ASD	0.02	0.09	0.5 (0.2718–0.9197)
	Overlap vs. ADHD	0.03	0.09	0.5 (0.2803–0.9467)
DRD 2-15 (rs61902807)	Overlap vs. CTR	0.04	0.24	0.5 (0.2742–0.9695)

**Empirical P-value: result of Chi-squared test or Fisher's Exact test.*
SNPs, single nucleotide polymorphisms; OR, odds ratio; ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

TABLE 6 | The genotype distribution of SNP *DRD 2-12* between overlap and the other clinical groups and risk prediction for overlap disorder, under the most significant genetic model of inheritance.

db *SNP* (rsID)	Compared groups	Most significant model	Genotype	Group1/Group2 (n, %)	#OR (95% CI)	Empirical *P*-value	Corrected *P*-value
DRD 2-12 (rs7131465)	Overlap vs. Controls	Dominant	C*/C* + A/C*	26 (87)/50 (67)	3.25 (1.11–11.91)	0.04	0.08
			A/A	4 (13)/25 (33)			
	Overlap vs. ASD	Dominant	C*/C* + A/C*	26 (87)/43 (57)	4.84 (1.68–17.61)	0.007	**0.021**
			A/A	4 (13)/32 (43)			
	Overlap vs. ADHD	Dominant	C*/C* + A/C*	26 (87)/40 (53)	5.69 (1.98 –20.69)	0.003	**0.017**
			A/A	4 (13)/35 (47)			

OR, odds ratio; SNP, single nucleotide polymorphism; CI, confidence interval.
**Minor allele.*
Dominant model: homozygous minor allele plus heterozygous vs. homozygous major allele.
#OR value associated with the minor allele genotype.
Significant SNPs after multiple testing correction bolded.

ground, including the impairment in cognitive functions (e.g., attention skills), in social abilities, and in the executive functions, recent studies underlined that both ASD and ADHD retain qualitative and quantitative clinical differences in their phenotype (Craig et al., 2015; Antshel and Russo, 2019). SNP *rs7131465* in 5′ UTR might be involved in alternative splicing resulting in mRNA instability and producing different isoforms of *DRD2* transcript.

Other *D1* and *D2* receptors have been previously identified in patients with ASD (Hettinger et al., 2008, 2012). A study on murine models showed that excessive striatal dopaminergic activation, deriving from specific mutations of the *D1* receptor, might promote autistic symptoms in mice, such as social deficits and repetitive behaviors. This interpretation was supported by the evidence that murine behavioral changes induced by excessive dopaminergic activity were inhibited by specific *D1* receptor antagonists (Lee et al., 2018).

Interestingly, Liu et al. (2020) demonstrated that certain SNPs of dopaminergic system genes might have a modulator effect on facial/emotion recognition in patients with ASD (Liu et al., 2020). Nevertheless, a recent Chinese study showed that some serotonin HTR2A receptor SNP might also be associated with a higher risk for ASD (Liu et al., 2021). Moreover, previous meta-analyses showed a significant association between some *D2* receptor polymorphisms and ADHD (Sullivan et al., 2012; Wu et al., 2012; Pan et al., 2015). As for ASD, some studies investigated the possible effects of gene polymorphisms of the DS on the functional activity of the dopaminergic circuits involved in ADHD. Different models have been proposed to explain the symptomatology of the disorder; among these, the executive functions model is the most described and studied (Arnsten and Li, 2005; Willcutt et al., 2005; Craig et al., 2016).

Lastly, more recent neuroimaging studies showed that the presence of some *DRD2* and *DRD4* might, respectively, modulate the gyrification and the functional activity of cortical areas involved in cognitive processes that are impaired in ADHD and other psychiatric disorders (Palaniyappan et al., 2019; Overs et al., 2021).

CONCLUSION

In conclusion, we found that carrying specific *DRD1/DRD2* SNPs could increase the risk for ASD, ADHD, even if only one SNP showed a statistically significant association with a higher risk

for and ASD/ADHD overlap. These findings might support the hypothesis of the involvement of the dopaminergic system in the neurobiology of these conditions. However, this study has some limitations that need to be mentioned. The study protocol approved by the Local Committee did not include also genetic examination of the parents' patient; therefore, we were not able to verify if a SNP was inherited or it is a *de novo* mutation. Moreover, this was a genetic preliminary study, so we did not proceed with a functional validation of the analyzed SNPs and with a correlation phenotype/genotype analysis; however, all these analyses would be considered for future investigations.

In addition, further studies on larger groups might explore more in-depth how the dopaminergic system SNPs could represent biomarkers for a clinical phenotype and eventually how they could modulate the efficacy of the pharmacological or rehabilitation therapy in these disorders.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethical Committee—Policlinico of Bari (protocol number 592/12). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MM, RP, and LM: conceptualization, writing—review and editing, supervision, and project administration. MM, RP, AnV, AlV, and RL: methodology and data curation. AnV, AlV, and RL: formal analysis. MM, RP, MP, AP, AG, OG, and RL: investigation. AnV, MP, AP, AG, and OG: resources. MM and RP: writing—original draft preparation. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.705890/full#supplementary-material

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Article

Exploring the Efficacy of a Mindfulness Program for Boys With Attention-Deficit Hyperactivity Disorder and Oppositional Defiant Disorder

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Abstract

Objective: This study was the first attempt to explore the efficacy of a mindfulness protocol for children with attention-deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), and their parents. **Method:** Fifty male children with ADHD and ODD diagnosis, aged 8 to 12, were randomly assigned to the mindfulness intervention ($n = 25$) or the wait-list ($n = 25$) group. Outcome measures included children, parents', and teachers' reports and objective measures of attention. **Results:** Children from the intervention group had a greater reduction in hyperactive behaviors in the school context (effect size [ES] = 0.59) and a greater improvement in visual sustained attention (ES = 0.77) and in Avoidance and Fusion Questionnaire scores (ES = 0.43) than those in the wait-list control group. No significant effect of the intervention on aggressive behaviors was revealed. **Conclusion:** A mindfulness intervention for children and their parents showed partial beneficial effects in children with ADHD + ODD. *(J. of Att. Dis. 2021; 25(11) 1544-1553)*

Keywords

mindfulness, randomized controlled trial, ADHD, attention, treatment efficacy, meditation

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most frequent disorders in children. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013) suggested a prevalence of 5%; similar findings emerged from systematic reviews, which indicated a community prevalence of ADHD between 2% and 7% (see, for instance, Sayal et al., 2018). Difficulties in sustaining attention and difficulties related to overactivity and poor impulse control are the main clinical characteristics of children with ADHD (APA, 2013). The presence of ADHD puts children at higher risk for several negative outcomes: Studies showed that ADHD children globally show poorer mental health, worst academic performances, and impaired social functioning (Efron et al., 2014; Lee et al., 2008; Sayal et al., 2018). From an economic perspective, ADHD represents a significant cost for society, with an estimated annual cost per patient between €9,860 and €14,483 in Europe (Le et al., 2014).

Currently, behavioral treatments and medications are the main treatment options for youths with ADHD. Behavioral interventions are usually delivered in the form of behavioral parent training, which mainly aims to teach parents to adequately use rewards and negative consequences to improve or diminish children's behaviors. Even though they are usually effective (Zwi et al., 2012), several studies showed that they also have some limitations (Goode et al., 2018; Pelham & Fabiano, 2008; Van den Hoofdakker et al., 2012).

Regarding medication for ADHD, psychostimulants are the most prescribed drugs (Graham et al., 2011). The stimulant treatment has been reported to improve symptoms in 70% to 80% of children with ADHD (Atkinson & Hollis, 2010). Furthermore, research has shown that children diagnosed with ADHD who take psychostimulant medication score higher on neuropsychological measures of attention and verbal learning (Biederman et al., 2008). Overall, stimulants have largely demonstrated their efficacy in reducing

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ADHD symptoms across numerous studies and that is why it is considered the first-line option for ADHD treatment (for a review, see Faraone et al., 2015). However, alongside all these assets, it is necessary to consider a series of concerns related to pharmacological interventions for ADHD. First, a small percentage of individuals who are prescribed medication to treat ADHD symptoms have adverse side effects (for a review, see Graham & Coghill, 2008); second, nonadherence rates within ADHD patients are estimated from 13% up to 64% (Adler & Nierenberg, 2010; Biederman et al., 2019); finally, parents sometimes do not consent to pharmacological treatment and/or prefer psychological approaches.

ADHD is often comorbid with other psychiatric disorders (Spencer et al., 2007), and this may have crucial implications on children's outcomes and intervention efficacy. Oppositional defiant disorder (ODD) is among the most frequent ADHD comorbidities (Harvey et al., 2016; Reale et al., 2017). Children with ADHD and ODD exhibit an earlier onset of ODD symptoms, which also appear more severe; they are more aggressive and have heightened difficulties in regulating their emotions and behavior than those with ADHD or ODD alone (Loeber et al., 2000; Nijmeijer et al., 2008). Comorbid behavioral problems in ADHD children are associated with diminishing medication effect size for aggression (Connor et al., 2002; Gurnani et al., 2016), although other studies do not support this finding (Masi et al., 2017). Also, intervention models for children with ODD usually diminish their effects when children have ADHD comorbidity (Jensen et al., 2001; Muratori et al., 2015). In summary, when ADHD is comorbid with ODD, clinical effects are harder to reach, and there are no guidelines providing for a standardized treatment for children with ADHD and ODD (Liu et al., 2019).

Mindfulness Interventions for Children With ADHD and ODD

Mindfulness has been defined as intentionally directing attention to moment-by-moment experiences with curiosity and acceptance (Kabat-Zinn, 2003). A recent review showed that mindfulness-based interventions have positive effects on attentional skills, executive functioning, and negative behaviors in children (Dunning et al., 2019). We also deem that mindfulness-based interventions can overcome, at least partially, some limitations encountered by traditional interventions for ADHD. Some authors posited, for instance, that behavioral parent training might significantly improve neither children's, nor parents', emotion regulation skills (see, for instance, Singh et al., 2010). Mindfulness-based interventions have been shown to promote emotion regulation skills in both children and adults (Chambers et al., 2009; Perry-Parrish & Sibinga, 2014). Although adherence and compliance might be a problem with ADHD patients, mindfulness interventions are usually relatively short, and hence the effort required is merely for a limited period of time. This may reduce the risk of dropout and enhance parents' and children's compliance (see, for instance, Singh et al., 2010). Finally, they can be a promising alternative when pharmacotherapy cannot be administered.

Previous studies showed that mindfulness interventions could reduce ADHD symptoms (for reviews, see Cairncross & Miller, 2020; Evans et al., 2018), with a significant reduction of inattention, impulsivity, and hyperactive behaviors, though these results were more prominent for adults rather than children (Cairncross & Miller, 2020). For instance, results from Felver et al. (2017) supported the hypothesis that participation in a mindfulness-based intervention significantly improves children's attention regulation; Lo et al. (2020), investigating the feasibility of a family-based mindfulness intervention in children with inattention and hyperactivity symptoms, found that children in intervention condition had greater improvements in ADHD symptoms than those in the wait-list control group. All these previous studies stated that mindfulness researchers should collect objective measures of attention inattention and hyperactivity, and collect the ratings of teachers, to evaluate the generalizability of the intervention.

Mindfulness-based interventions have also been increasingly considered a promising approach to address childhood aggressive and externalizing problems. They aim to implement the ability to recognize, label, and accept the internal experiences, including thoughts, feelings, and physical sensations as well as promoting stress management and relaxation strategies (Greco & Hayes, 2008; Krisanaprakornkit et al., 2010). Thus, we can hypothesize that they may help children to become more capable of managing their anger and, consequently, to reduce the emission of oppositional defiant core behaviors. In parallel, a mindful program for parents could improve parent–child interaction and parenting strategies, by reducing parental stress and parental reactivity to children's negative behaviors and improving parental attention and executive functioning (Bögels et al., 2010, 2014). We can speculate that all these changes may foster an improvement in children's externalizing behavior, too.

For instance, the "Meditation on the Soles of the Feet" is a mindfulness-based intervention that aims to improve aggression and anger management (Singh et al., 2003). This technique enables participants to shift their attention from an emotionally arousing situation or thought, to a neutral part of the body, the soles of the feet in this case. Like that, people can stop and settle down, and then decide which is the best way to respond to a trigger situation. Through practice, this mechanism becomes more and more automatic and easier to be applied within different life contexts. Studies showed that the "Meditation on the Soles of the Feet" is effective in reducing aggressive behaviors in

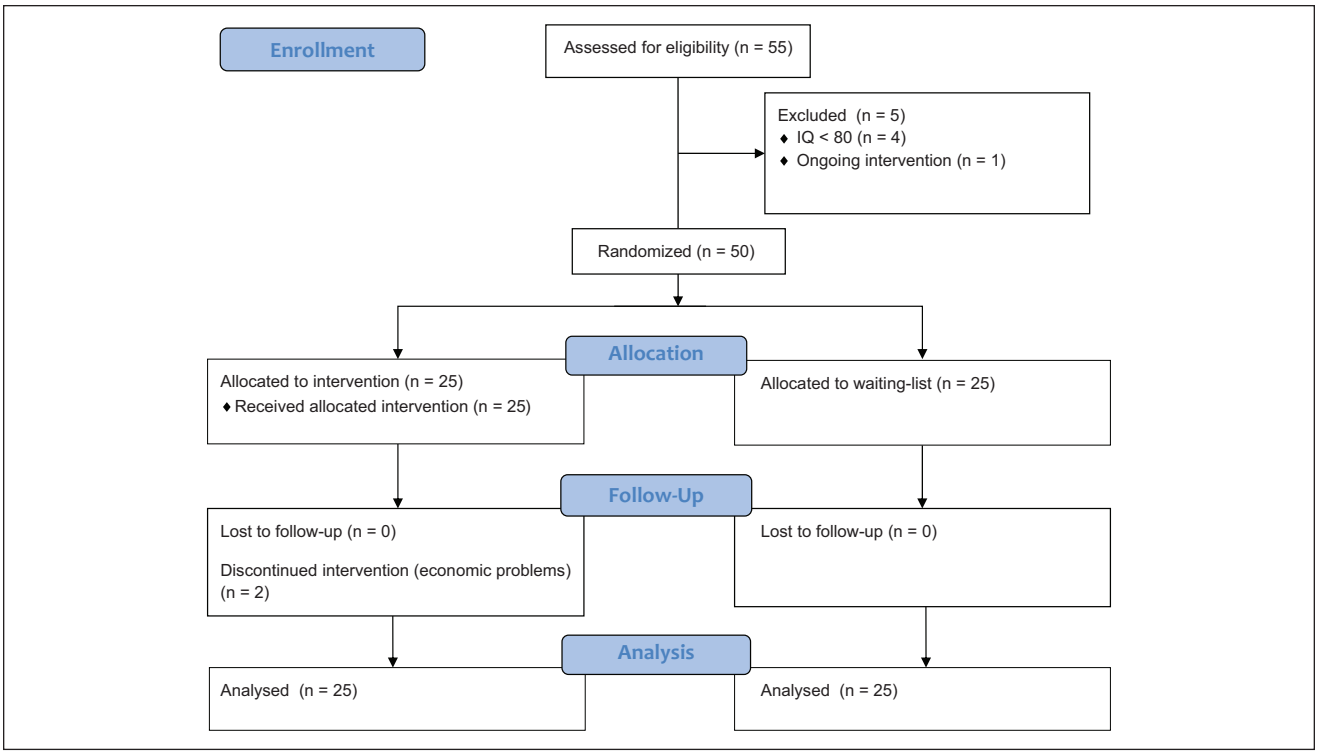

Figure 1. CONSORT flow diagram.
Note. CONSORT = Consolidated Standards of Reporting Trials; IQ = Intelligence Quotient.

several populations (Singh et al., 2003, 2007, 2017). Similar findings were found by Bögels et al. (2008).

Considering the aforementioned promising findings, this pilot study was a first attempt to examine the efficacy of a mindfulness-based intervention for children with ADHD + ODD. The outcome measures of the work included child-, parent-, and teacher-report questionnaires, and objective measures of attention. Even though ADHD and ODD frequently co-occur, there are no randomized controlled trials (RCTs) investigating the efficacy of mindfulness-based interventions with clinical samples of children with both ADHD and ODD. The objective of this study was to examine whether a mindfulness-based intervention can reduce children's ADHD symptoms and aggressive behaviors.

Method

Procedures

The study has been conducted in an outpatient hospital, working with children and adolescents with psychiatric problems (Masi et al., 2016). Usually, pediatricians refer children to our hospital to receive a psychiatric assessment. In this clinical context, we started a parallel RCT with pre- and posttreatment measurements to explore the effects of a mindfulness training versus a wait-list control condition. The eligibility criteria were male sex and diagnoses of ADHD and ODD, verified by the K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version; Kaufman et al., 1997). Participants were excluded from participation if (a) they were suffering from autism spectrum disorder, (b) Intelligence Quotient (IQ), assessed with Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV; Wechsler, 2012), was below 80, and (c) they were undergoing other ongoing interventions (pharmacological and/or psychosocial). Psychologists assessed every patient for the eligibility and exclusion criteria of this study. We asked children who received ADHD + ODD diagnosis from October 4, 2018 to November 30, 2018 to participate in the study. Parents and children signed an informed consent, and then they were enrolled in the study and were randomized to the mindfulness intervention or to a wait-list control group. The first author allocated participants using a computer-generated list of random numbers. The random allocation had an allocation ratio of 1:1. Then, all participants filled in the pretest (T1) and children from the mindfulness condition started the treatment they were assigned to. Participants in the control condition did not receive any kind of active treatment during this 8-week-long period. After that, participants in the wait-list condition could get enrolled in an intervention. See Figure 1 for a flowchart of

recruitment and study procedures. This study was approved by the Ethics Review Board "Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana" (No. 177/2017). The study is registered on ClinicalTrials.gov (No. NCT03698240).

Participants

Participants ($n = 50$) were male children between 8 and 12 years of age with ADHD and ODD, and their parents ($n = 73$; 20 couples, 30 mothers, and three fathers). Participating in this study was completely voluntary and participants were free to quit the study and/or the treatment at any moment without having to give a reason and without any consequences for further treatment.

The experimental group included 25 male children with diagnoses of both ADHD and ODD, with a mean age of 8.75 years ($SD = 0.71$). Mean IQ was 100.29 ($SD = 8.87$), whereas baseline externalizing problems score, assessed with the *T* scores of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001; Hudziak et al., 2004), was 65.55 ($SD = 1.43$). The wait-list control group also included 25 male children with diagnoses of both ADHD and ODD. Their mean age was 9.05 years ($SD = 1.05$). Mean IQ was 97.73 ($SD = 8.29$) and baseline externalizing problems score was 66.15 ($SD = 1.13$). All participants were Caucasian. Parent-reported approximate family yearly incomes ranged from less than €15,000 to more than €40,000, with a cluster (75.0%) between €20,000 and €30,000, which aligns with the Italian mean household income. All the participants, except two children and their parents, completed the study. These children dropped out due to economic reasons.

Table 1. Mindfulness Training for Children.

Session	Theme	Goal
1	The "Secret Garden"	• Introduce mindfulness • Establish general rules • Mindful listening
2	Explore mind and body	• Introduce the beginner's mind concept • Awareness in daily life • Mindful eating • Breathing meditation
3	The wandering mind	• Introduce the mind wandering concept • Recognize unkind thoughts • Body scan meditation
4	Emotions and feelings	• Promote emotional learning • Experience the importance of accepting feelings • Body scan meditation
5	The negative feelings	• Exploration of stressful events • Experience the nonjudgmental observation • Body scan meditation • Yoga
6	The minute before the action	• Introduce the STOP model to solve problems • Body scan meditation • Yoga
7	Practice of loving kindness	• Mindfulness as support in communication • Mindful eating • Yoga
8	Conclusion of the course	• Loving kindness to myself • Consolidate learning

Source. Adapted from Montano and Villani (2016).
Note. STOP = Stop, Think, Options, Plan.

Intervention

Mindfulness trainers were qualified by the Center for Mindfulness in Medicine, Health Care, and Society, Medical School, University of Massachusetts. The mindfulness training for children was conducted in groups of five boys and consisted of nine weekly (eight treatment sessions + one introductive session) 1.5-hr-long sessions. For the children's training, the "Fiore Dentro" protocol was used (Montano & Villani, 2016). It is an adaptation of the mindfulness-based stress reduction (MBSR) protocol (Kabat-Zinn, 2003). Children learned to focus and enhance their attention, awareness, and self-control by doing mindfulness exercises during training and home practice.

Each session shared a common structure: (a) opening meditations; (b) homework revision; (c) brainstorming and sharing of experiences; (d) formal meditation; (e) readings, fables, and nursery rhymes related to the main objective of the session; (f) closing meditation; and (g) homework assignment. Exercises included sitting and walking meditation, mindful eating, hatha yoga, and body scan. Children were asked to focus on meditation practices only for a few minutes at a time: This ensured that children would consider meditation as a feasible and not too hard activity, enhancing their motivation and compliance (see Table 1 for a detailed description of the intervention for children). At the same time, parents attended a parallel mindfulness intervention delivered in group setting. Generally, they learned to be more present in the here and now with their children without judgment, to take care of themselves, and to respond instead of reacting to their children's negative behaviors. This intervention highlighted the importance for parents to practice meditation every day, to improve their mindful attitude, and to be a better model for their children. Meditations included sitting and walking meditation, mindful eating, body scan, and yoga exercises (see Table 2 for a detailed description of the intervention for parents).

Table 2. Mindfulness Training for Parents (Developed by P.M., C.C., and S.V.).

Session	Theme	Goal
1	Stress of being a parent	• The automatic parenting • Body scan meditation
2	The beginner's mind	• Expectations and interpretations • Sitting meditation
3	Reconnection to the body	• Attention to the sensations of the body • Awareness of pleasant events • Seated yoga
4	Respond to children mindfully	• Stressful events and acceptance • Standing yoga • Introduce 3-min breathing as coping
5	Parenting patterns	• Introduce the concept of parental schema • Walking meditation
6	Conflicts and parenting	• Apply mindfulness to parental difficulties
7	Self-compassion	• Loving kindness • Self-compassion • Organize a family mindful day
8	Mindful parenting	• Body scan meditation • Care plan of children and self • Consolidate learning

Outcome Measures

Modified Overt Aggression Scale. Modified Overt Aggression Scale (MOAS; Kay et al., 1988) is a clinician-administered scale that measures four types of overt aggression over the past week: verbal aggression, physical aggression against property, auto-aggression, and physical aggression against other people. It was used to evaluate the changes in children's aggressive behaviors in the home context. MOAS raters were not aware of the treatment condition of the child. The MOAS uses a Likert-type scale from 0 to 3. The mean Cronbach's alpha for each assessment point was .83.

Strengths and Difficulties Questionnaire. In this study, we used the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) teacher report to evaluate children's hyperactive behaviors and conduct problems in the school context. Teachers were not aware of the treatment's aims and activities, and thus we thought they could provide us with a more objective evaluation of children's behavior. The Italian validated version of the SDQ (Tobia et al., 2011) is a 25-item questionnaire that assesses behaviors in children ages 4 to 16. The SDQ uses a Likert-type scale from 0 to 2. For each of the two scales, the score can range from 0 to 10. In the current sample, the SDQ reliability was generally satisfactory, as demonstrated by the mean internal consistency of subscales (mean Cronbach's alpha for each assessment point): .83 for conduct problems and .86 for hyperactivity.

Bells Test—Revised. The Bells Test—Revised (Biancardi & Stoppa, 1997) is an objective measure to evaluate sustained attention in children. Speed and Accuracy in selecting the target stimuli (bells) were assessed. The Speed score refers to the number of bells found by the child in the first 30 s of the task, whereas the Accuracy score refers to the total number of bells found during the whole task (120 s).

Matching Familiar Figures test from Italian Battery for ADHD. The Matching Familiar Figures (MF-20) test from Italian Battery for ADHD (Marzocchi et al., 2010) measures objectively the children's impulsiveness. In the MF-20 test, participants were shown a figure and were asked to find the matching one among six choices. The MF-20 test includes 20 items. It is an objective measure of children's impulsivity.

Child and Adolescent Mindfulness Measure. Children completed the Child and Adolescent Mindfulness Measure (CAMM; Greco et al., 2011), a questionnaire that assesses present-moment awareness and nonjudgmental, nonavoidant responses to thoughts and feelings in youths (i.e., "I keep myself busy so I don't notice my thoughts or feelings"), and the 10 items are rated on a five-point scale. The CAMM has been shown to be reliable ($\alpha = .81$) in the current sample.

Avoidance and Fusion Questionnaire for Youth. We used the Italian version of the Avoidance and Fusion Questionnaire for Youth (AFQ-Y; Schweiger et al., 2017) proposed by Greco et al. (2008) to assess psychological inflexibility as intended by the Acceptance and Commitment Therapy theoretical framework (i.e., "The bad things I think about myself must be true"). It is a 17-item child-report questionnaire. The AFQ-Y uses a five-point Likert-type scale. The AFQ has been shown to be reliable ($\alpha = .84$) in the current sample.

Statistical Analyses

We used a multilevel (mixed-model) analysis, as data collected at different measurement occasions (T1, T2) form a hierarchical structure of measurements nested within persons. Experimental effects are indicated by significant parameters for group-by-time interactions and effect sizes. For each group, 25 participants were included in the analysis. We tested the hypotheses in SPSS 25 with linear mixed-effects models (MIXED) with full information maximum likelihood (ML) estimation (West, 2009). The main intervention effect was tested across the whole sample and the

Table 3. Statistics for the Children's Variables.

Variable	Experimental group ($N = 25$) T1 M (SD)	Experimental group ($N = 25$) T2 M (SD)	Wait-list control group ($N = 25$) T1 M (SD)	Wait-list control group ($N = 25$) T2 M (SD)	Group by time B (SE)	p
Age	8.75 (0.71)	—	9.05 (1.05)	—	—	—
IQ	100.29 (8.87)	—	97.73 (8.29)	—	—	—
CBCL Ext.	65.55 (1.43)	—	66.15 (1.13)	—	—	—
MOAS	12.25 (1.65)	10.25 (1.85)	12.45 (1.55)	10.85 (1.90)	0.200 (0.048)	.222
SDQ–Conduct	2.85 (1.66)	2.55 (1.46)	3.05 (1.09)	2.30 (2.07)	−0.824 (0.620)	.192
SDQ–Hyperactivity	6.20 (2.60)	4.16 (2.50)	6.25 (1.88)	6.25 (1.83)	**2.05 (0.442)**	**.000**
Bells Test–Speed	−0.15 (1.53)	0.41 (1.14)	−0.02 (0.99)	0.34 (1.20)	−0.288 (0.238)	.233
Bells Test–Accuracy	−0.35 (1.10)	0.56 (0.56)	−0.30 (0.89)	−0.28 (1.00)	**−0.933 (0.283)**	**.002**
MF-20–Speed	0.36 (1.49)	−0.06 (1.26)	0.83 (1.53)	0.37 (1.22)	0.438 (0.285)	.134
MF-20–Accuracy	1.05 (1.50)	0.64 (1.29)	0.57 (1.30)	−0.28 (1.00)	0.169 (0.330)	.612
CAMM	25.52 (6.50)	26.00 (8.38)	24.65 (7.30)	24.70 (6.70)	−0.045 (2.28)	.984
AFQ	27.21 (13.80)	19.5 (10.08)	25.70 (11.04)	27.20 (12.50)	**8.86 (3.20)**	**.009**

Note. Statistically significant results ($p < .05$) from the deviance tests for the fixed effects and from the Wald tests for the random effects are in boldface. IQ = Intelligence Quotient; CBCL Ext. = Child Behavior Checklist–Externalizing Domain; MOAS = Modified Overt Aggression Scale; SDQ = Strengths and Difficulties Questionnaire; MF-20 = Matching Familiar Figures; CAMM = Child and Adolescent Mindfulness Measure; AFQ = Avoidance and Fusion Questionnaire for Youth.

slope within each sample was then calculated together with effect size estimates. Cohen's (1988) effect size of the pre–post change in the treatment group and in the control group was calculated as standardized effect size in a mixed/multilevel model, where standard deviations were derived from the standard errors of the estimated marginal means (Hedges & Hedberg, 2007). The data supporting the results presented in this article can be requested from the corresponding author.

Results

There were no differences between the intervention and wait-list control groups in the measures at the baseline assessment. The rate of attendance to the intervention was 85% of the sessions for both child and parent groups. Table 3 describes the trend of the variables in the two groups across time and reports the group-by-time interactions for all variables. In relation to the experimental group, significant interactions of group by time were found for AFQ scores, SDQ–Hyperactivity, and the Accuracy scores of the Bells Test. As detailed by the descriptive statistics in Table 3, scores in SDQ–Hyperactivity and AFQ decreased across time only in the experimental group. At the same time, the accuracy scores of the Bells Test increased across time in the experimental group, whereas accuracy scores remain unchanged in the control group. No intervention effects were found for MOAS scores, SDQ–conduct problems, CAMM scores, and performances in the MF-20 test.

Table 4 presents the intervention effect sizes in the two groups. The higher effect sizes for the experimental group were for Bells Test–Accuracy scores and it was 0.77; the effect sizes for the SDQ–Hyperactivity subscale and AFQ scores were, respectively, 0.59 and 0.43. These effect sizes were much higher than those in the control group, which ranged from 0.00 to 0.09 for the same measures. The higher effect size for the control group was for SDQ–conduct problems scores.

Table 4. Effect Size Estimates.

Variable	Experimental group	Wait-list control group
AFQ	0.43	0.09
SDQ–Hyperactivity	0.59	0.00
Bells Test–Accuracy	0.77	0.04
MOAS	0.10	0.09
SDQ–Conduct	0.10	0.12
Bells Test–Speed	0.11	0.11
MF-20–Speed	0.08	0.08
MF-20–Accuracy	0.04	0.04
CAMM	0.02	0.00

Note. AFQ = Avoidance and Fusion Questionnaire for Youth; SDQ = Strengths and Difficulties Questionnaire, teacher report. MOAS = Modified Overt Aggression Scale; MF-20 = Matching Familiar Figures; CAMM = Child and Adolescent Mindfulness Measure.

Discussion

Recently, mindfulness interventions have been widely applied to promote mental health and well-being in children and adolescents (Dunning et al., 2019). One of their main fields of application is the treatment of ADHD (Evans et al., 2018). Even though ADHD and ODD frequently co-occur,

there are no studies investigating the efficacy of mindfulness-based interventions with clinical samples of children with both ADHD and ODD. This study sought to explore the efficacy of a mindfulness-based intervention for children with both ADHD and ODD diagnoses. The current findings were promising: Hyperactive behaviors, assessed with the SDQ teacher report, decreased in children from the experimental group, compared with those in the wait-list group. We also evaluated children's attentional skills with a set of objective measures. Results showed a significant improvement in their visual sustained attention, as indicated by the Bells Test–Accuracy scores. Meditation and mindfulness-based activities could help children to be more focused on moment-by-moment experiences and to intentionally direct their attention to what they are doing in the present. This may help them maintain their commitment during prolonged activities, leading to better performances in tasks evaluating sustained attention (see also Felver et al., 2017).

Importantly, we did not find effects of the intervention on children's aggressive behaviors. Although our study indicated that a mindfulness intervention model could be suitable for children with ADHD and ODD diagnosis, it did not promote a reduction in aggressive behaviors, evaluated in both home (MOAS) and school contexts (SDQ). Probably, improving mindfulness skills is not sufficient to obtain a significant reduction in children's aggressive behavioral problems. Future mindfulness protocols could integrate specific activities to target also specific risk factors for aggressive behavioral problems (Huguet et al., 2019).

Finally, children from the experimental group showed an improvement in psychological inflexibility as suggested by the AFQ-Y scores. Children learned to see thoughts for what they are, that is, just thoughts: They are not the ultimate truth, and as they come up to their minds they go away. In this way, negative feelings and thoughts may become less scary and easier to accept for children. Anyway, further studies are needed to evaluate whether all these effects are maintained across time. It is noteworthy that all the abovementioned changes were not found in the wait-list control group, and thus they cannot be attributed just to the effect of time or assessment procedures.

Results appeared promising, though it is important to interpret them in light of the limitations of this work. First, the small sample size appears an important limitation, even if it is similar to that of most previous studies (see, for example, Biegel et al., 2009; Felver et al., 2017; Schonert-Reichl et al., 2015; Tan & Martin, 2015). We also did not include an evaluation of children's characteristics, such as callous–unemotional traits, which are usually considered a predictor of weaker treatment response (Pisano et al., 2017). A significant limitation in this research is the lack of an active control group, and thus the results from the mindfulness condition could be due to nonspecific aspects of the treatment. Finally, this sample was restricted to males and therefore does not inform how this treatment might impact females.

ADHD and ODD commonly co-occur in clinical practice. Even though medication and psychosocial treatments have good effects in children with ADHD and ODD (Masi et al., 2017; Muratori et al., 2019), mindfulness interventions could be promising alternatives for children who do not adequately respond to these interventions or for those whose parents do not provide their consent for pharmacological intervention. Moreover, the group format helps create a unique sharing and learning environment: All the participants have the opportunity to engage with people with similar issues, to share feelings and thoughts, and to practice the strategies learned during the sessions in a realistic manner, but in a safe context. Besides, brief group interventions like the one tested in this work meet the needs of outpatient clinics that have to take care of several patients on a daily basis and can benefit from the implementation of economical and efficient treatments. More generally, because attention regulation is critical to healthy psychosocial development and childhood represents the time frame during which these processes are susceptible to change, these findings suggest that mindfulness interventions can be considered effective for supporting the development of attention regulation in children. Future studies will investigate the generalizability of these preliminary findings in different settings and populations.

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Ethical Approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent

Parents signed the informed consent for their own and their child's participation. Children were also requested to sign their own informed consent.

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"Nella mia mente": la salute mentale dei bambini e dei giovani

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"La salute mentale è una parte della salute fisica, non possiamo permetterci di continuare a vederla in altro modo. Per troppo tempo abbiamo visto poca comprensione e troppo pochi investimenti in un aspetto essenziale per massimizzare il potenziale di ogni bambino e adolescente. Tutto questo deve cambiare".

Lo studio condotto dalla Società Italiana di Pediatria sugli accessi nei Pronto Soccorso per problemi neuropsichiatrici nella fase pre-pandemica e in quella pandemica, riportato sul News Box (pag. 561)[1], conferma quello che in qualche modo è noto e che è oggetto di attenzione e di grida di allarme da diversi mesi[2] anche nel panorama italiano[3]. Abbiamo avuto modo di parlarne recentemente anche sulle pagine di *Medico e Bambino*[4]. È di questi giorni la pubblicazione del rapporto dell'UNICEF sulla condizione dell'infanzia nel mondo nel 2021[5]. Si pone l'obiettivo di promuovere, tutelare e sostenere la salute mentale dei bambini e dei giovani. Nella premessa del Rapporto si riporta che la pandemia Covid-19 ha sconvolto il mondo, innescando una crisi globale senza precedenti, e suscitando una serie di preoccupazioni sulla salute mentale dei bambini, dei giovani e delle loro famiglie. La pandemia può offrire anche opportunità per ricostruire una realtà migliore. Rappresenta un'occasione unica per impegnarsi, comunicare e agire per promuovere, tutelare e supportare la salute mentale di un'intera generazione.

Che cos'è la salute mentale

Non è un disturbo e nemmeno l'assenza di disturbi. È uno stato di salute. È descritta come "uno stato dinamico di equilibrio interiore" che comporta la capacità di utilizzare le abilità sociali, emotive e cognitive fondamentali per destreggiarsi nella vita e nel mondo in modo efficace. Secondo altre definizioni la salute mentale è correlata alla capacità di "godersi la vita e affrontare le sfide che ci pone". In generale, la maggior parte delle definizioni fa riferimento alle capacità emotive, cognitive, funzionali, sociali, fisiche e spirituali. Spesso la salute mentale è legata al benessere, un concetto più ampio che coinvolge la salute, il reddito, la nutrizione e il benessere psicologico. I disturbi mentali possono esistere su un *continuum*, che comprende disturbi di diversa entità, dal disagio lieve e temporaneo a disturbi gestibili, che possono diventare cronici o meno, a disturbi psichici progressivi e gravi[5].

Per i bambini e i giovani, in particolare, comprendere la salute mentale può significare riconoscere che il concetto stesso di salute è interconnesso con i valori trasmessi dalla società e dalla famiglia, le norme culturali, le aspettative sociali e le capacità di svi-

luppo. Ad esempio, le percezioni legate ai comportamenti consentiti e a un funzionamento sociale appropriato sono diverse e dipendono dalla situazione, dall'età e dalla cultura.

I dati sulla salute mentale nei giovani

Secondo le ultime stime disponibili, contenute nel nuovo rapporto UNICEF più di 1 adolescente su 7 tra i 10 e i 19 anni convive con un disturbo mentale diagnosticato; tra questi, 89 milioni sono ragazzi e 77 milioni sono ragazze. 86 milioni hanno fra i 15 e i 19 anni e 80 milioni hanno tra i 10 e i 14 anni. In corso di pandemia l'interruzione della *routine*, dell'istruzione, delle attività ricreative, così come la preoccupazione per il reddito familiare e la salute, rende molti giovani spaventati, arrabbiati e preoccupati per il loro futuro. L'ansia e la depressione rappresentano il 40% dei disturbi mentali diagnosticati. I tassi in percentuale di problemi diagnosticati sono più alti in Medio Oriente e Nord Africa, in Nord America e in Europa Occidentale[5].

Globalmente, quasi 46.000 adolescenti muoiono a causa di suicidio ogni anno - più di uno ogni 11 minuti - una fra le prime cinque cause di morte per la loro fascia d'età. Per le ragazze fra i 15-19 anni è la terza causa di morte più comune, mentre per i ragazzi nella stessa fascia di età è la quarta più comune. In Europa Occidentale diventa la seconda causa di morte fra gli adolescenti fra i 15 e i 19 anni, con 4 casi su 100.000, dopo gli incidenti stradali.

Anche prima del Covid-19, bambini e giovani portavano il peso delle problematiche relative alla salute mentale senza che ci fossero investimenti significativi volti ad affrontarle. E in questo momento le future generazioni potrebbero risentire per molti anni a venire dell'impatto della pandemia sul loro benessere, con ampi divari tra i bisogni presenti e i finanziamenti dedicati (alla salute mentale viene destinato circa il 2% dei fondi governativi per la salute).

"Sono stati 18 lunghi mesi per tutti noi, specialmente per i bambini. Con i *lockdown* a livello nazionale e le restrizioni legate alla pandemia, i bambini hanno trascorso anni indelebili della loro vita lontano dagli amici, dalle aule, dal gioco - elementi chiave dell'infanzia stessa", ha dichiarato il Direttore generale dell'UNICEF Henrietta Fore. "L'impatto è significativo, ed è solo la punta dell'*iceberg*. Anche prima della pandemia, troppi bambini erano gravati dal peso di problemi non affrontati di salute mentale. I governi stanno investendo troppo poco per affrontare questi bisogni fondamentali. Non viene data abbastanza importanza alla relazione tra la salute mentale e le conseguenze future sulla vita"[5].

Sebbene l'impatto sulla vita dei bambini sia incalcolabile, un'analisi della *London School of Economics* presente nel rapporto indica che il mancato contributo alle economie a causa dei problemi di salute mentale che portano a disabilità o morte tra i giovani è stimato, globalmente, in quasi 390 miliardi di dollari all'anno.

Fattori protettivi e barriere

Dal rapporto emerge che fin dai primissimi periodi della vita opera un *mix* di genetica, esperienze e fattori ambientali, tra cui giocano un ruolo fondamentale i genitori, la scolarizzazione, la qualità delle relazioni, l'esposizione alla violenza o ad abusi, la discriminazione, la povertà, le crisi umanitarie e le emergenze sanitarie come il Covid-19, influenzando la salute mentale dei bambini per tutta la loro vita. Il diritto alla salute mentale va tutelato; è uno stato positivo di benessere e un investimento indispensabile per i bambini e il mondo. Eppure, troppo spesso, viene considerata come un aspetto secondario dai responsabili decisionali, i *leader* politici e le famiglie e spesso non viene considerata affatto. Di conseguenza milioni di bambini e giovani lottano in silenzio, ostacolati da stigma e incomprensione.

Le raccomandazioni dell'UNICEF

Il rapporto invita i governi e i *partner* del settore pubblico e privato a impegnarsi, comunicare e agire per promuovere la salute mentale di tutti i bambini, adolescenti e persone che se ne prendono cura, proteggere chi ha bisogno di aiuto e assistere i più vulnerabili, tra cui:

- investimenti urgenti nella salute mentale dei bambini e degli adolescenti in tutti i settori, non solo in quello sanitario, per sostenere un approccio alla prevenzione, alla promozione e alle cure che coinvolga tutta la società;
- integrare e aumentare gli interventi basati su evidenze nei settori della salute, dell'istruzione e della protezione sociale - compresi programmi per i genitori - che promuovano un'assistenza attenta e amorevole e sostengano la salute mentale di genitori e persone che si prendono cura dei bambini; e garantire che le scuole supportino la salute mentale attraverso servizi di qualità e relazioni positive.
- Rompere il silenzio che circonda le problematiche di salute mentale, affrontando la stigmatizzazione, promuovendo una migliore comprensione e prendendo sul serio le esperienze dei bambini e dei giovani.

"La salute mentale è una parte della salute fisica - non possiamo permetterci di continuare a vederla in altro modo", ha dichiarato Fore. "Per troppo tempo, sia nei Paesi ricchi che in quelli poveri, abbiamo visto troppo poca comprensione e troppo pochi investimenti in un aspetto essenziale per massimizzare il potenziale di ogni bambino. Tutto questo deve cambiare".

L'appello dell'AAP, AACAP e CHA

È di questi giorni l'appello dell'*American Academy of Pediatrics* (AAP), dell'*American Academy of Child and Adolescent Psychiatry* (AACAP) e della *Children's Hospital Association* (CHA) che si sono unite per dichiarare uno stato di emergenza nazionale sulla salute mentale dei bambini[6]. "Le sfide che affrontano i bambini e gli adolescenti sono così diffuse che richiamano i responsabili delle politiche di governo e tutti quelli che si occupano a diverso titolo dei bambini e adolescenti a unirsi a noi in questa Dichiarazione". La dichiarazione/appello si articola in diversi punti che sono simili in gran parte a quelli riportati dall'UNICEF, con alcuni aspetti programmatici che sono declinati in modo ulteriormente pragmatico e che sono riportati nel *Box*.

Box - ALCUNI PUNTI DELL'APPELLO DELL'AAP, AACAP E CHA

Si invocano e si richiamano:

a. finanziamenti dedicati a garantire che tutte le famiglie, bambini e adolescenti possano accedere a screening della salute mentale basati sull'evidenza, con particolare attenzione rivolta alle famiglie con difficoltà socio-economiche;

b. l'importanza di piani di azione globali che superino le difficoltà normative e potenzino l'accesso alle tecnologie per un'assistenza che utilizzi (anche) la telemedicina (*vedi* pag. 583)[7];

c. l'attuazione e il finanziamento sostenibile di modelli efficaci di assistenza sanitaria sulla salute mentale basati sulla scuola, comprese, in caso di problemi, strategie e modelli clinici in grado di garantire l'accesso alle cure;

d. l'adozione di modelli efficaci e finanziariamente sostenibili di assistenza sanitaria mentale integrata nell'ambito delle cure primarie;

e. il potenziamento delle struttura di prima accoglienza per le situazioni critiche, in forte integrazione con i servizi territoriali per una successiva e rapida presa in carico.

Lo stato delle cose in Italia

I reparti di Pediatria (e i pochi esistenti di neuropsichiatria) sono pieni di ragazzi che presentano una o più delle condizioni che sono state elencate. I servizi di NPI non riescono a rispondere alle domande di visite e di presa in carico. Di prevenzione ne sentiamo parlare poco soprattutto o anche in ambito scolastico (sportelli di ascolto, presenza di psicologi/infermieri/ educatori dedicati in ogni presidio). È arrivato il tempo per - come si scrive da più parti - far emergere la volontà e la capacità di organizzare piani di lavoro che abbiano alcuni requisiti: programmazione di mirati interventi sul breve e lungo periodo; ruoli e competenze differenziate e professionalmente capaci; investimenti per specifici obiettivi da raggiungere per soluzioni corrispondenti ai bisogni; integrazione e formazione qualificata sul campo (non solo teorica).

Se non ora, quando?

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IL BOOM DI ACCESSI PER DISTURBI NEUROPSICHIATRICI NEI PRONTO SOCCORSO

I risultati di un'indagine condotta dalla Società Italiana di Pediatria in 9 Regioni italiane restituiscono la fotografia di cosa è successo (e di cosa sta succedendo) durante la pandemia.

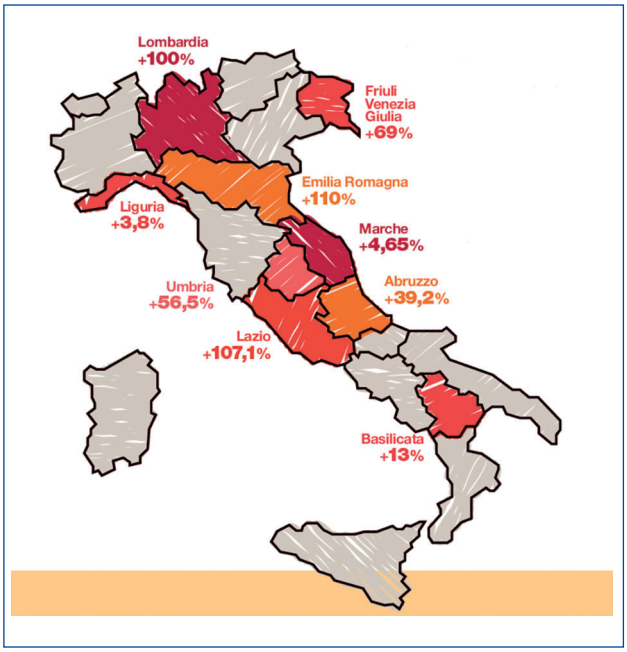
I primi due casi italiani di Covid-19 sono stati confermati il 30 gennaio 2020, quando due turisti provenienti dalla Cina sono risultati positivi al virus SARS-CoV-2 a Roma. Dal 23 febbraio, dopo la scoperta di alcuni focolai, vengono posti in quarantena dieci Comuni nel Nord Italia e, in alcune Regioni, chiuse momentaneamente scuole e università.
Tra l'8 e il 9 marzo la quarantena viene estesa a 26 Province italiane. Dal 5 marzo viene sospesa in tutto il territorio nazionale la didattica in presenza per le scuole di ogni grado e le Università. Con un nuovo DPCM il 9 marzo vengono quindi estesi a tutta Italia il divieto di spostamento per motivi non necessari, la sospensione delle attività sportive, di manifestazioni ed eventi, la chiusura di musei, luoghi di cultura e Centri sportivi.
Ulteriori misure restrittive entrano in vigore con il «Decreto IoRestoaCasa», pubblicato l'11 marzo, che prevede la sospensione delle comuni attività commerciali al dettaglio, dei servizi di ristorazione, delle celebrazioni religiose, e vieta gli assembramenti di persone in luoghi pubblici o aperti al pubblico.
Il 22 marzo una nuova ordinanza, adottata congiuntamente dal ministro della Salute e dal Ministro dell'Interno, vieta a tutte le persone fisiche di spostarsi in qualsiasi Comune diverso da quello in cui si trovano, e viene pubblicata una lista di altre attività non ritenute necessarie, che devono essere sospese. Tutte queste misure vengono più volte prorogate, fino a inizio maggio, allorché le misure restrittive si allentano, consentendo lo spostamento tra Regioni e l'apertura tra l'altro di luoghi di ritrovo per i giovani, quali le sale da ballo e discoteche. Tuttavia, con l'aumento dei contagi, si assiste tra l'altro alla successiva chiusura dei luoghi di ritrovo dei giovani, coprifuoco notturno e didattica a distanza per le superiori, nonché misure restrittive per gli spostamenti. A livello mondiale e nazionale vi è un aggiornamento costante, quotidiano, dei casi di infezione e morti da virus SARS-CoV-2.
Ma c'è un'altra pandemia, inaspettata, subdola che negli ultimi mesi sta colpendo i nostri ragazzi. E di questa pandemia non abbiamo un bollettino giornaliero, ma i numeri che la Società Italiana di Pediatria (SIP) ha raccolto ed esaminato parlano chiari. Non ci troviamo cioè solo a fronteggiare la classica malattia SARS-CoV-2-correlata, con febbre, tosse e insufficienza respiratoria. Subdolamente si è diffusa tra giovani e giovanissimi una patologia della mente, che, per comodità di classificazione, si può genericamente definire patologia neuropsichiatrica (NPI). Restrizioni, incertezza, *lockdown* hanno contribuito negli ultimi mesi a un incremento di ansia, depressione, ideazione suicidaria, disturbi della condotta alimentare. E la richiesta di aiuto ai nostri Pronto Soccorso si fa sempre più insistente.

E se quindi da un lato il numero di accessi ai Pronto Soccorso italiani è calato rispetto all'epoca pre-Covid, per la paura dei contagi e per il diverso contesto epidemiologico che si è creato, quello per patologia neuropsichiatrica è stato in controtendenza. È questa la fotografia che del resto ci viene restituita da un'analisi della SIP, condotta lungo lo stivale.
Le 9 sezioni regionali che hanno analizzato l'andamento epidemiologico in uno o più Centri ospedalieri confermano un incremento di +84% di accesso ai Pronto Soccorso italiani per patologia NPI nel periodo marzo 2020 - marzo 2021 rispetto al periodo pre-Covid (marzo 2019 - marzo 2020). Le Regioni in cui si è documentato un maggiore incremento di accessi per patologie NPI sono Emilia-Romagna (+110%), Lazio (+107,1%) e Lombardia (+100%). Nel dettaglio, le patologie per le quali si è osservato un maggiore incremento percentuale degli accessi sono state ideazione suicidaria (+147%), depressione (+115%) e disturbi della condotta alimentare (+78,4%). Psicosi e disturbi del comportamento alimentare hanno costituito nel campione osservato le prime due cause di accesso in Pronto Soccorso per patologia NPI (rispettivamente 375 accessi su 2242 pari al 16,7% e 358 accessi pari al 15,9%). In particolare il maggior incremento di accessi per ideazione suicidaria si è osservato in Lazio (+56%) e Friuli-Venezia Giulia (+204,8%); il maggior incremento per disturbi della condotta alimentare in Lombardia (+174,3). I casi di depressione sono stati segnalati soprattutto in Lazio (+63,4%). Ma non solo. Posti letto occupati al massimo della loro capienza per settimane e netto innalzarsi delle richieste di aiuto, ovvero un sensibile incremento delle ospedalizzazioni, che hanno sfiorato il 40%. Anche in questo caso la principale causa è l'ideazione suicidaria (+134%) seguita da depressione (+41,4%) e disturbi della condotta alimentare (+31,4%).
Questi dati ci restituiscono cioè la fotografia di una patologia in costante aumento tra i nostri ragazzi, sempre più di difficile gestione sul territorio e che richiede pertanto un attento monitoraggio e un rapido intervento capillare da parte delle Istituzioni.

Metodologia dello studio

- Uno o più Centri di riferimento per ciascuna delle Sezioni SIP regionali.
- Ricercare retrospettivamente i codici di dimissione dal PS/DEA o, in caso di ricovero dal reparto, compatibili con disturbi mentali, in particolare disturbi psicotici (codifica 291-299), disturbi nevrotici e altri non psicotici (codifica 300-314), ideazione suicidaria (codifica v 62.84) quale diagnosi principale. Totale codici esaminati: 310.
- Periodo di riferimento: 1 marzo 2019-1 marzo 2021, da suddividere in 2 sotto periodi (1° marzo 2019 - 1° marzo 2020 e 2 marzo 2020 - 2 marzo 2021, rispettivamente denominati periodo pre-Covid e Covid).

news box



GRUPPO DI LAVORO DELLA SOCIETÀ ITALIANA DI PEDIATRIA

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Aspetti positivi e limiti della telemedicina: esperienze di lavoro in Neuropsichiatria infantile in tempo di Covid-19

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La telemedicina oggi è uno dei temi di maggiore interesse in ambito sanitario. Il Covid19 ne è stato l'acceleratore. La possibilità di poter (in parte) seguire i pazienti tramite un pc o uno smartphone potrebbe rivoluzionare alcuni paradigmi dell'assistenza. L'articolo riporta un'esperienza concreta nell'ambito della Neuropsichiatria infantile che è forse quella con i maggiori sviluppi applicativi. Ma non mancano alcuni dubbi e limiti (andando oltre quelli strettamente burocratici-amministrativi) su cui è necessario in concreto riflettere.

L'attuale pandemia causata da Covid-19 non solo rappresenta una grande minaccia per la salute fisica della popolazione, ma comporta anche conseguenze dannose per la salute mentale a breve e lungo termine. Il distanziamento sociale, sebbene sia un intervento cruciale per rallentare gli effetti distruttivi della pandemia, può portare a isolamento, solitudine, inattività, minore accesso ai servizi di base e scarso supporto sociale. Tali fattori di rischio, insieme a imprevedibilità e incertezza, potrebbero aggravare la condizione delle persone con malattie mentali preesistenti e quelle più vulnerabili[1]. Inoltre, il flusso di notizie quotidiano e negativo sulla situazione del Covid-19 alimenta preoccupazioni e angosce[2]. Le prime indagini trasversali negli Stati Uniti, in Canada e in Europa mostrano, infatti, un aumento dei sintomi di depressione, ansia (16-28%) e stress (8%) per la popolazione generale, associati alle preoccupazioni per il Covid-19[3-5]. In aggiunta, il rallentamento dell'economia porterà a disoccupazione, insicurezza e povertà, che ostacoleranno l'accesso ai servizi sanitari, influendo sulla qualità della vita[6].

Alcuni studi mostrano inoltre che l'essere posti in quarantena può contribuire a percepire stress e alti livelli di rabbia[7] e ad aumentare i comportamenti a rischio come il gioco d'azzardo *online* e l'abuso di alcol[8]. In precedenti pandemie, ad esempio i bambini in quarantena erano più soggetti a sviluppare disturbi da stress acuti, disturbi dell'adattamento ed essere vittime di violenza domestica rispetto a quelli che non erano stati in quarantena[9].

Pertanto, questa situazione di crisi sta esacerbando le condizioni di salute mentale esistenti, creando i presupposti per lo sviluppo di nuove patologie. Anche dopo che l'epidemia sarà controllata, ci sarà probabilmente un aumento sostanziale della necessità di supporto psicologico[2].

POSITIVE ASPECTS AND LIMITS OF TELEMEDICINE: WORK EXPERIENCES IN INFANT NEUROPSYCHIATRY DURING COVID-19
(Medico e Bambino 2021;40(9):583-586. doi: 10.53126/MEB40583)

Key words
Covid-19 pandemic, Telemedicine, Telepsychology

Summary
The pandemic situation caused by Covid-19 has led to changes in the clinical practice of hospital services, including Infant Neuropsychiatry. During the lockdown period the services had to use new intervention strategies, particularly telemedicine to meet the needs of children, teenagers and parents. The online therapy is a useful tool during situations of serious crises such as a global pandemic but like any mode of intervention have strengths and limits. Therefore, the article reports the positive and critical aspects of telemedicine and describes some work experiences in the specialist services of Infant Neuropsychiatry at the ASST Santi Paolo e Carlo in Milan.

Come già rimarcato da altri è infatti irrinunciabile (e di fatto costituisce un'urgenza organizzativa-assistenziale) continuare a confrontarsi con la situazione traumatica che inevitabilmente in modo pervasivo lascia delle conseguenze su tutta la popolazione, con un impatto a livello psicologico su bambini, adolescenti e genitori in termini di sintomi somatici, ansia, depressione, disturbi del pensiero, tentativi di suicidio e disturbo post-traumatico da stress[10].

CARATTERISTICHE DEGLI INTERVENTI DI TELEMEDICINA

Per cercare di fornire un supporto e per garantire la continuità delle cure ai pazienti e alle loro famiglie, i servizi di salute mentale hanno dovuto attuare in gran parte interventi di *telemedicina* definita come l'erogazione di servizi sanitari tramite tecnologie di telecomunicazione. Le modalità includono la terapia tramite telefono, videocolloquio, *app* per la salute mentale e programmi forniti *online*[11]. Inoltre, gli interventi di telemedicina possono essere sincroni, ovvero una comunicazione interattiva che avviene in tempo reale (telefonata e videocolloquio) e sono simili agli interventi effettuati di persona, o asincroni, che includono *e-mail*, *app* e programmi *online*. Molti professionisti utilizzavano già interventi asincroni per controllare i progressi dei pazienti, fornire materiali supplementari, effettuare valutazioni online e raccomandare app per la salute mentale. La logica generale degli interventi di telemedicina è cercare di affrontare le problematiche degli interventi standard nell'ambito della salute mentale. Recenti *review*, infatti, indicano una serie di vantaggi associati alla telemedicina basata sul videocolloquio, come ad esempio: aggirare lo stigma relativo a partecipare a servizi in Centri per la salute mentale[12,13]; superare la difficoltà di accesso alle cure per motivi geografici raggiungendo potenzialmente una popolazione più ampia e fornendo cure in aree pericolose o poco servite[14]; ridurre i costi; e alleviare le preoccupazioni relative al tempo e al trasporto[12].

Inoltre, gli interventi di telemedicina riducono il numero di appuntamenti persi e il *drop-out,* aumentando potenzialmente l'adesione al trattamento e l'efficienza dei servizi di salute mentale[15,16]. Infine, i trattamenti effettuati online possono anche essere utilizzati in aggiunta agli interventi standard effettuati di persona[17].

La maggior parte degli studi in tale ambito ha dimostrato che l'efficacia dei videocolloqui online è paragonabile ai colloqui effettuati in presenza per tutti i disturbi, tra cui depressione, disturbo da stress post-traumatico e disturbi d'ansia[18,19].

Rispetto al livello di soddisfazione di psicologi e medici per la telemedicina, la soddisfazione era maggiore per gli interventi con adulti con disturbi più facilmente curabili come i disturbi d'ansia[20,21] rispetto a interventi con persone con disturbi più gravi come il disturbo da stress post-traumatico (PTSD)[22]. Risultati simili sono stati trovati anche per interventi di telemedicina con bambini e adolescenti, che risultano efficaci ma meno utilizzabili in casi di esperienze traumatiche[23].

Oltre ai vantaggi, bisogna però tenere conto anche dei limiti degli interventi di telemedicina. Ad esempio, potrebbe esserci un divario digitale significativo nell'accesso alla tecnologia e all'alfabetizzazione digitale[24]; i soggetti con uno status socioeconomico (SES) basso rispetto alle persone con un SES più elevato potrebbero non avere lo stesso accesso alle tecnologie digitali, su cui i servizi sanitari *online* dipendono fortemente. Inoltre, bisogna considerare che chi ha un basso SES è più vulnerabile per problematiche legate alla salute mentale e la pandemia aumenterà il rischio di disparità[25].

Altre preoccupazioni riguardano una potenziale disumanizzazione del legame terapeutico[26], comunicazioni non verbali ridotte, situazioni di crisi gravi[27], questioni di riservatezza e difficoltà nel pagamento[28], mancanza di *privacy* dei pazienti a casa e la bassa disponibilità dei pazienti a utilizzare la telepsicoterapia[29].

TELEMEDICINA CON BAMBINI, ADOLESCENTI E GENITORI

Nel lavoro in terapia online con i bambini bisogna adottare alcuni accorgimenti. Alcuni Autori[30] suggeriscono di incoraggiare il bambino a partecipare attivamente alla conversazione e a giocare con gli altri membri della famiglia. I bambini possono spostarsi nella stanza o cambiare posizione. Ai *caregiver* può essere chiesto di aiutare a creare uno spazio terapeutico con i giocattoli e cose da condividere. Una sfida significativa è mantenere la concentrazione di un bambino nei colloqui svolti online; avere una conversazione giocosa, flessibile e utilizzare una varietà di giocattoli, oggetti e materiali può essere utile. I bambini più piccoli spesso traggono vantaggio da colloqui brevi di 30 minuti, alternati da momenti di colloquio con i *caregiver*. È importante posizionare la telecamera in modo che l'intera stanza si possa vedere e il bambino sia libero di muoversi e di usare diversi giocattoli, peluche, libri che il *caregiver* ha (idealmente) fornito in anticipo.

Con i bambini in età scolare può essere utile il gioco virtuale dove il terapeuta condivide lo schermo e può utilizzarlo come strumento per migliorare le capacità di nominare e riflettere sulle emozioni. Con gli adolescenti invece la disponibilità a effettuare videocolloqui è più variabile. Un elemento importante è definire uno spazio fisico che il ragazzo utilizzerà, anche se non è sempre facile a causa dei vincoli in casa. Alcuni adolescenti sono preoccupati per la *privacy* che potrebbero non avere con i genitori presenti nella stessa casa, mentre altri sembrano ignari. Una soluzione è di chiedere ai genitori di fare una passeggiata durante il colloquio del figlio, guardare la TV in un'altra stanza, indossare delle cuffie oppure per gli adolescenti di effettuare il colloquio in macchina. Molti ragazzi, specialmente quelli nella prima e metà dell'adolescenza, riferiscono che con la teleterapia "si sentono strani". Un terapeuta può quindi invitare l'adolescente a un periodo di sperimentazione, come ad esempio una telefonata per iniziare,

seguito da sessioni di videocolloqui di durata gradualmente crescente[30].

ESPERIENZE NEI SERVIZI DI NEUROPSICHIATRIA INFANTILE

Di seguito sono riportati gli aspetti positivi e i limiti delle attività svolte da alcuni servizi specialistici dell'ASST Santi Paolo e Carlo di Milano durante la pandemia causata dal Covid-19.

Servizio SAGA

Jessica ha 17 anni ed è la mamma di una bambina di 9 mesi. Quando scatta il lockdown è costretta a rimanere a casa tutta la giornata con la bambina che diventa sempre più irritabile e difficile da gestire, inoltre il compagno è in smart working dalla mattina alla sera e lei, oltre a non ricevere aiuto nella gestione della bambina, deve abituarsi all'idea di avere qualcuno a casa e a non avere più i suoi spazi.

Il Servizio di Accompagnamento alla Genitorialità in Adolescenza (SAGA) è rivolto alle giovani mamme fino ai 21 anni e ai loro *partner* con l'obiettivo di accompagnare i ragazzi durante la gravidanza e nelle prime fasi della crescita del bambino fino al secondo anno di vita. Essendo rivolto ad adolescenti e giovani adulti, gli operatori del servizio sono riusciti a utilizzare la modalità dei videocolloqui, attivati in maniera prevalente durante il *lockdown* e alternati con incontri in presenza nelle fasi successive. L'uso dei colloqui via *Skype* e/o via *WhatsApp* ha permesso al servizio di mantenere con costanza gli incontri con le giovani pazienti, riducendo il numero di appuntamenti saltati e raggiungendo anche le giovani madri che abitano distanti dal servizio, attivando per la prima volta interventi brevi fuori Regione.

Durante la gravidanza, le ragazze sono state accompagnate con videocolloqui psicologici, visione condivisa sullo sviluppo del feto e delle diverse fasi della gravidanza sia da un punto di vista gestazionale sia emotivo e con incontri *online* di rilassamento corporeo.

Nel post-partum, gli operatori hanno seguito i giovani genitori effettuando videocolloqui di supporto psicologico, osservazioni di brevi momenti di interazione libera e di gioco genitore-bambino e osservazioni mirate alla verifica delle specifiche competenze motorie nelle diverse fasi di sviluppo (es. stare seduti, gattonare, camminare).

Inoltre, la possibilità di utilizzare le videochiamate ha reso più agevole organizzare le riunioni di rete all'interno del servizio e con altri servizi, riducendo le tempistiche e aumentando la frequenza degli incontri.

Le difficoltà maggiori, invece, hanno riguardato il monitoraggio ampio dello sviluppo del bambino e della qualità delle interazioni genitori-bambino e del loro legame in via di formazione; oltre all'impossibilità di interagire direttamente con il bambino.

Servizio DSA

Il Centro per la Diagnosi e lo Studio dei Disturbi Specifici dell'Apprendimento si occupa di studio, diagnosi e cura dei disturbi specifici dell'apprendimento (DSA) nei pazienti in età evolutiva (6-18 anni) frequentanti la scuola primaria e la scuola secondaria di primo e secondo grado. Nel periodo del *lockdown*, le restrizioni hanno portato all'impossibilità di effettuare valutazioni in presenza (riprese successivamente quando sono stata allentate le misure restrittive). Gli interventi di telemedicina hanno permesso agli operatori del servizio di effettuare colloqui telefonici con i genitori e incrementare i contatti con le insegnanti delle scuole dei pazienti e con gli altri servizi, migliorando la qualità del lavoro di rete. Inoltre, il servizio ha potuto constatare che grazie alla didattica a distanza e l'accessibilità a strumenti tecnologici sempre più presenti nelle nostre vite, i bambini e i ragazzi con diagnosi di DSA hanno incrementato l'uso di strumenti informatici compensativi con conseguente aumento delle prestazioni scolastiche.

CONCLUSIONI

Il Covid-19 ha avuto un impatto su individui, famiglie, comunità e interi sistemi di assistenza in tutto il mondo e ha portato a un aumento di problematiche relative alla salute mentale di bambini, adolescenti e genitori[31,32]. È quindi necessario non sottovalutare l'impatto della pandemia e attuare interventi di promozione della salute mentale anche per soggetti non considerati a rischio ma che possono aver subito gli effetti della pandemia o le cui conseguenze si vedranno a distanza di tempo[33]. Fondamentale diventa il coinvolgimento di tutte le figure di professionisti sanitari quali pediatri, medici di base, psicologici e neuropsichiatri infantili[10].

Con la pandemia c'è stato anche un avanzamento dello sviluppo della tecnologia per la cura della salute mentale. A tale proposito, utile potrebbe essere la formazione degli operatori della Neuropsichiatria infantile all'uso di nuove modalità di intervento. Da un

SINTESI DEGLI ASPETTI POSITIVI E NEGATIVI DELLA TELEMEDICINA

Aspetti positivi	Aspetti negativi
• Aggirare lo stigma relativo a partecipare a servizi in Centri per la salute mentale	• Divario digitale
• Superare la difficoltà di accesso alle cure per motivi geografici raggiungendo potenzialmente una popolazione più ampia	• Potenziale disumanizzazione del legame terapeutico
• Ridurre il drop-out	• Situazioni di crisi gravi (inclusa la tendenza al suicidio)
• Alleviare le preoccupazioni relative al tempo e al trasporto	• Comunicazioni non verbali ridotte
• Efficacia dei videocolloqui paragonabile ai colloqui in presenza	• Mancanza di esperienza da parte dei terapeuti per la terapia online
• Ridurre i costi	• Mancanza di privacy dei pazienti a casa
	• Questioni di riservatezza
	• Difficoltà per il pagamento

Tabella I

MESSAGGI CHIAVE

- ❏ La pandemia mondiale causata dal Covid-19 ha portato numerosi cambiamenti nella pratica clinica dei servizi ospedalieri, compreso la Neuropsichiatria Infantile.
- ❏ Nel periodo del *lockdown* i servizi hanno dovuto utilizzare nuove strategie di intervento, in particolare la telemedicina, al fine di fronteggiare i bisogni di bambini, ragazzi e genitori.
- ❏ Il videocolloquio è un utile strumento durante le situazioni di gravi crisi come quelle di pandemia globale, ma come ogni modalità di intervento ha pregi e limiti.

lato gli studi suggeriscono l'efficacia della telemedicina, dall'altro si deve tenere conto non solo degli aspetti positivi ma anche di quelli negativi (sintetizzati nella *Tabella I*). Un'alternativa valida potrebbe essere quindi quella di integrare gli interventi *online* con gli interventi standard effettuati in presenza a seconda della necessità e soprattutto in situazioni di pandemia.

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