NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD AGOSTO 2022

Acta Obstet Gynecol Scand. 2022 Sep;101:996-1006.

ASSOCIATION BETWEEN ANTENATAL GLUCOCORTICOID EXPOSURE AND THE ACTIVITY OF THE STRESS SYSTEM, COGNITION, AND BEHAVIOR IN 8- TO 9-YEAR-OLD CHILDREN: A PROSPECTIVE OBSERVATIONAL STUDY.

Rakers F, et al.

INTRODUCTION: Glucocorticoid (GC) -induced fetal programming of the activity of the hypothalamus-pituitary-adrenal axis (HPAA) and its associated cognitive and behavioral consequences in later life have been well characterized in several animal species. However, information on humans is scarce. In this study, we examined HPAA activity markers and associated outcomes at 8 to 9 years of age among children prenatally exposed to GC for suspected preterm birth. Our hypothesis was that antenatal exposure to the betamethasone (BM) is associated with exacerbation of HPAA activity in childhood.

MATERIAL AND METHODS: Prospective observational study in 31 children whose mothers received single (n = 19) or multiple (n = 12) courses of BM for threatened preterm birth but born with normal weight appropriate for the gestational age (median 37+(6) weeks of gestation) compared with 38 non-exposed, age-matched children. Primary end point was the activity of the HPAA in response to the Trier Social Stress Test. Secondary end points were changes in autonomic nervous system (ANS) activity, cognitive performance (IQ), attention-deficit/hyperactivity disorder (ADHD) symptoms, and electrocortical activity (EEG).

RESULTS: There was no statistically significant difference in HPAA activity markers between antenatal BM exposed and unexposed groups. ANS activity in BM-exposed children shifted towards a higher parasympathetic tone reflected by a higher overall high-frequency band power of heart rate variability. IQ scores were within normal limits for both groups; however, BM-exposed children had lower IQ scores than the unexposed group. BM-exposed group had marginally more ADHD core symptoms and increased electrocortical activity in the occipital brain region compared with controls. A monotonic dose-response relation between BM exposure and activity of the ANS and IQ was estimated in post-hoc analyses.

CONCLUSIONS: Antenatal exposure to BM in the context of threatened preterm birth was not associated with changes in HPAA activity in childhood. However, BM exposure may be associated with changes in ANS activity. Antenatal GC prophylaxis is a valuable and often life-saving therapy, but its prescription may warrant a well-balanced risk-benefit assessment

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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 Int J Paediatr. 2022.

CHILDHOOD-ONSET TYPE 1 DIABETES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH EDUCATIONAL ATTAINMENT: A POPULATION-BASED SIBLING-COMPARISON STUDY.

Liu S, Larsson H, Lichtenstein P, et al.

Aim: To examine the association of childhood-onset type 1 diabetes (T1D) and attention-deficit/hyperactivity disorder (ADHD) with educational outcomes from compulsory school to university.

Methods: Using multiple Swedish nationwide registers, we followed up on 1,474,941 individuals born in Sweden from 1981-1995 to December 31, 2013. Associations of T1D and ADHD with achieving educational milestones (from compulsory school to university) and school performances were estimated using logistic and linear regression models and sibling comparison models.

Results: Compared to their peers, children with both T1D and ADHD were less likely to achieve any of the educational attainments, including completing compulsory school (adjusted OR [aOR] [95% CI]: 0.43 [0.26, 0.72]), be eligible to and finishing upper secondary school (0.26 [0.19, 0.36], 0.24 [0.17, 0.35], respectively), and starting university (0.38 [0.17, 0.90]). The odds of achieving these educational milestones were substantially lower in children with ADHD alone (aORs: 0.14-0.44), but were slightly worse or no differences in children with T1D alone (aORs: 0.86-1.08). All associations above remained similar in the sibling comparison models.

Conclusion: Children and adolescents with both T1D and ADHD had long-term educational underachievement, with ADHD being the major contributor. Our findings suggest the importance of assessing ADHD in children with T1D and targeted support for minimising the education gap between the affected children and their peers

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Addictive Behaviors. 2022;135.

THE MODERATING ROLE OF SEX AND SELF-, TEACHER-, AND FATHER-REPORTED ADHD HYPERACTIVITY-IMPULSIVITY SYMPTOMS, ON THE ASSOCIATION BETWEEN EARLY ADOLESCENT INTERNALIZING SYMPTOMS AND SUBSTANCE USE.

Pocuca N, et al.

Aims: Internalizing symptoms are theorized to lead to substance use (SU) via a tendency to use substances to cope with or self-medicate negative feelings and emotions; however, empirically, this association is mixed, pointing to the existence of moderating factors. The present study aimed to examine how self-, teacher-, and father-reported attention-deficit/hyperactivity disorder hyperactivity-impulsivity symptoms (ADHD-HI) and sex, moderated the association between self-reported internalizing symptoms and SU, in early adolescence.

Methods: Cross-sectional data obtained at 13 years of age, drawn from the Quebec Longitudinal Study of Child Development (N = 1,424; 53 % female). Alcohol, cigarette, and cannabis use, and internalizing and ADHD-HI symptoms were assessed.

Results: There was a significant three-way interaction between internalizing, ADHD-HI, and sex, for cigarette use, with Bayes factor (BF) indicating very strong evidence for an effect (BF = 48.40). While the three-way interaction for cannabis use did not reach statistical significance (self-report: p <.066; father-report: p <.053), BF indicated substantial evidence for an effect (self-report: BF = 3.54; father-report: BF = 9.08). Further analyses revealed internalizing was associated with cigarette and cannabis use only among females with high ADHD-HI symptoms (cigarette use: +¦ = 0.15, SE = 0.04, 95 %CI [0.07, 0.22]; cannabis use (self-reported ADHD-HI): +¦ = 0.14, SE = 0.06, 95 %CI [0.04, 0.25]; cannabis use (father-reported ADHD-HI): +¦ = 0.21, SE = 0.10, 95 %CI [0.01, 0.41]).

Conclusions: Findings aid in clarifying the inconsistent relationship between internalizing symptoms and SU among adolescent females by underscoring the moderating role of ADHD-HI. Further, findings also support a growing body of literature which highlights the need for both self- and adult-informants (i.e., teacher and parent) in assessing ADHD-HI symptoms in females

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Adicciones. 2022 Jul;34:208-17.

INTERNET, VIDEO GAME AND MOBILE PHONE ADDICTION IN CHILDREN AND ADOLESCENTS DIAGNOSED WITH ADHD: A CASE-CONTROL STUDY.

Menandez-Garcia-a A, et al.

The use of new technologies has become widespread worldwide. There is increasing concern about "Internet addiction disorder" (IAD), "Internet gaming disorder" (IGD), and "Mobile phone addiction" (MPA). Attention Deficit Hyperactivity Disorder (ADHD) has been associated with IAD and IGD. However, evidence is lacking about the relationship between ADHD and MPA. Naturalistic case-control study. 112 patients (51 children with and 61 children without ADHD) between 7 and 17 years old were compared regarding IAD, IGD, and MPA. We used the TEA questionnaire for the assessment of executive function and ADHD (ATENTO), and the ADITEC questionnaire to get gender-differentiated information for IAD, IGD, and MPA. Female children scored higher on MPA (Mean Â± Standard Deviation, M ± SD) (25.93 ± 17.64 vs. 14.77 ± 19.43, p=0.03), while male children scored higher on IGD (30.09 Â± 21.65 vs. 12.51 ± 16.61, p < 10^-3). Severity of hyperactivity/impulsivity and IGD were moderately correlated (r=0.349, p=0.013), but the correlation disappeared after controlling for the impact on the social domain as measured by the ATENTO questionnaire (r=171, p=0.250). Most parents are concerned that their children may be addicted to IAD/IGD/MPA. Female gender is associated with MPA, while male gender is associated with IGD. ADHD is a risk factor for developing IAD and IGD. Combined type and predominantly hyperactive/impulsive ADHD are each associated with IGD. Good social adjustment protects against developing IGD. There are gender vulnerabilities for IAD/IGD/MPA. ADHD is a risk factor for IGD, but good social adjustment buffers this association

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Am J Obstet Gynecol. 2022 Sep;227:414-29.

LONG-TERM HEALTH OUTCOMES OF CHILDREN BORN TO MOTHERS WITH HYPEREMESIS GRAVIDARUM: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Nijsten K, Jansen LAW, Limpens J, et al.

OBJECTIVE: Hyperemesis gravidarum is characterized by severe nausea and vomiting in pregnancy, frequently resulting in severe maternal nutritional deficiency. Maternal undernutrition is associated with adverse offspring health outcomes. Whether hyperemesis gravidarum permanently affects offspring health remains unclear. This review aimed to evaluate the effects of maternal hyperemesis gravidarum on offspring health.

DATA SOURCES: MEDLINE and Embase were searched from inception to September 6, 2021.

STUDY ELIGIBILITY CRITERIA: Studies reporting on health at any age beyond the perinatal period of children born to mothers with hyperemesis gravidarum were included.

METHODS: Two reviewers independently selected studies and extracted data. The Newcastle-Ottawa Quality Assessment Scale was used to assess risk of bias. We conducted a narrative synthesis and meta-analysis where possible. In meta-analyses with high heterogeneity (I(2)>75%), we did not provide a pooled odds ratio.

RESULTS: Nineteen studies were included in this systematic review (n=1,814,785 offspring). Meta-analysis (n=619, 2 studies: 1 among adolescents and 1 among adults) showed that hyperemesis gravidarum was associated with anxiety disorder (odds ratio, 1.74; 95% confidence interval, 1.04-2.91; I(2), 0%) and sleep problems in offspring (odds ratio, 2.94; 95% confidence interval, 1.25-6.93; I(2), 0%). Hyperemesis gravidarum was associated with testicular cancer in male offspring aged up to 40 years on meta-analysis (5 studies, n=20,930 offspring), although heterogeneity was observed on the basis of a wide 95% prediction interval (odds ratio, 1.60; 95% confidence interval, 1.07-2.39; I(2), 0%; 95% prediction interval, 0.83-3.08). All 6 studies reporting on attention deficit (hyperactivity) disorder and autism spectrum disorder reported an increase among children of mothers with hyperemesis gravidarum in comparison with children of unaffected mothers. Meta-analysis showed high heterogeneity, precluding us from reporting a pooled odds ratio. Most studies reporting on cognitive and motor problems found an increase among hyperemesis gravidarum-exposed children. One study investigated brain structure and found smaller cortical volumes and areas among children from hyperemesis gravidarum-affected pregnancies than among those from unaffected

pregnancies. Studies evaluating anthropometry and cardiometabolic disease risk of hyperemesis gravidarum-exposed children had inconsistent findings.
CONCLUSION: Our systematic review showed that maternal hyperemesis gravidarum is associated with small increases in adverse health outcomes among children, including neurodevelopmental disorders, mental health disorders, and possibly testicular cancer, although evidence is based on few studies of low quality

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Am J Med Genet Part B Neuropsychiatr Genet. 2022;189:185-95.

A PHENOME-WIDE ASSOCIATION STUDY OF POLYGENIC SCORES-ÁFOR ATTENTION DEFICIT HYPERACTIVITY DISORDER ACROSS TWO GENETIC ANCESTRIES IN ELECTRONIC HEALTH RECORD DATA.

Niarchou M, Sealock JM, Straub P, et al.

Testing the association between genetic scores for Attention Deficit Hyperactivity Disorder (ADHD) and health conditions, can help us better understand its complex etiology. Electronic health records linked to genetic data provide an opportunity to test whether genetic scores for ADHD correlate with ADHD and additional health outcomes in a health care context across different age groups. We generated polygenic scores (ADHD-PGS) trained on summary statistics from the latest genome-wide association study of ADHD (N = 55,374) and applied them to genome-wide data from 12,383 unrelated individuals of African-American ancestry and 66,378 unrelated individuals of European ancestry from the Vanderbilt Biobank. Overall, only Tobacco use disorder (TUD) was associated with ADHD-PGS in the African-American ancestry group (Odds ratio [95% confidence intervals] = 1.23[1.16-1.31], p = 9.3 × 10-09). Eighty-six phenotypes were associated with ADHD-PGS in the European ancestry individuals, including ADHD (OR[95%CIs] = 1.22[1.16-1.29], p = 3.6 × 10-10), and TUD (OR[95%CIs] = 1.22[1.19-1.25], p = 2.8 × 10-46). We then stratified outcomes by age (ages 0-11, 12-18, 19-25, 26-40, 41-60, and 61-100). Our results suggest that ADHD polygenic scores are associated with ADHD diagnoses early in life and with an increasing number of health conditions throughout the lifespan (even in the absence of ADHD diagnosis). This study reinforces the utility of applying trait-specific PGSs to biobank data, and performing exploratory sensitivity analyses, to probe relationships among clinical conditions

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Am J Obstet Gynecol. 2022.

ARE INFANTS BORN AFTER AN EPISODE OF SUSPECTED PRETERM LABOR AT RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER? A 30-MONTH FOLLOW-UP STUDY.

Navalin P, et al.

Background: An episode of suspected preterm labor may be by itself a pathologic event that may alter the normal course of pregnancy and the offspring's neurodevelopment. Certainly, the association between preterm birth and neurodevelopmental disorders can only be partially explained by the immaturity of the nervous system, as evidenced by the increased risk of attention deficit hyperactivity disorder in late-preterm infants without any neurologic alteration.
Objective: This study aimed to examine whether infants born after suspected preterm labor may be at an increased risk of developing attention deficit hyperactivity disorder. Moreover, potential obstetrical, perinatal, and psychosocial risk factors associated with attention deficit hyperactivity disorder in this population are examined.
Study Design: A prospective cohort study of 120 mother-infant pairs was conducted from the moment the mothers received a diagnosis of suspected preterm labor until the infants 30 months of life. Infants were divided according to the prematurity status: full-term infants born after a suspected preterm labor (n=28; born at 37 weeks of gestation), late-preterm infants (n=56; born between 32 and <37 weeks of gestation), very-preterm infants (n=36; born before <32 weeks of gestation). At-term infants born without obstetric complications served as a control group (n=46). Infants attention deficit hyperactivity disorder symptoms were assessed at the age of 30 months. Furthermore, obstetrical, perinatal, and psychosocial risk factors were recorded.

Results: All groups of infants born after a suspected preterm labor showed more attention deficit hyperactivity disorder symptoms at the age of 30 months than the control group. Concretely, very-preterm infants showed higher restless or impulsive behaviors, whereas full-term infants born after a suspected preterm labor and late-preterm infants showed higher emotional lability behaviors. Among potential risk factors, male sex and maternal experience of posttraumatic stress symptoms predicted the severity of attention deficit hyperactivity disorder symptoms in infants born after a suspected preterm labor.
Conclusion: Infants born after a suspected preterm labor had a higher risk of developing attention deficit hyperactivity disorder symptoms, including those born at term. Infants born after a suspected preterm labor showed a distinctive phenotype and shared specific risk factors suggesting that they conform an undescribed population at risk of attention deficit hyperactivity disorder

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Arch Iran Med. 2022 May;25:285-393.
COMPARISON OF VITAMIN D, NEUROFEEDBACK, AND NEUROFEEDBACK COMBINED WITH VITAMIN D SUPPLEMENTATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Rahmani M, Mahvelati A, Farajinia AH, et al.
BACKGROUND: Nowadays, some treatments such as neurofeedback and Vitamin D Supplementation are of great importance in the treatment of attention-deficit/hyperactivity disorder (ADHD). To determine the efficacy of the combined treatment, the present trial was conducted to investigate the effectiveness of each one of them with combined neurofeedback and vitamin D supplementation in the reduction of ADHD symptom in children suffering from this disorder.
METHODS: In this study from March 2020 to June 2020, we enrolled a total of 120 patients (6-15 years old) who were referred to the Mehr psychiatric hospital (affiliated to Lorestan University of Medical Sciences). Patients were then randomly categorized into three experimental groups and one control group. The first, the second, and the third experimental groups consumed vitamin D pearl, neurofeedback combined with vitamin D, and neurofeedback for 12 weeks, respectively. The control group was given no treatment. Vitamin D serum level was evaluated at baseline, 4, 8, and 12 weeks in all participants. For data collection, the Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) was applied. The obtained information was analyzed using repeated measure variance analysis.
RESULTS: The mean scores were significantly different across the groups. Repeated measure variance analysis showed that the mean score was lower in the combined group in comparison with the other three groups ($P<0.05$).
CONCLUSION: Combined treatment could be considered as more effective compared to separate treatments. In addition, in this study, by applying the combined intervention, the duration of treatment decreased significantly

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Arch Ital Biol. 2022 Jul;160:81-88.
NEUROPSYCHOLOGICAL HETEROGENEITY IN ADHD PUPILS: FURTHER EVIDENCE FROM INCIDENTAL MEMORY TESTING.
Gronchi G, Peru A.
This paper reports on a study where the incidental memory of 18 children with ADHD and 18 typically developing peers was assessed by means of a conventional two-phase recognition memory test. In the study phase participants were required to categorize as a living or non-living a set of 64 stimuli from 8 semantic categories. In the test phase, they were required to recognize "target" (i.e., stimuli from the first set) from "non-target" stimuli. Children with ADHD were overall less accurate and much slower than TD controls in identifying both living and non-living items. Moreover, while most of TD participants made very few, if any, errors, only 7 out of 18 participants with ADHD scored near ceiling, and 2 of them scored below chance level. Following the Signal Detection Theory approach, the participants' performance on the test phase was scored in terms of d prime (d') values. Children with ADHD had lower d' indexes compared to controls both for living and non-living stimuli, although this difference did not reach statistical significance. More interestingly, the

variability of the d' values was higher in the ADHD compared to Controls. Taken together, findings from this study indicate that at least some of the children with ADHD have a genuine impairment in processing visual stimuli. More generally, these results cast doubts on the idea that ADHD represents a stable nosographic entity

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Asian J Psychiatr. 2022 Sep;75:103205.

GENDER-BASED DIFFERENCES IN PREVALENCE AND EFFECTS OF ADHD IN ADULTS: A SYSTEMATIC REVIEW.

Faheem M, Akram W, Akram H, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that starts from childhood and lasts through adulthood. Historically thought as male dominant disorder, researches now emphasized that ADHD also effects females equally. Despite the ascending research on gender differences of ADHD, there is little known about its differences in prevalence and effects and there is a dearth of reviews that can draw a firm conclusion especially in adults. Data from the available medical literature published in English language literature of all time was reviewed systematically and tabulated to evaluate the gender-based differences in prevalence and effects of ADHD in adults. The studies revealed gender differences in adult ADHD in prevalence, and effects. Results showed that males have more prevalence as compared to females but females too have a significant presence of disorder. Females were more impaired as compared to men in most of the effects of ADHD like social functioning, time perception, stress tackling and mood disorder. Males were more impaired in working memory and educational functioning as compared to females. The review shows sufficient evidence of gender differences in adult ADHD in prevalence, and effects, that similarity across genders should not be assumed. It is concluded that there are plenty of conflicting evidence regarding gender differences in many areas of adult ADHD research, and to remove such discrepancies, the existing research is the need for more studies on gender differences and similarities in functioning of adults with ADHD

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Asian J Psychiatry. 2022;76.

TREATMENTS FOR CHILD AND ADOLESCENT ATTENTION DEFICIT HYPERACTIVITY DISORDER IN LOW AND MIDDLE-INCOME COUNTRIES: A NARRATIVE REVIEW.

Pipe A, Ravindran N, Paric A, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects approximately 2-7 % of children globally and is associated with a myriad of difficulties that have long-term consequences. Most children and adolescents live in low- and middle-income countries (LMICs), but there are few reports and no consolidation of findings on ADHD treatment outcomes in this population. We conducted a review of ADHD treatment literature for children and adolescents living in LMICs.

Methods: Studies were identified using databases (PsychoINFO, Pubmed, MEDLINER, EMBASE, Global Health, Academic Search Complete, Google Scholar). The initial search produced 139 articles. These were filtered for language, title, abstract, and full-text keyword identification to yield a final 20 articles to be included in this review.

Results: Reports on outcomes of both psychological and pharmacological treatment were relatively sparse, particularly the former, which mostly referred to parent training and multimodal programs in pre-school children. Most evidence exists for the benefit of methylphenidate-IR with a few reports on other agents, including clonidine, atomoxetine, and lisdexamfetamine. Methylphenidate is the most common agent to treat ADHD in youth in LMICs. Younger age, combined subtype, and comorbid oppositional defiant disorder were associated with poorer treatment outcome.

Conclusion: Access to treatment for ADHD is overall limited in LMICs and varied among individual countries. Pharmacological treatments were generally more available than psychological interventions. Several barriers including stigma, cost, and lack of resources were reported to impact treatment acceptance. More research in LMICs is needed to improve and expand mental health services in these regions

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Autism. 2022 Aug;26:1591-97.

PREVALENCE OF CO-OCCURRING AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER AMONG CHILDREN IN THE UNITED STATES.

Casseus M.

Autism spectrum disorder and attention deficit/hyperactivity disorder are neurodevelopmental disorders that often co-occur in children. However, there are few large, nationally representative studies examining the prevalence of co-occurring autism spectrum disorderâ€‰andâ€‰attention deficit/hyperactivity disorder in children. The aim of this study was to estimate the prevalence of parent-reported co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder in the United States and examine associations between having co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder and sociodemographic and household factors. Data were analyzed from the 2016-2018 National Survey of Children's Health. A total of 88,051 children aged 3-17 years old were included in the analysis. Statistical analyses were conducted to assess the associations between sociodemographic and household characteristics and current co-occurrence of autism spectrum disorder and attention deficit/hyperactivity disorder. Approximately 1.2% of children (740,816) aged 3-17 years had co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder. Children who were male, older, reported poor health, or had public or combined public and private health insurance were more likely to have co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder. Conversely, children who were Black, non-Hispanic or multi-racial/other, non-Hispanic were less likely to report co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder than White non-Hispanics. Findings suggest implementing early developmental screening and surveillance for co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder, and coordinating strategies that optimize early identification and intervention for all children suspected of having co-occurring autism spectrum disorder and attention deficit/hyperactivity disorder, particularly those from underrepresented groups

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Autism Res. 2022.

PATHWAYS TO ADAPTIVE FUNCTIONING IN AUTISM FROM EARLY CHILDHOOD TO ADOLESCENCE.

Chandler S, Carter Leno V, White P, et al.

Adaptive functioning is lower in many autistic individuals to a greater extent than would be expected based on IQ. However, the clinical features associated with these difficulties are less well understood. This study examines longitudinal and contemporaneous associations of adaptive functioning in autistic youth across a wide ability range. Parent-reported autism symptoms, co-occurring emotional, behavioral and attention deficit hyperactivity disorder (ADHD) symptoms, and IQ were assessed in early childhood (M age 7 years; T1) and 6 years later in adolescence (M age 13 years; T2) in 179 autistic youth. Adaptive functioning was assessed at T2. Structural equation modeling estimated pathways to adaptive functioning from autism, and psychiatric symptoms at T1 and T2, testing whether associations were driven by continuity of behaviors from T1 to T2 or their contemporaneous effect at T2, or both, controlling for T1 IQ. Lower adaptive functioning at T2 was associated with higher T1 and T2 ADHD symptoms (β = -0.14, and β = -0.21) but not behavioral nor emotional symptoms at either timepoint. Lower adaptive functioning at T2 was also associated with lower T1 IQ (β = 0.43) and higher social communication symptoms (β = -0.37) at T2 but not T1, but the relationship with ADHD symptoms remained. Paths were not moderated by sex or IQ. Increased symptoms of ADHD, both in early childhood and contemporaneously, were associated with reduced adaptive functioning in adolescence. Co-occurring ADHD may be a modifiable risk factor for adaptive function impairments and should be routinely assessed and when present evidence-based treatments initiated which may benefit adaptive functioning outcomes. LAY SUMMARY: Adaptive functioning is lower in many autistic individuals to a greater extent than would be expected based on IQ. However, the clinical features associated with these difficulties are less well understood. In a community sample higher attention deficit/hyperactivity disorder (ADHD) symptoms, but not

emotional or behavioral symptoms, in both early childhood and contemporaneously were associated with lower adaptive functioning in autistic adolescents. Co-occurring ADHD may be a modifiable risk factor for adaptive function difficulties in autism

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Basic Clin Neurosci. 2022;13:215-24.

NEUROFEEDBACK TRAINING VERSUS PERCEPTUAL-MOTOR EXERCISES INTERVENTIONS IN VISUAL ATTENTION FOR CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CONTROLLED TRIAL.

Sani NG, Akbarfahimi M, Akbari S, et al.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders characterized by poor attention and subsequently lower learning abilities than normal children. This study aimed to compare the effectiveness of neurofeedback and perceptual-motor exercises as two common nonpharmacological treatments for visual attention.

Methods: A total of 40 combined medicated ADHD children (aged 5-12 years) were randomly allocated into two groups: neurofeedback training and perceptual-motor exercises. Visual attention and motor proficiency were assessed before and after the treatment by continuous performance test (CPT) and Bruininks-Oseretsky Test (BOT), respectively.

Results: According to repeated measures analysis of variance (ANOVA), both groups showed significant improvement in three attention-related areas of CPT, including reaction time, omission, and commission errors ($P<0.001$), while the difference between the two groups was not significant ($P>0.05$). However, in the perceptual-motor exercises group, motor proficiency improved significantly ($P<0.01$).

Conclusion: Neurofeedback training intervention, as well as perceptual-motor exercises, are effective in improving ADHD symptoms, and given the similar effect of both interventions and their lack of side effects, perceptual-motor exercises appear to be the more appropriate option for reducing symptoms of ADHD, because of its additional effect on motor proficiency, rich content of purposeful activities, and social interactions

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Biol Psychiatry. 2022 Aug;92:299-313.

VIRTUAL ONTOGENY OF CORTICAL GROWTH PRECEDING MENTAL ILLNESS.

Patel Y, Shin J, et al.

BACKGROUND: Morphology of the human cerebral cortex differs across psychiatric disorders, with neurobiology and developmental origins mostly undetermined. Deviations in the tangential growth of the cerebral cortex during pre/perinatal periods may be reflected in individual variations in cortical surface area later in life.

METHODS: Interregional profiles of group differences in surface area between cases and controls were generated using T1-weighted magnetic resonance imaging from 27,359 individuals including those with attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, schizophrenia, and high general psychopathology (through the Child Behavior Checklist). Similarity of interregional profiles of group differences in surface area and prenatal cell-specific gene expression was assessed.

RESULTS: Across the 11 cortical regions, group differences in cortical area for attention-deficit/hyperactivity disorder, schizophrenia, and Child Behavior Checklist were dominant in multimodal association cortices. The same interregional profiles were also associated with interregional profiles of (prenatal) gene expression specific to proliferative cells, namely radial glia and intermediate progenitor cells (greater expression, larger difference), as well as differentiated cells, namely excitatory neurons and endothelial and mural cells (greater expression, smaller difference). Finally, these cell types were implicated in known pre/perinatal risk factors for psychosis. Genes coexpressed with radial glia were enriched with genes implicated in congenital abnormalities, birth weight, hypoxia, and starvation. Genes coexpressed with endothelial and mural genes were enriched with genes associated with maternal hypertension and preterm birth.

CONCLUSIONS: Our findings support a neurodevelopmental model of vulnerability to mental illness whereby prenatal risk factors acting through cell-specific processes lead to deviations from typical brain development during pregnancy

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BMC Psychiatry. 2022 Aug;22:549.

VALIDATION OF BRIEF SCREENING INSTRUMENTS FOR INTERNALIZING AND EXTERNALIZING DISORDERS IN MOZAMBICAN ADOLESCENTS.

Lovero KL, Adam SE, Bila CE, et al.

Background: Mental disorders are the leading cause of disability for youth worldwide. However, there is a dearth of validated, brief instruments to assess mental health in low- and middle-income countries (LMIC). We aimed to facilitate identification of mental disorders in LMIC contexts by adapting and validating measures of internalizing and externalizing disorders for adolescents in Mozambique, an LMIC in southeastern Africa.

Methods: We selected instruments with good support for validity in high-income and other LMIC settings: the Patient Health Questionnaire Adolescent (PHQ-A), Generalized Anxiety Disorders 7 (GAD-7), and Strengths and Difficulties Questionnaire (SDQ). Instruments were adapted by local and international mental health specialists followed by cognitive interviews (n = 48) with Mozambican adolescents. We administered the instruments along with the Miniature International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)to 485 adolescents aged 12-19 years attending two secondary schools in Maputo City, Mozambique. One week later, we re-administered instruments to a randomly selected sample of 49 adolescents.

Results: Participants were 66.2% (n = 321) female and the average age was 15.9 (S.D = 1.7).Internal consistency (alpha = 0.80, PHQ-A; 0.84, GAD-7; 0.80, SDQ) and test-retest reliabilty (ICC = 0.74, PHQ-A; 0.70, GAD-7; 0.77, SDQ) were acceptabe for the PHQ-A, GAD-7, and the full SDQ. The SDQ internalizing subscale showed poor test-retest reliability (ICC = 0.63) and the SDQ externalizing subscale showed poor internal consistency (alpha = 0.65). All instruments demonstrated good sensitivity and specificity (> 0.70). Youden's index identified optimal cutoff scores of 8 for the PHQ-A, 5 for the GAD-7, 10 for the SDQ internalizing and 9 for the SDQ externalizing subscales, though a range of scores provided acceptable sensitivity and specificity.

Conclusions: Our data supports reliability and validity of the PHQ-A, GAD-7, and SDQ instruments for rapidly assessing mental health problems in Mozambican adolescents. Use of these tools in other contexts with limited specialists may asist with expanding mental health assessment. Specific instrument and cutoff selection should be based on screening goals, treatment resources, and program objectives

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BMC Psychiatry. 2022 Aug;22:564.

TIME-DEPENDENT AFFECTIVE DISTURBANCES IN ABSTINENT PATIENTS WITH METHYLPHENIDATE USE DISORDER.

Xu J, Zhang Y, Wang N, et al.

BACKGROUND: Methylphenidate (MPH), also called Ritalin, is used to treat attention-deficit hyperactivity disorder (ADHD) patients. With occasional reports of subjects suffering from Methylphenidate use disorder (MPHUD), few studies analyzed the neuropsychological changes in this population.

PURPOSE: This study aims to evaluate the clinical outcomes of individuals with MPHUD.

METHODS: We retrospectively analyzed 61 MPH patients (aged 16-27 years) admitted to the Beijing Gaoxin Hospital drug rehabilitation program from Jan 2017 to Mar 2019. The drug use history and drug abuse motivation scale were collected at admission. Clinicians rated the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and DSM-5 Stimulant use disorder criteria each week during the 4Â weeks rehabilitation program. Correlation analyses were conducted between drug use history and affective disturbances.

RESULTS: The results showed that the adolescent period is the peak for MPH exposure, and 1/3 of patients got their first exposure to MPH from their parents. MPH abstinence accompanies severe anxiety and depression symptoms, significantly alleviating after four weeks of treatment.

CONCLUSIONS: MPHUD is associated with substantial affective disturbances, which warrants a more considerable sample investigation

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BMC Psychiatry. 2022;22.

TREATMENT PATTERNS AMONG CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE UNITED STATES ΓÇô A RETROSPECTIVE CLAIMS ANALYSIS.

Schein J, Childress A, Adams J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting approximately 10.0% of children and 6.5% of adolescents in the United States (US). A comprehensive assessment of the current treatment landscape is warranted to highlight potential unmet needs of children and adolescents with ADHD. Therefore, this study described treatment patterns and healthcare costs among commercially insured children and adolescents with ADHD in the US.

Methods: Children and adolescents with ADHD initiating pharmacological treatment indicated for ADHD were identified from IBM MarketScan Commercial Database (2014-2018). A treatment sequence algorithm was used to examine treatment patterns, including discontinuation (180 days following the last day of supply of any ADHD treatment), switch, add-on, and drop (discontinuation of an agent in combination therapy), during the 12-month study period following the index date (i.e., first observed ADHD treatment). Total adjusted annual healthcare costs were compared between patients with and without treatment changes.

Results: Among 49,756 children and 29,093 adolescents included, mean age was 9 and 15 years, respectively, and 31% and 38% were female. As the first treatment regimen observed, 92% of both children and adolescents initiated a stimulant and 11% initiated combination therapy. Over half of the population had a treatment change over 12 monthsΓÇö59% of children and 68% of adolescents. Treatment discontinuation over 12 months was common in both populations 21% of children and 36% of adolescents discontinued treatment. Healthcare costs increased with the number of treatment changes observed; children and adolescents with treatment changes (i.e., 1, 2, or 3) incurred an incremental annual cost of up to $1,443 and $2,705, respectively, compared to those without a treatment change ($p < 0.001$). Costs were largely driven by outpatient visits.

Conclusions: Over a 12-month period, treatment changes were commonly observed and were associated with excess costs, highlighting the unmet treatment needs of children and adolescents with ADHD in the US

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BMJ Open. 2022;12.

IS IN-UTERO EXPOSURE TO CANNABIS ASSOCIATED WITH THE RISK OF ATTENTION DEFICIT WITH OR WITHOUT HYPERACTIVITY DISORDER? A COHORT STUDY WITHIN THE QUEBEC PREGNANCY COHORT.

Tchuente V, Sheehy O, Zhao JP, et al.

Importance and objective: Prenatal cannabis effect on attention deficit with or without hyperactivity disorder (ADHD) remains to be determined. Our aim is to quantify the impact of in-utero exposure to cannabis on the risk of ADHD.

Design: Cohort study.

Setting: Questionnaires were mailed to women sampled from the Quebec Pregnancy Cohort (QPC). Data from questionnaires were then linked with their QPC (built with administrative health databases, hospital patient charts and birth certificate databases).

Participants: Respondents who gave birth to a singleton live born between January 1998 and December 2003 and were continuously enrolled in the Régie de l'assurance maladie du Québec (RAMQ) medication insurance plan for at least 12 months before the first day of gestation and during pregnancy.

Exposure: In-utero cannabis exposure was based on mothers' answers to the question on cannabis use during pregnancy (yes/no) and categorised as occasionally, regularly exposed and unexposed if they chose one of these categories.

Outcomes: ADHD was defined by a diagnosis of ADHD through the RAMQ medical services or MedEcho databases or a prescription filled for ADHD medication through RAMQ pharmaceutical services between birth and the end of the follow-up period. Follow-up started at the birth and ended at the index date (first diagnosis or prescription filled for ADHD), child death (censoring), end of public coverage for medications (censoring) or the end of study period, which was December 2015 (censoring), whichever event came first.
Results: A total of 2408 children met the inclusion criteria. Of these children, 86 (3.6%) were exposed to cannabis in-utero and 241 (10.0%) had an ADHD diagnosis or medication filled. After adjustments for potential confounders, no significant association was found between in-utero cannabis exposure (occasional (1.22 (95% CI 0.63 to 2.19)) or regular (1.22 (95% CI 0.42 to 2.79))) and the risk of ADHD in children.
Conclusions: In-utero exposure to cannabis seemed to not be associated with the risk ADHD in children.

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BMJ Open. 2022 Aug;12:e057303.

GENERAL PRACTICE DATABASE ON MORTALITY IN ADULTS ON METHYLPHENIDATE: COHORT STUDY.

Stricker B, Cheung K, Verhamme K.

OBJECTIVES: Methylphenidate is a 'prescription only' drug against attention disorders which is increasingly used by adults. We investigated whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt and overall mortality.
DESIGN: A population-based matched cohort design.
SETTING: The Integrated Primary Care Information system, a general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants.
PARTICIPANTS: During the study period between 1 June 1996 and 1 January 2018, 8905 adults started methylphenidate and were matched to 10 non-users on sex, age, GP practice and ad prescription date. The total study population consisted of 97 198 participants.
MAIN OUTCOME MEASURES: Serious psychiatric events such as depression and suicide attempts, and overall mortality.
ANALYSES: Risks of development of each event during the use of methylphenidate were expressed as HR with 95% CI, adjusted for relevant confounders with methylphenidate as a time-dependent determinant. Additional adjustment was performed for the intervention ('intention-to-treat').
RESULTS: Although during follow-up, the unadjusted risks of depression and suicide attempt were strongly increased in users, depression and psychosis became non-significant after adjustment for alcohol-abuse and substance-abuse and psychiatric disease in the medical history and after adjustment for 'intention-to-treat'. However, the risk of suicide attempts remained significantly increased after full adjustment (HR 2.0; 95% CI 1.1 to 3.6), and was highest in women and in participants within the age-group of 18-40 years. The unadjusted risk of overall mortality was strongly increased, but this lowered to a significant 30% risk increase (HR 1.3; 95% CI 1.1 to 1.6) after full adjustment.
CONCLUSION: There is an increased risk of suicide attempts in adults up to 40 years of age after starting methylphenidate and this risk should be carefully considered before prescribing to this group

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Brain Behav. 2022.

A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS ON EFFICACY AND SAFETY OF TRANSCRANIAL DIRECT CURRENT STIMULATION IN MAJOR NEURODEVELOPMENTAL DISORDERS: ADHD, AUTISM, AND DYSLEXIA.

Salehinejad MA, Ghanavati E, Glinski B, et al.

Objective: Among the target groups in child and adolescent psychiatry, transcranial direct current stimulation (tDCS) has been more applied in neurodevelopmental disorders specifically, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and dyslexia. This systematic review aims to provide the latest update on published randomized-controlled trials applying tDCS in these disorders for evaluating its efficacy and safety.

Methods: Based on a pre-registered protocol (PROSPERO: CRD42022321430) and using-áthe PRISMA approach, a literature search identified 35 randomized controlled trials investigating the effects of tDCS on children and adolescents with ADHD (n=17), ASD (n=11), and dyslexia (n=7).
Results: In ADHD, prefrontal anodal tDCS is reported more effective compared to stimulation of the right inferior frontal gyrus. Similarly in ASD, prefrontal anodal tDCS was found effective for improving behavioral problems. In dyslexia, stimulating temporoparietal regions was the most common and effective protocol. In ASD and dyslexia, all tDCS studies found an improvement in at least one of the outcome variables while 64.7% of studies (11 of 17) in ADHD found a similar effect. About 88% of all tDCS studies with a multi-session design in 3 disorders (16-áof 18) reported a significant improvement in one or all outcome variables after the intervention. Randomized, double-blind, controlled trials consisted of around 70.5%, 36.3%, and 57.1% of tDCS studies in ADHD, ASD, and dyslexia, respectively. tDCS was found safe with no reported serious side effects in 6587 sessions conducted on 745 children and adolescents across 35 studies.
Conclusion: tDCS was found safe and partially effective. For evaluation of clinical utility, larger randomized controlled trials with a double-blind design and follow-up measurements are required. Titration studies that systematically evaluate different stimulation intensities, duration, and electrode placement are lacking

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Brazilian Journal of Psychiatry. 2022;44:388-400.

INATTENTION SYMPTOMS IN EARLY PREGNANCY PREDICT PARENTING SKILLS AND INFANT MALTREATMENT DURING THE FIRST YEAR OF LIFE.

de Oliveira JV, Fatori D, Shephard E, et al.

Objective: Maternal attention-deficit/hyperactivity disorder has not been investigated in relation to parenting skills in adolescent mothers. This study investigated whether maternal inattention and hyperactivity/ impulsivity symptoms early in pregnancy predict poorer parenting skills and infant maltreatment during the first year of life in adolescent mothers living in adverse environmental conditions.
Methods: The participants in this study were 80 adolescent mothers aged 14-19 years and their babies who were taking part in a randomized controlled trial on the effects of a home-visiting program on infant development. Symptoms of maternal attention-deficit/hyperactivity disorder were assessed in the first trimester of pregnancy. Parenting skills (maternal competence, attachment to the baby, home environment) and child maltreatment were assessed when the infants were aged 6 and 12 months. Multilevel linear regression models were constructed to test the extent to which prenatal maternal inattention and hyperactivity/impulsivity symptoms predicted these parenting variables during the first year of the infant's life.
Results: Prenatal inattention symptoms significantly predicted lower maternal competence and attachment, a poorer home environment, and greater maltreatment during the first year of life. Hyperactivity did not significantly predict parenting skills or maltreatment.
Conclusions: Our findings suggest that inattention symptoms may interfere with parenting abilities in adolescent mothers and should be considered in early intervention programs

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Canadian Journal of Neurological Sciences. 2022;49:S31.

FAMILY IDENTIFIED BARRIERS TO ACCESSING SERVICES FOR CHILDREN WITH ATTENTION DEFICITS AND NEURODEVELOPMENTAL DISORDERS.

Wiley B, Taylor K, Murias K.

Background: Obtaining early intervention services is crucial for improving outcomes in children with neurodevelopmental disorders (NDDs) such as Autism or Attention Deficit/Hyperactivity Disorder. Identifying barriers in accessing services in the healthcare system is necessary to optimize the Patient and Family-Centered Care approach.
Methods: Parents of children with an NDD co-occurring with attention deficits were recruited from the Neurodevelopmental Attention Clinic at the Alberta Children's Hospital. Parents completed a semi-structured interview and the Barriers to Accessing Services (BAS) questionnaire.

Results: Nine families participated representing 10 children. Interviews were evenly spread between biological mothers and fathers. All children had attention deficits; 4 children were also diagnosed with Autism and 5 with other neurologic conditions. The two barriers most identified by families (67%) through the BAS questionnaire were Didn't know where to find help and Steps to seek help are too overwhelming, consistent with information obtained in the interview.
Conclusions: Children with an NDD and attention deficits often have complex medical needs. Parents have identified challenges initiating, and navigating the many steps involved to secure services. We will collect information from more families to determine how services for children with complex medical needs can become more accessible

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Canadian Journal of Neurological Sciences. 2022;49:S30.

THE RELATIONSHIP BETWEEN SLEEP AND BEHAVIOR IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Ghanim F, Harkness K, Guadagni V, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that is associated with long-term reduced quality of life and impaired functioning. ADHD is commonly associated with sleep disturbances that can contribute to many difficulties in a child's life. This study aims to elucidate this complex relationship by utilizing a subset of the Adolescent Brain Cognitive Development (ABCD) database.
Methods: The population included a group of children with ADHD age 10-13 years (n=212) and a matched typically developing (TD) group (n=212). Sleep data was obtained through Fitbit actigraphy measures, and the Parent Sleep Disturbance Scale (SDS). Behavioural and emotional subscores were obtained from the Child Behaviour Checklist (CBCL).
Results: There were no significant correlations between the actigraphy and SDS sleep data. SDS sleep data were significantly different between ADHD and control groups, while actigraphy data was not. Sleep latency (measured by actigraphy) and 3 out of 6 of the SDS subscores were significantly related to behavioural scores.
Conclusions: The results of this study indicate that sleep may not be an important mediator of behaviour and emotional responses in children with ADHD. Future studies should explore both influences on sleep parameters as well as behaviour and other measures important to families

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Chem Res Toxicol. 2022 Aug;35:1312-33.

NEUROTRANSMISSION TARGETS OF PER- AND POLYFLUOROALKYL SUBSTANCE NEUROTOXICITY: MECHANISMS AND POTENTIAL IMPLICATIONS FOR ADVERSE NEUROLOGICAL OUTCOMES.

Brown-Leung JM, Cannon JR.

Per- and polyfluoroalkyl substances (PFAS) are a group of persistent environmental pollutants that are ubiquitously found in the environment and virtually in all living organisms, including humans. PFAS cross the blood-brain barrier and accumulate in the brain. Thus, PFAS are a likely risk for neurotoxicity. Studies that measured PFAS levels in the brains of humans, polar bears, and rats have demonstrated that some areas of the brain accumulate greater amounts of PFAS. Moreover, in humans, there is evidence that PFAS exposure is associated with attention-deficit/hyperactivity disorder (ADHD) in children and an increased cause of death from Parkinson's disease and Alzheimer's disease in elderly populations. Given possible links to neurological disease, critical analyses of possible mechanisms of neurotoxic action are necessary to advance the field. This paper critically reviews studies that investigated potential mechanistic causes for neurotoxicity including (1) a change in neurotransmitter levels, (2) dysfunction of synaptic calcium homeostasis, and (3) alteration of synaptic and neuronal protein expression and function. We found growing evidence that PFAS exposure causes neurotoxicity through the disruption of neurotransmission, particularly the dopamine and glutamate systems, which are implicated in age-related psychiatric illnesses and neurodegenerative diseases. Evaluated research has shown there are highly reproduced increased glutamate levels in the hippocampus and catecholamine levels in the hypothalamus and decreased

dopamine in the whole brain after PFAS exposure. There are significant gaps in the literature relative to the assessment of the nigrostriatal system (striatum and ventral midbrain) among other regions associated with PFAS-associated neurologic dysfunction observed in humans. In conclusion, evidence suggests that PFAS may be neurotoxic and associated with chronic and age-related psychiatric illnesses and neurodegenerative diseases. Thus, it is imperative that future mechanistic studies assess the impact of PFAS and PFAS mixtures on the mechanism of neurotransmission and the consequential functional effects

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Child Adolesc Ment Health. 2022 Sep;27:305-06.

DEBATE: CONDUCT DISORDER AND THE SEGREGATION OF CHILD MENTAL HEALTH.

Hawes DJ.

Should conduct disorder (CD) be classified as a psychiatric diagnosis? The model of CD found in current diagnostic systems is not without its flaws. The criteria for CD have often been criticised for lacking developmental sensitivity with regard to young children, and questions concerning the subtyping of the disorder and its overlap with comorbid conditions remain contentious. Compelling evidence nonetheless supports the view that this 'behaviour disorder' represents a complex mental health issue that belongs in these diagnostic systems. Most importantly, it identifies a group of children and adolescents for whom early intervention appears to be particularly critical and may serve to divert chronic trajectories of poor mental health. This debate has significant implications for science and practice and is addressed here with a particular focus on the Australian context

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Child Adolesc Ment Health. 2022 Sep;27:215-22.

A SELF-HELP VERSION OF THE NEW FOREST PARENTING PROGRAMME FOR PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A QUALITATIVE STUDY OF PARENT VIEWS AND ACCEPTABILITY.

Tarver J, Daley D, Sayal K.

BACKGROUND: Although parent interventions are recommended as a frontline treatment approach for children with attention deficit hyperactivity disorder (ADHD), a number of practical and situational barriers can impact accessibility and availability. Self-help parent interventions offer a potential alternative to therapist-led interventions when barriers prevent access to face-to-face treatment. This qualitative study aims to explore participant views and acceptability of self-help parent interventions.

METHOD: Semi-structured interviews were conducted with parents/carers of 12 children (age 6-10 years) with ADHD who received the self-help version of the New Forest Parenting Programme (NFPP-SH) as part of a randomised controlled trial. Thematic analysis (as proposed by Braun and Clarke) was used to analyse the data.

RESULTS: Overall, participants had favourable views of the self-help intervention but also experienced some barriers to treatment adherence. Six key themes were identified in parent interviews related to parental desire to learn more; acquisition of new skills; the flexibility of the intervention; self-help intervention vs. traditional therapist-led formats; barriers to engagement in the home environment; and need for earlier access to help.

CONCLUSIONS: NFPP-SH was an acceptable intervention for parents. However, some parents may need additional support to overcome barriers associated with completing an intervention at home. Implications for healthcare providers and researchers developing self-help parent interventions for ADHD and child behaviour are discussed

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Child Care Health Dev. 2022 Sep;48:724-35.

WHY YOUNG PEOPLE STOP TAKING THEIR ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATION: A THEMATIC ANALYSIS OF INTERVIEWS WITH YOUNG PEOPLE.

Titheradge D, Godfrey J, Eke H, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that can persist into adulthood. Young people often stop taking ADHD medication during adolescence despite evidence that continuation would be beneficial. Increasingly, young people are restarting medication in early adulthood suggesting that cessation was premature. In this paper we explore the reasons given by young people for discontinuing ADHD medication.

Methods: Qualitative data from the Children and Adolescents with ADHD in Transition between Children's and Adult Services (CATCh-uS) project was analysed to look for reasons for stopping medication. Semi-structured interviews with three groups of young people were analysed using thematic and framework analysis; this included young people prior to transition (n = 21); young people that had successfully transitioned to adult services (n = 22); and young people who left children's services prior to transition but re-entered adult services later (n = 21).

Results: Reasons given by young people for stopping ADHD medication included the following: the perceived balance between benefits and adverse effects of medication; perceptions of ADHD as a childhood or educational disorder; life circumstance of the young person and challenges young people faced in accessing services.

Conclusions: A multidimensional approach is needed to address discontinuation of ADHD medication in order to improve the long-term prospects and quality of life for these young people. Possible approaches include access to non-pharmacological treatments and improved psychoeducation. As many reasons given by young people are not unique to ADHD, these findings are also of relevance to medication adherence in other chronic childhood conditions

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Child Care Health Dev. 2022 Sep;48:852-61.

PARENTS' PRIORITIES AND PREFERENCES FOR TREATMENT OF CHILDREN WITH ADHD: QUALITATIVE INQUIRY IN THE MADDY STUDY.

Lu SV, Leung BMY, Bruton AM, et al.

BACKGROUND: Parents' lived experiences of having a child with ADHD may shape their decision making regarding ADHD treatment options for their child. The aim of this study was to explore parents' experiences of living with a child with ADHD in the family and how their experiences influence their perspectives on treatment preferences and priorities.

METHODS: A phenomenological qualitative design was used. Semistructured interviews were conducted with parents of children with ADHD who were enrolled in a multisite randomized controlled trial. Interviews were transcribed verbatim, and transcripts at each site were double coded. Initial codes were derived directly from the text. Qualitative data were analysed with an inductive approach.

RESULTS: Twenty-three parents were interviewed: eight from Alberta, Canada; eight from Portland, Oregon, USA; and seven from Columbus, Ohio, USA. Among the parents, 69% were married, 86% completed college education and 52% reported household income over $80,000. Among the children, the mean age was 9.6Â years (SD=1.8 years), 78% were boys and 48% were never medicated for their ADHD. Two major themes emerged from the analysis. Theme 1 was 'impact of ADHD on families within and outside the home' with the following subthemes: 'reconfiguring the home life', 'trial-and-error of accommodations at school' and 'responding to social pressures to fit in'. Theme 2 was 'enabling appropriate and accessible treatments for families' with the following subthemes: 'finding the "right fit" with professionals and treatments' and 'factors influencing inequitable access to treatments'.

CONCLUSIONS: Parents described shared experiences and identified similar barriers, preferences and priorities for ADHD treatments regardless of demographic differences by site. Families desired access to family-centred, multimodal approaches to ADHD treatment. Further research is needed to identify the specific structural changes to healthcare, services and policies that will better support this approach

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Child Dev. 2022 Sep;93:e563-e580.

PATHS TO POSTSECONDARY EDUCATION ENROLLMENT AMONG ADOLESCENTS WITH AND WITHOUT CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A LONGITUDINAL ANALYSIS OF SYMPTOM AND ACADEMIC TRAJECTORIES.

Di Lonardo Burr SM, LeFevre JA, Arnold LE, et al.

We examined developmental trajectories of attention-deficit/hyperactivity disorder (ADHD) symptoms, standardized achievement, and school performance for adolescents with and without ADHD who did and did not enroll in postsecondary education (PSE; NÂ =Â 749; 79% boys; 63% White, 17% non-Hispanic Black, 10% Hispanic, and 10% other ethnicities). In a multisite study (recruitment based in New York, North Carolina, Pennsylvania, California, and Quebec), participants were originally enrolled between 1994 and 1998 at ages 7 to 9.9 and followed up through 2012 (M(age) = 25 at final follow-up). Adolescents who eventually enrolled in PSE had less severe symptoms, but differences were modest and trajectories were similar over time. For all adolescents, standardized achievement trajectories declined up to two thirds of a standard deviation from ages 9 to 17. By the end of high school, the average GPA of adolescents with ADHD was three quarters of a point higher for those who eventually enrolled in PSE compared to those who did not. Overall, school performance mattered more than academic achievement for understanding eventual enrollment of adolescents with ADHD

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Child Neuropsychol. 2022 Oct;28:979-96.

MULTIVARIATE BASE RATES OF SCORE ELEVATIONS ON THE BRIEF2 IN CHILDREN WITH ADHD, AUTISM SPECTRUM DISORDER, OR SPECIFIC LEARNING DISORDER WITH IMPAIRMENT IN READING.

Aita SL, Holding EZ, Greene J, et al.

There is a paucity of research examining multivariate base rates (MBRs) of elevated scores in pediatric rating scales of cognition. We present novel MBR information on the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF2) for several clinical groups: Attention-Deficit/Hyperactivity Disorder Combined Presentation (ADHD-C); ADHD Inattentive Presentation (ADHD-I); Autism Spectrum Disorder (ASD); and Specific Learning Disorder with impairment in Reading (SLD-R). Participants included children diagnosed as having ADHD-C (n = 350), ADHD-I (n = 343), ASD (n = 390), or SLD-R (n = 240). Cumulative MBRs (e.g., the % of a sample having one or more elevated scores) were examined for each BRIEF2 form (Parent, Teacher, and Self-Report) and at three T-score cutoffs (T ≥ 60, T ≥ 65, and T ≥ 70). The MBR of obtaining at least one elevated score was common across clinical groups and forms at T ≥ 60 (ADHD-C = 90.5–98.1%; ADHD-I = 83.9–98.7%; ASD = 90.3–96.9%, SLD-R = 60.0–78.4%), T ≥ 65 (ADHD-C = 66.7–97.2%; ADHD-I = 77.5–94.9%; ASD = 77.3–92.7%; SLD-R = 38.5–64.0%), and T ≥ 70 (ADHD-C = 52.4–89.4%; ADHD-I = 64.8–84.2%; ASD = 54.5–83.2%; SLD-R = 26.9–44.1%). MBRs appeared to differ as a function of group (ADHD-C > ADHD-I > ASD > SLD-R) and form (Parent > Teacher > Self-Report) though future research with well-defined samples is needed to investigate this. We provide novel MBR information to enhance clinical interpretation of BRIEF2 data

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Child Neuropsychol. 2022.

LATENT STRUCTURE OF WORKING MEMORY AND EMOTION REGULATION IN PEDIATRIC ADHD.

Leib SI, Miller SA, Chin E.

Working memory is a key cognitive function that is often implicated in ADHD and may represent an underlying cognitive endophenotype of the disorder. Working memory is related to emotion regulation, which is a common area of impairment in children with ADHD. Given the high rate of comorbid diagnoses with ADHD, children with comorbid internalizing, externalizing, and developmental disorders may present with variable working memory profiles and subsequent emotion regulation deficits. This study aimed to adequately characterize the latent structure of working memory impairments and emotional regulation outcomes in a clinical sample of children ages 6ΓÇô16 with ADHD. This study also examined the interplay between the identified working memory/emotion regulation patterns, demographic characteristics, and the role of

comorbid diagnoses. Results highlighted two distinct, invariant, unrestricted classes of working memory/emotion regulation. Class 1 (Average; 62% of the sample) had significantly lower digit-span scores, and generally persevered emotion regulation functioning per parent/teacher report. Class 2 (Emotionally Dysregulated) had average working memory scores, and elevated emotion regulation problems. The working memory indicators had small correlations with parents (and not teacher) measures of emotion regulation. Finally, latent class membership did not differ by comorbid diagnosis, age, gender, or verbal IQ. Findings elucidate heterogeneity in common domains affected by ADHD and suggest that this heterogeneity may not be due to demographic/comorbidity factors. The role of varying information reports is discussed, and potential assessment and treatment implications are highlighted

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Child Neuropsychol. 2022.

DISSOCIABLE EFFECTS OF POSITIVE FEEDBACK ON THE CAPTURE AND INHIBITION OF IMPULSIVE BEHAVIOR IN ADOLESCENTS WITH ADHD VERSUS TYPICALLY DEVELOPING ADOLESCENTS.

Grandjean A, Suarez I, Da Fonseca D, et al.

The present study investigated how enhancing motivation by delivering positive feedback (a smiley) after a successful trial could affect interference control in adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and in their typically developing (TD) peers. By using a Simon task within the theoretical framework of the ΓÇ£activation-suppressionΓÇØ model, we were able to separately investigate the expression and the inhibition of impulsive motor behavior. The experiment included 19 adolescents with ADHD and 20 TD adolescents in order to explore whether data found in adolescents with ADHD were similar to those found in TD adolescents. Participants performed the Simon task in two conditions: a condition with feedback delivered after each successful trial and a condition with no feedback. The main findings were that increasing motivation by delivering positive feedback increased impulsive response in both groups of adolescents. It also improved the efficiency of impulsive motor action inhibition in adolescents with ADHD but deteriorated it in TD adolescents. We suggest that 1/increased motivation could lead adolescents to favor fast responses even if incorrect, and 2/the differential effect of feedback on the selective suppression of impulsive motor action in both groups could be due to different baseline DA levels

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Child Psychiatry Hum Dev. 2022 Aug;53:786-96.

EFFECTS OF COMORBID DEVELOPMENTAL COORDINATION DISORDER AND SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER ON PHYSICAL ACTIVITY IN CHILDREN AGED 4–5 YEARS.

James ME, King-Dowling S, Graham JD, et al.

Developmental coordination disorder (DCD) is often comorbid with attention-deficit/hyperactivity disorder (ADHD). While children with DCD engage in less moderate-to-vigorous physical activity (MVPA) compared to typically developing (TD) children, research pertaining to how ADHD affects this relationship is limited. We investigated the effect of ADHD on MVPA among children at risk for DCD (DCDr). 507 children aged 4–5 years (DCDr = 233, TD = 274) participated. Motor skills were assessed using the Movement Assessment Battery for Children-2nd edition (DCDr; = 16th percentile), ADHD symptoms were assessed using the Child Behaviour Checklist, and Actigraph accelerometers measured MVPA over seven days. DCD did not negatively affect MVPA, however, after adjusting for ADHD symptoms, the effect of DCD became significant and was driven by symptoms of inattention. Symptoms of ADHD may be suppressing the negative effects of DCD on MVPA, highlighting the importance of assessing and controlling for ADHD symptoms in this population

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Clin Neuropsychol. 2022 Aug;36:1533-72.

THE STRUCTURE OF POST-CONCUSSION SYMPTOMS IN ADOLESCENT STUDENT ATHLETES: CONFIRMATORY FACTOR ANALYSIS AND MEASUREMENT INVARIANCE.

Karr JE, Iverson GL.

Objective: This study examined factor models for the Post-Concussion Symptom Scale (PCSS) at baseline and after suspected sport-related concussion, and measurement invariance from pre-injury to post-injury assessments and across age, gender, and health history groups (e.g., attention-deficit/hyperactivity disorder, psychiatric history).

Methods: Adolescent student athletes (ages 13-18) completed a baseline PCSS (n=39,015; 54.3% boys) and a subsample within 21 days of a suspected concussion (n=1,554; 56.7% boys) completed a post-injury PCSS. Five models were evaluated for fit and invariance.

Results: Confirmatory factor analyses showed good baseline and post-injury model fit for a previously supported four-factor model (i.e., cognitive-sensory, sleep-arousal, vestibular-somatic, and affective), an alternative four-factor model (i.e., cognitive, sleep-arousal, physical, and affective), and an incomplete bifactor model with vestibular-somatic and affective specific factors, along with partial invariance from pre-injury to post-injury assessments. Partial-to-full invariance was established for each model at baseline across demographic and health history groups.

Conclusions: Results showed empirical and conceptual support for both PCSS subscales (i.e., cognitive, sleep-arousal, physical, and affective) and a total score for use in pre-injury to post-injury assessments and across demographic and health history groups at baseline. Future normative data, stratified by demographics and health history, could provide more precise symptom assessments for concussion management

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Clin Neurophysiol. 2022;137:e42.

P 48 TDCS IN THE DAILY ROUTINE ΓÇô EXPERIENCES ON FEASIBILITY AND INTEGRABILITY OF HOME-BASED TDCS FOR CHILDREN AND ADOLESCENTS SUFFERING FROM ADHD.

Schlechter F, Wrachtrup-Calzado I, Siemann J, et al.

Although tDCS is receiving more and more attention in research, there are still few studies addressing a home-based setting of tDCS sessions. In our clinical trial we are investigating not only the potential beneficial effects of anodal multi-channel tDCS over bilateral dlPFC applied to children and adolescents suffering from ADHD on related behavioral symptoms as well as on relevant neuropsychological and neurophysiological measures, but also, we are examining whether home-based tDCS is a feasible and safe tool for the participants and their caregivers. The study is conducted within the framework of the Horizon2020 project ΓÇ£Stimulation in Pediatrics ΓÇØ. The home-based use of tDCS takes advantage of several features such as the device being easily portable and the well reported safety record. Furthermore, there is strong empirical evidence that tDCS should be applied in multiple sessions in order to increase its effects. Consequently, the ability to perform tDCS independently at home also saves resources on the part of the clinic, as well as frequent trips to the clinic for the participants. The resulting reduced time effort, in addition to the low side effects, may have a beneficial effect on patient compliance. Based on the empirical evidence and guidelines for the implementation of tDCS as home treatment we conceptualized and currently perform home-based tDCS for children and adolescents with ADHD. This includes several procedures such as the selection of an appropriate patient sample in terms of resources and potential compliance, detailed theoretical instruction as well as practical training in the application of the device, safety questions before each session, real-time remote monitoring incl. on-call services, and recording of possible side effects after each session. In addition, on the technical side, it is ensured that no misuse of the device can take place, e.g. by allowing sessions to be (un-)blocked by the responsible investigator. Besides a good quality of stimulation parameters is achieved through individual MRI-based electrode montages and a user-friendly software incl. instructions and integrated impedance checks. Furthermore the training of parents and children in the use of the device will be evaluated. We also ask about their concerns, expectations, satisfaction and the usability regarding home-based tDCS before and after its application. We would like to share our experiences (clinician's and participant's view) with the home-based use of tDCS in the context of the study presented above. The focus is to give recommendations for a safe, user-friendly and optimized home-based application of tDCS and to discuss its feasibility. The results of the study are contributing to a possible integration of tDCS as an

innovative, safe and cost-effective treatment approach in the daily routine of children and adolescents with ADHD

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Clin Psychopharmacol Neurosci. 2022;20:514-25.

THE LOUDNESS DEPENDENCE OF AUDITORY EVOKED POTENTIALS IS ASSOCIATED WITH THE SYMPTOM SEVERITY AND TREATMENT IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Park EJ, Park YM, Lee SH, et al.

Objective: The loudness dependence of the auditory evoked potential (LDAEP) is associated with central serotonergic neurotransmission. Recent studies have proposed that LDAEP is also influenced by dopaminergic activity. Evidence shows attention deficit hyperactivity disorder (ADHD) symptoms are associated with dopamine dysfunction. This study aimed to evaluate the relation between ADHD symptoms and LDAEP, as well as medication-mediated changes of LDAEP.

Methods: A total of 38 male children (6-12 years old) with ADHD were analyzed in this study. Symptom severity was assessed using the ADHD rating scale (ARS) and the continuous performance test. To determine LDAEP, the auditory event-related potential was evaluated before medication. Changes in LDAEP were measured after 12 weeks of treatment with methylphenidate.

Results: The subjects had a mean age of 9.24 -¦ 1.74 years with an average IQ of 109.4 -¦ 13.8. Before pharmacological treatment with methylphenidate, LDAEP was positively associated with the ARS score after adjusting for age and IQ (r = 0.592, p = 0.005). LDAEP was correlated with inattention (r = 0.522, p = 0.015) and hyperactivity-impulsivity (r = 0.6, p = 0.004). However, the LDAEP of 15 subjects decreased following methylphenidate treatment (Z = 1.988, p = 0.047).

Conclusion: In boys with ADHD, LDAEP appears to be associated with symptom severity. LDAEP showed a significant association with impulsivity and inattention. Importantly, LDAEP was shown to decrease after drug treatment. Our findings support the utility of LDAEP as a noninvasive and clinically useful method to assess symptom severity in children with ADHD

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Clin Ther. 2022.

PEDIATRIC OFF-LABEL ANTIPSYCHOTIC USE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lee H, Zhang C, Rose R, et al.

Purpose: Off-label antipsychotic use for behavioral symptoms in pediatric attention-deficit/hyperactivity disorder (ADHD) poses safety concerns, and evidence to support such use is limited. This study aims to investigate the risk of off-label antipsychotic use associated with comorbid disruptive behavior disorder (DBD) among a cohort of youth with ADHD.

Methods: A cohort study was conducted using IQVIA PharMetrics Plus for Academics data from 2007 to 2020. Youth 5 to 15 years of age at the index ADHD visit were included in the cohort. The index ADHD visit meets at least 1 of the following criteria: (1) 1 inpatient ADHD visit, (2) 2 outpatient ADHD visits within 90 days, or (3) an ADHD medication prescription fill within 30 days of an outpatient ADHD visit. We excluded youth who had a diagnosis of DBD or a US Food and Drug Administration (FDA) approved indication for antipsychotics at baseline. Youth were followed up until antipsychotic initiation or were censored at a loss of coverage, receipt of an FDA-indicated diagnosis, or end of the study. A Cox proportional hazards regression model with DBD as a time-varying covariate estimated the hazard of antipsychotic use after the index ADHD visit.

Findings: Of 41,098 youth with ADHD who met the study criteria, 4557 were diagnosed with DBD during follow-up. The incidence of antipsychotic initiation was 19.6 (95% CI, 18.7- 20.5) per 1000 person-years. After adjustment for baseline covariates, the hazard ratio of antipsychotic initiation associated with DBD was 4.64 (95% CI, 4.15-5.18).

Implications: Antipsychotic use among youth with ADHD is more likely in the presence of DBD, suggesting that an off-label use is for behavior problems

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CNS Drugs. 2022 Aug;36:897-915.

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder.

Nasser A, Hull JT, Chaturvedi SA, et al.

BACKGROUND AND OBJECTIVE: Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder that typically begins in childhood and often persists into adulthood. Recent phase III trials have demonstrated the efficacy and safety of viloxazine extended-release capsules (viloxazine ER; Qelbree(®)) in pediatrics (6-17 years of age). The aim of this study was to evaluate the efficacy and safety of viloxazine ER in adults with attention-deficit/hyperactivity disorder.

METHODS: This was a phase III, randomized, double-blind, placebo-controlled, two-arm trial in adults (18-65 years of age) with attention-deficit/hyperactivity disorder. Eligible subjects were randomized 1:1 to viloxazine ER (flexible dose of 200-600 mg/day) or matched placebo. The primary efficacy endpoint was the change from baseline at end of study (week 6) in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score. The key secondary endpoint was the change from baseline at end of study in the Clinical Global Impressions-Severity of Illness (CGI-S) score. Additional secondary outcome measures included the AISRS Inattention and Hyperactivity/Impulsivity subscales, the Behavior Rating Inventory of Executive Function-Adult (BRIEF-A), the Generalized Anxiety Disorder-7 Item (GAD-7), and the Clinical Global Impressions-Improvement (CGI-I); each was analyzed at end of study. Responder rates on CGI scales and the AISRS were also assessed.

RESULTS: A total of 374 subjects were randomized. At end of study, the mean viloxazine ER dose was 504 mg. The reduction in the change from baseline at end of study AISRS total score (least-square means Â± standard error) was significantly greater in subjects treated with viloxazine ER (-15.5 ± 0.91) compared with placebo (-11.7 ± 0.90), p = 0.0040. The reduction in the CGI-S score was also significantly greater in subjects treated with viloxazine ER (-1.4 ± 0.10) compared with placebo (-1.0 Â± 0.10), p = 0.0023. The viloxazine ER group demonstrated significantly greater improvements in the AISRS Inattention (p = 0.0015) and Hyperactivity/Impulsivity (p = 0.0380) subscales, the CGI-I (p = 0.0076), and the BRIEF-A Global Executive Composite (p = 0.0468) and Metacognition Index (p = 0.0100). Analysis of categorical secondary endpoints revealed that the viloxazine ER group had a significantly higher AISRS 30% response rate compared with placebo (p = 0.0395); all other comparisons were not significant. Many treatment effects (including the primary and key secondary endpoints) were significant by week 2. The most common treatment-related adverse events that occurred in 5% of subjects receiving viloxazine ER were insomnia (14.8%), fatigue (11.6%), nausea (10.1%), decreased appetite (10.1%), dry mouth (9.0%), and headache (9.0%). Viloxazine ER was well tolerated, with a 9.0% discontinuation rate due to adverse events compared with 4.9% in the placebo group.

CONCLUSIONS: Treatment with viloxazine ER resulted in a statistically significant improvement in primary and key secondary endpoints, indicating improvements in attention-deficit/hyperactivity disorder symptomology, executive function, and overall clinical illness severity in adults. Viloxazine ER was well tolerated at the tested doses in adults with attention-deficit/hyperactivity disorder.

CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT04016779

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Communication Disorders Quarterly. 2022.

Development of Structural and Pragmatic Language Skills in Children With Attention-Deficit/Hyperactivity Disorder.

Vassiliu C, Mouzaki A, Antoniou F, et al.

The few reports on the language skills of children with attention-deficit/hyperactivity disorder (ADHD) offer conflicting evidence on whether they face significant challenges, and if so, whether these challenges are

present in all aspects of language. Here, we investigated a sample of Greek-speaking children with ADHD (n = 29) using a structural language (vocabulary, grammar) and a pragmatic language assessment. To ascertain the extent of strengths and weaknesses, we compared the performance of children with ADHD to typically developing (TD) peers (n = 29) and also to children with developmental language disorder (DLD; n = 25), who face challenges particularly in structural language. As regards structural language, ADHD children performed significantly lower than their TD peers but significantly higher than the DLD group. In pragmatics, ADHD children performed numerically lower than any other group, but differences did not reach statistical significance. Children with ADHD face difficulties with language skills and especially with structural language. Sophisticated linguistic assessment is crucial, as it facilitates the identification of children with different challenges by measuring performances on distinct components. Language difficulties in ADHD should not be overlooked but must be evaluated thoroughly for more effective intervention planning

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Crim Behav Ment Health. 2022 Jun;32:159-74.

THE ALL-WALES FORENSIC ADOLESCENT CONSULTATION AND TREATMENT SERVICE (FACTS): A 5-YEAR REFERRAL COHORT STUDY.

Kalebic N, Argent S, Austin H, et al.

BACKGROUND: FACTS is a Wales-wide mental health service for 10-17-year-olds with needs beyond the remit of mainstream child and adolescent mental health services (CAMHS). As a purely consultation-liaison service, it differs from other UK services in the field.

AIMS: To describe a complete cohort of referrals to FACTS 2013-2017 with service exit by June 2018.

METHODS: Clinical, social and offending data were extracted from FACTS records.

RESULTS: 80 young people completed a FACTS episode, averaging nearly a year (309 days; range 13-859 days). Mostly boys (65, 81%) of mean age 15.4 years (range 9-18), two-thirds (n = 53) had three or more referral reasons, one invariably being threatened/actual harm to others; only half were criminal-justice involved. Half (41, 51%) were committing sexually harmful acts. Half were self-harming (41, 51%). All but seven had had at least one adverse childhood experience (ACE), nearly half (35, 44%) four or more. Nevertheless, post-traumatic stress disorder (PTSD) was rarely diagnosed (7, 9%); just over one-quarter (23, 29%) had no diagnosis at all. Correspondence analyses endorsed two distinct Attention deficit hyperactivity disorder groups, distinguished by presence/absence of evidenced brain damage or dysfunction. Suicide-related behaviours clustered with the other diagnoses, flashbacks and psychotic symptoms with no diagnosis. Change in home circumstances during a FACTS episode was slight.

CONCLUSIONS: The complexity of presenting problems and service involvement evidences need for FACTS. The extent of persistently harmful sexual behaviours is a novel finding, suggesting need for more expert input for this at other service levels. Rarity of PTSD diagnoses was surprising given the extent of ACEs. This raises concerns that services focus on disorder signs rather than the child's inner life. Given the extent of problems, minimal change may be a positive outcome - especially when remaining in the community. Further development of this service should include explicit case-by-case goals and indicative outcome markers

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Curr Environ Health Rep. 2022 Sep;9:406-22.

PARENTAL OCCUPATIONAL EXPOSURE AND NEURODEVELOPMENTAL DISORDERS IN OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Bemanalizadeh M, Khoshhali M, Goli P, et al.

PURPOSE OF REVIEW: Parental occupational exposures might be associated with neurodevelopmental disorders (NDDs) in offspring. We aimed to conduct a systematic review and meta-analysis to summarize and synthesize the current literature and to estimate the pooled magnitude of the underlying association(s) between parental occupational exposures and subsequent risk of NDDs.

RECENT FINDINGS: In the meta-analysis of 20 included studies, significant associations were found between parental occupational exposure to pesticides or solvents and the risk of attention deficit hyperactivity

disorder in offspring. Prenatal occupational exposure to pesticides was significantly associated with motor development or cognition disorders in children. Furthermore, some evidence showed that metals might have a role in the development of autism spectrum disorders. Further studies need to identify the level of parental occupational exposures that can be significantly associated with NDDs. Moreover, utilizing standardized outcome and exposure scales is recommended to incorporate paternal, maternal, and parental as well as both prenatal and postnatal exposure in future studies

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Curr Top Behav Neurosci. 2022;57:199-220.

SLEEP IN INDIVIDUALS WITH ADHD: PREVALENCE, IMPACTS, CAUSES, AND TREATMENTS.

Sciberras E.

Sleep problems are common in children and adolescents with ADHD. This chapter covers the basics of sleep and the prevalence and types of sleep problems experienced by children and adolescents with ADHD. The impacts of sleep problems on the day-to-day lives of children with ADHD and their families are covered including impacts on child daily functioning and cognition, as well as family well-being. There is no one cause of sleep problems in children with ADHD with both biological and environmental factors implicated. There are a small number of randomized controlled trials that support the efficacy of treating sleep problems in children with ADHD using behavioral strategies. A small number of studies also have found improvements in sleep onset delay in children with ADHD following treatment with melatonin. Little is known about how to best support adolescents and adults with ADHD with sleep, although a small emerging literature largely in adults with ADHD suggests that bright light therapies could potentially be helpful given the extent of circadian involvement in the sleep problems experienced by individuals with ADHD. This chapter ends with consideration of future research directions largely related to approaches to supporting individuals with ADHD and sleep difficulties

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Curr Top Behav Neurosci. 2022;57:1-18.

ADHD IN CHILDREN AND ADULTS: DIAGNOSIS AND PROGNOSIS.

Leffa DT, Caye A, Rohde LA.

Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent neuropsychiatric disorder associated with significant impairment and distress throughout the lifespan. Recent investigations have shed light on different aspects regarding the trajectory of ADHD, including reports on risk factors in childhood, that are associated with remission or persistence in adulthood. Despite significant advances in our understanding of the pathophysiology of the disorder, the diagnosis of ADHD remains strictly clinical and is based on behavioral symptoms of inattention, impulsivity, and hyperactivity. In this chapter we review the diagnostic process of ADHD, discuss the clinical presentation of the disorder across the lifespan, and examine patterns of comorbidity and longitudinal predictor of outcomes

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Curr Top Behav Neurosci. 2022;57:19-50.

CURRENT PHARMACOLOGICAL TREATMENTS FOR ADHD.

Groom MJ, Cortese S.

Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition associated with impaired function and increased risk of poor outcomes in children, young people and adults with the condition. Currently approved pharmacological treatments for ADHD include a range of stimulant (methylphenidate, amphetamine) and nonstimulant (atomoxetine, guanfacine, clonidine) medications. All have been shown to be effective in treating the symptoms of ADHD and improving other functional outcomes including quality of life, academic performance, rates of accidents and injuries, and do not appear to be associated with significant adverse outcomes or side effects. In this chapter, we review medications for ADHD by summarising the mechanisms of action of each of the two main classes of compounds (stimulants

and nonstimulants), the formulations of the most commonly prescribed medications within each class, their efficacy in treating ADHD symptoms and other outcomes, and other factors that influence treatment decisions including side effects and tolerability, comorbidities and medical history. We conclude with a summary of the treatment decisions made by clinicians and suggest some next steps for research. Further research is needed to understand the mechanisms of action of these medications and how exactly they improve symptoms, and to examine their effects on commonly occurring comorbidities

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Curr Top Med Chem. 2022;22:1236-49.

PERSONALIZATION OF PHARMACOLOGICAL TREATMENTS FOR ADHD: WHY IT IS ADVISABLE AND POSSIBLE OPTIONS TO ACHIEVE IT.

Herrera-Morales WV, RamÃ-rez-Lugo L, Cauich-Kumul R, et al.

Attention-deficit hyperactivity disorder is a neurodevelopmental disorder diagnosed primarily in children, although it is also present in adults. Patients present inattention, impulsivity, and hyperactivity symptoms that create difficulties in their daily lives. Pharmacological treatment with stimulants or non-stimulants is used most commonly to reduce ADHD symptoms. Although generally effective and safe, pharmacological treatments have different effects among patients, including lack of response and adverse reactions. The reasons for these differences are not fully understood, but they may derive from the highly diverse etiology of ADHD. Strategies to guide optimal pharmacological treatment selection based on individual patients' physiological markers are being developed. In this review, we describe the main pharmacological ADHD treatments used and their main drawbacks. We present alternatives under study that would allow the customization of pharmacological treatments to overcome these drawbacks and achieve more reliable improvement of ADHD symptoms

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Current Opinion in Psychiatry. 2022;35:345-51.

CHILDREN WITH NEURODEVELOPMENTAL DISORDERS: HOW DO THEY SLEEP?

Belli A, Breda M, Di Maggio C, et al.

Purpose of reviewIn this review we summarized the available evidence on sleep disorders in children with neurodevelopmental disorders (NDDs) in particular: intellectual disability (including some genetic conditions such as Prader-Willi Syndrome, Smith-Magenis Syndrome), Autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), Developmental Coordination Disorder, language disorders, and specific learning disorders.Recent findingsChildren with NDDs frequently suffer from sleep disturbances, with a higher prevalence than that of the general pediatric population.SummaryThese problems tend to be chronic and may cause additional cognitive and behavioral difficulties, often affecting the whole family's well-being. Sleep behaviors are also related to other important developmental skills, such as attention and listening. Investigating sleep disorders in children with NDDs is therefore crucial in clinical practice. For a systematic approach in clinical practice, we propose the use of a short and easy to remember sleep screening tool

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Dev Med Child Neurol. 2022 Sep;64:1077-84.

DELIVERING PAEDIATRIC PRECISION MEDICINE: GENOMIC AND ENVIRONMENTAL CONSIDERATIONS ALONG THE CAUSAL PATHWAY OF CHILDHOOD NEURODEVELOPMENTAL DISORDERS.

Woolfenden S, Farrar MA, Eapen V, et al.

Precision medicine refers to treatments that are targeted to an individual's unique characteristics. Precision medicine for neurodevelopmental disorders (such as cerebral palsy, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, Tourette syndrome, and autism spectrum disorder) in children has predominantly focused on advances in genomic sequencing technologies to increase our ability to identify single gene mutations, diagnose a multitude of rare neurodevelopmental disorders, and gain insights into pathogenesis. Although targeting specific gene variants with high penetrance will help some children with

rare disease, this approach will not help most children with neurodevelopmental disorders. A 'pathway' driven approach targeting the cumulative influence of psychosocial, epigenetic, or cellular factors is likely to be more effective. To optimize the therapeutic potential of precision medicine, we present a biopsychosocial integrated framework to examine the 'gene-environment neuroscience interaction'. Such an approach would be supported through harnessing the power of big data, transdiagnostic assessment, impact and implementation evaluation, and a bench-to-bedside scientific discovery agenda with ongoing clinician and patient engagement. WHAT THIS PAPER ADDS: Precision medicine has predominantly focused on genetic risk factors. The impact of environmental risk factors, particularly inflammatory, metabolic, and psychosocial risks, is understudied. A holistic biopsychosocial model of neurodevelopmental disorder causal pathways is presented. The model will provide precision medicine across the full spectrum of neurodevelopmental disorders

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Dev Med Child Neurol. 2022 Sep;64:1156-67.

MOBILITY, EDUCATIONAL, AND SOCIAL PERFORMANCE OF CHILDREN WITH LEARNING PROBLEMS IN TAIWAN: A 3-YEAR FOLLOW-UP STUDY.

Lin LC, Liou TH, Chi WC, et al.

AIM: This study evaluated the performance of children with learning problems in Taiwan by using the Taiwan Data Bank of Persons with Disability.

METHOD: We included 3854 children (2343 males, 1511 females; mean [SD] age 9y 11mo [2y 4mo]) with specific learning disorder (SLD), attention-deficit/hyperactivity disorder (ADHD), autism, epilepsy, or intellectual disabilities for analysis. We used the Functioning Scale of the Disability Evaluation System-Child version to investigate performance at follow-up for at least 3 years.

RESULTS: These participants demonstrated improvement across all the domains of the International Classification of Functioning, Health, and Disability including for mobility, learning, social participation, and daily living. The children with SLD (p=0.3) and epilepsy (p=0.442) did not demonstrate significant improvement in learning, whereas those with ADHD (p<0.001), autism (p<0.001), and intellectual disabilities (p<0.001) did. The children with epilepsy displayed the most impairment and least improvement.

INTERPRETATION: This cross-diagnostic study of learning problems indicated the children with autism or ADHD received more structural education. However, education strategies for those with SLD or epilepsy required improvement. Finally, SLD is possibly underdiagnosed in children, and children with epilepsy are affected in multiple aspects.

WHAT THIS PAPER ADDS: Specific learning disorder (SLD), ADHD, autism, epilepsy, and intellectual disability can cause learning problems in children. Children with ADHD and autism showed more improvement in academic performance. SLD has been neglected and underdiagnosed, resulting in poor improvement. Children with epilepsy have multiple impairments and exhibited minimal improvement

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Dev Psychopathol. 2022 Aug;34:841-53.

EXAMINATION OF DEVELOPMENTAL PATHWAYS FROM PRESCHOOL TEMPERAMENT TO EARLY ADOLESCENT ADHD SYMPTOMS THROUGH INITIAL RESPONSIVENESS TO REWARD.

Bunford N, Kujawa A, Dyson M, et al.

To identify sources of phenotypic heterogeneity in attention-deficit/hyperactivity disorder (ADHD) accounting for diversity in developmental/ pathogenic pathways, we examined, in a large sample of youth (N = 354), (a) associations between observed temperamental emotionality at age 3, an electrocortical index (i.e., reward positivity [RewP]) of initial responsiveness to reward at age 9, and ADHD symptoms at age 12, and (b) whether the association between emotionality and ADHD symptoms is mediated by initial responsiveness to reward. Bivariate analyses indicated greater positive emotionality (PE) was associated with enhanced RewP, lower age-9ADHD and lower age-12 inattention (IA). Negative emotionality (NE) was not associated with RewP or ADHD. Mediation analyses revealed the association between PE and hyperactivity/impulsivity (H/I) was mediated by RewP; enhanced RewP was associated with greater H/I. Greater PE was associated with

enhanced RewP at a trend level. These effects held accounting for age-9 ADHD, age-12 IA and age-12 oppositional defiant and conduct disorder symptoms. As such, preschool emotionality is associated with adolescent ADHD-H/I symptoms through late childhood initial responsiveness to reward. These relations indicate that individual differences in emotionality and reward responsiveness may be informative for personalizing ADHD interventions

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Developmental Medicine & Child Neurology. 2022 Aug;64:944-49.

WHO BENEFITS FROM DIAGNOSTIC LABELS FOR DEVELOPMENTAL DISORDERS?

Werkhoven S, Anderson JH, Robeyns IAM.

The number of diagnoses of developmental disorders is on the rise and the use of labels for developmental disorders, such as attention-deficit/hyperactivity disorder and autism spectrum disorder, is widening. Diagnostic labels can play an important role in helping those who display atypical behaviour and their caregivers to cope with associated challenges and, possibly, to get treatment. But these labels are increasingly contested and associated with a variety of harmful effects. In this paper, we analyze the role diagnostic labels can play in four different contexts (scientific, therapeutic, social, and administrative) and identify what various stakeholders stand to gain or lose with continued, expanded, or abolished use of those labels. Our analysis reveals labels serve different purposes in each of these contexts, benefitting different stakeholders. Any overall evaluation, critique, or defence of labels needs to consider the interests of all stakeholders in these contexts

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Disabil Rehabil Assist Technol. 2022 Oct;17:738-46.

A MAP OF ASSISTIVE TECHNOLOGY EDUCATIVE INSTRUMENTS IN NEURODEVELOPMENTAL DISORDERS.

Pontikas CM, Tsoukalas E, Serdari A.

PURPOSE: The use of assistive technology in mental health has gained an increased interest over the last decades. A growing number of studies have investigated diverse applications of technological interventions for rehabilitation of children with neurodevelopmental disorders. This article presents a map of the technological devises applied as therapeutic instruments.

METHODS: The research question of this review was which technological applications could be referred as an educational instrument for the management of children with autism spectrum disorders (ASDs), intellectual disability and attention deficit disorder. The articles included in this review were collected after a structured literature search in electronic databases using keywords such as "Assistive Technology", "technology devices", "robots", "Autism Disorder", "Intellectual Disabilities" and "Mental Retardation".

RESULTS: Assistive technology with the most up-to-date devices and applications helps children with intellectual disability and ASDs enhance cognitive skills and improve challenging behaviour, social communication and academic performance. Different technological tools are used to foster attention span and improve time management skills in children with attention deficit syndrome.

CONCLUSION: It is important that therapists choose the instrument that will offer the best approach towards the goal that is set. Future research could provide evidence based data, evaluating each specific methodology and tailoring each therapeutic approach specifically to a case.

IMPLICATIONS FOR REHABILITATION Technology creates environments in which children could practice and learn in a safer, more predictable and pleasant manner.Assistive Technologies provide the opportunity for better acquisition of selfhelp skills and the power of social interaction for individuals with disabilities.By mapping out the wide array of Assistive Technology that is available today, future applications for rehabilitation of children with neurodevelopmental disorders could help extend therapeutic strategies out of the clinical and school settings and into the home, thereby incorporating the family and emphasizing personalization.Future studies could develop a model for the choice and use of each tool, tailoring each therapeutic approach specifically to each case

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Drug Topics. 2021;165:29.
NEW NONSTIMULANT MEDICATION IS APPROVED FOR ADHD IN CHILDREN.
Wheeler K.

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Drug Topics. 2022;166:22.
QUICK LOOK: THE NEWEST DRUGS FOR ADHD.
Levine L.

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Encephale. 2022.
RETROSPECTIVE DIAGNOSIS OF CHILDHOOD ADHD USING THE WENDER UTAH RATING SCALE.
Caci H, Didier C, Wynchank D.
Objective: An external validation of the Wender Utah Rating Scale (WURS) against a clinical assessment is lacking, especially for French-speaking populations.
Method: Participants completed three subsets of the WURS-61 and were assessed for ADHD using the DIVA 2.0 semi-structured interview. Exploratory factor analyses were performed. Logistic regression models and Receiver-Operating Curves were used to determine the cut-off scores that predicted childhood ADHD with best accuracy.
Results: One hundred three adults were included. Three factors were extracted for the WURS-25 and WURS-K, and four for the WURS-29. Cut-off scores are 44, 24 and 42, respectively. When considering DSM-5 rather than DSM-IV criteria, these values changed to 44, 36 and 44, respectively. More than 83% of the participants had been correctly classified.
Conclusion: All three subsets of the WURS-61 retrospectively predict the presence of ADHD in childhood. This result might prove to be useful in screening and research procedures

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Epilepsy Behav. 2022;135.
INTERVENTIONS FOR ADHD IN CHILDREN & ADOLESCENTS WITH EPILEPSY: A REVIEW AND DECISION TREE TO GUIDE CLINICIANS.
Ono KE, Bearden DJ, Lee SM, et al.
Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common pediatric epilepsy comorbidities. Treating ADHD in the context of epilepsy can be overwhelming for parents and clinicians. Current frontline treatment for ADHD is stimulant medication. However, some parents of pediatric patients with epilepsy have concerns about adding additional medication to their child's epilepsy regimen and/or about adverse effects of stimulant medication. Non-medication ADHD treatments including psychosocial interventions and ketogenic diet have also shown success in improving ADHD symptoms. Our focused review provides an easy-to-use guide for clinicians on ADHD interventions and combinations of interventions for pediatric patients with epilepsy and ADHD. Our guide includes information from 8 electronic databases for peer-reviewed, English language studies of psychosocial treatments for youth with epilepsy and ADHD. One hundred eight studies were selected based on inclusion criteria (21 systematic reviews, 12 meta-analyses, 8 literature reviews, 6 population surveys, 31 clinical trials, 20 cross-sectional studies, and 10 retrospective reviews). Results indicated that stimulant medication is a frontline treatment for ADHD symptoms in youth with epilepsy, with important caveats and alternatives

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Eur Arch Paediatr Dent. 2022 Aug;23:537-46.

PERIODONTAL OUTCOMES OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Drumond VZ, Andrade AA, de Arruda JAA, et al.

Background: This systematic review and meta-analysis aimed to answer the following question: Are children and adolescents with attention deficit hyperactivity disorder (ADHD) more likely to have gingival or periodontal disease-related outcomes than their non-ADHD peers?

Methods: Searches were conducted in the following databases: Embase, Scopus, Web of Science, and PubMed. Google Scholar and OpenGrey were also verified. Observational studies were included in which children and adolescents with ADHD were compared with their healthy peers in terms of gingival and/or periodontal endpoints. Bias appraisal was performed using the Joann Briggs tool for case-control and cross-sectional studies. Meta-analysis was performed using R language. Results are reported as mean difference (MD) and odds ratio (OR). Statistical analyses were performed in RStudio.

Results: A total of 149 records were identified in the searches. Seven studies were included. The meta-analysis showed that children and adolescents with ADHD had a higher mean gingival bleeding index (percentage) than their non-ADHD peers (MD = 11.25; CI = 0.08-22.41; I2 = 73%). There was no difference between groups for plaque index (MD = 4.87; CI = - 2.56 to 12.30; I2 = 63%) and gingivitis (OR = 1.42; CI = 0.22-9.21; I2 = 76%). Regarding the assessment of risk of bias, the major issue found in the articles was the absence of analyses for the control of confounding factors.

Conclusion: Children and adolescents with ADHD had more gingival bleeding than their non-ADHD peers, but no difference regarding plaque or gingivitis was detected between groups.

Clinical registration: CRD42021258404

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Eur Child Adolesc Psychiatry. 2022 Jul;31:1-12.

RISK AND PROTECTIVE FACTORS RELATED TO CHILDREN'S SYMPTOMS OF EMOTIONAL DIFFICULTIES AND HYPERACTIVITY/INATTENTION DURING THE COVID-19-RELATED LOCKDOWN IN FRANCE: RESULTS FROM A COMMUNITY SAMPLE.

Moulin F, El-Aarbaoui T, Bustamante JJH, et al.

OBJECTIVE: The COVID-19 epidemic has spread worldwide since December 2019. To contain it, preventive measures including social distancing, economic shutdown, and school closures were introduced, carrying the risk of mental health burden in adults and children. Although the knowledge base regarding children's response to trauma and adverse events in general has broadened, descriptions of their mental health during epidemics remain scarce. In particular, the role of family socioeconomic characteristics and parental mental health are poorly understood.

METHODS: We assessed the correlates of children's emotional difficulties and symptoms of hyperactivity/inattention during the COVID-19 lockdown in a French community-based sample. Data came from 432 community-based parents (27-46 years, TEMPO cohort) and their children (mean age 6.8± 4.1) interviewed online. Children's symptoms of emotional difficulties and hyperactivity/inattention were assessed using the parent-reported Strengths and Difficulties Questionnaire during the 5th week of home confinement. Family socioeconomic characteristics and parental mental health and substance use were assessed weekly during the first 5 weeks of home confinement. Data were analyzed using logistic regression models.

RESULTS: 7.1% of children presented symptoms of emotional difficulties and 24.7% symptoms of hyperactivity/inattention. Family financial difficulties and parental symptoms of anxiety and depression, as well as children's sleeping difficulties and screen time, were associated with the presence of psychological difficulties.

CONCLUSION: Children's emotional and behavioural difficulties are associated with parental mental health and socioeconomic difficulties. In the unprecedented situation of the COVID-19 epidemic, parents and professionals involved in caring for children should pay special attention to their mental health needs

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Eur Child Adolesc Psychiatry. 2022 Aug;31:1-11.

CHARACTERIZING THE HETEROGENEOUS COURSE OF INATTENTION AND HYPERACTIVITY-IMPULSIVITY FROM CHILDHOOD TO YOUNG ADULTHOOD.

Vos M, Rommelse NNJ, Franke B, et al.

To advance understanding of the heterogeneity in the course of ADHD, joint symptom trajectories of inattention and hyperactivity-impulsivity from childhood to young adulthood were modelled and associated with genetic, demographic, and clinical characteristics. Data were obtained from the NeuroIMAGE cohort which includes 485 individuals with ADHD, their 665 siblings, and 399 typically developing children. Trajectories were based on scores of the Conners Parent Rating Scale Revised and estimated over seven homogeneous age bins (from 5 to 28Â years) using parallel process latent class growth analysis on data collected across 2-4 time points. Multilevel multinomial logistic regression was used to identify characteristics that differentiated between the derived classes. A seven-class solution revealed "severe combined stable" (4.8%), "severe combined decreasing" (13%), "severe inattentive stable" (4.8%), "moderate combined increasing" (7.5%), "moderate combined decreasing" (12.7%), "stable mild" (12.9%), and "stable low" (44.3%) classes. Polygenic risk for depression, ADHD diagnosis, ADHD medication use, IQ, comorbid symptom levels (foremost oppositional behaviour), and functional impairment levels differentiated classes with similar ADHD symptom levels in childhood but a diverging course thereafter. The course of ADHD is highly heterogeneous, with stable, decreasing, and increasing trajectories. Overall, severe symptom levels in childhood are associated with elevated-to-severe symptom levels in adolescence and young adulthood, despite substantial symptom reductions. Beyond symptom severity in childhood, genetic, demographic, and clinical characteristics distinguish the heterogeneous course

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Eur Child Adolesc Psychiatry. 2022 Aug;31:1-9.

BURDEN OF MENTAL DISORDERS IN CHILDREN IN THE GENERAL POPULATION AND IN HEALTH FACILITIES: DISCREPANCIES IN YEARS LIVED WITH DISABILITY BASED ON NATIONAL PREVALENCE ESTIMATES BETWEEN POPULATIONS RECEIVING CARE OR NOT.

Chen YL, Kuo RN, Gau SS.

Little is known about the discrepancies in the burden of child mental disorders based on differences in prevalence between populations with and without care. Identifying such discrepancies may help to elucidate the unmet needs related to child mental disorders. We compared the years lived with disability (YLD) between children with and without care for mental disorders using a representative national survey, Taiwan's National Epidemiological Study of Child Mental Disorders (TNESCMD), and a national health facility database, the Taiwan National Health Insurance Research Database (TNHIRD). The comorbidity-adjusted YLD rate ratio (RR) was reported to quantify the YLD discrepancy. The overall YLD rate for all mental disorders in the TNESCMD was 9.05 times higher than that in the TNHIRD with the lowest and highest YLD RRs for autism spectrum disorder (RR 3.51) and anxiety disorders (RR 360.00). Unlike the YLD proportion explained by attention-deficit/hyperactivity disorder and autism spectrum disorder, the proportions explained by anxiety disorders and conduct disorder/oppositional defiant disorder relative to the total YLD were relatively lower in the TNHIRD than in TNESCMD and the Global Burden of Disease 2016. The discrepancies in YLD between populations with and without care in child mental disorders ranged from±55% to 99% and had an overall value of±80.1%. High YLD discrepancies in child mental disorders between estimates based on the general population and those in health facilities suggest significant unmet needs for care in child mental disorders and that estimates of disease burden that rely heavily on a single source may result in unreliable results

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Eur Child Adolesc Psychiatry. 2022 Sep;31:1367-75.

STIMULANT TREATMENT EFFECTIVENESS, SAFETY AND RISK FOR PSYCHOSIS IN INDIVIDUALS WITH 22Q11.2 DELETION SYNDROME.

Basel D, Mosheva M, Maeder J, et al.

This study aimed to retrospectively evaluate an association between stimulant treatment for attention-deficit/hyperactivity disorder (ADHD) in individuals with 22q11.2DS and the development of psychotic disorders, to evaluate long-term effectiveness and safety of stimulant treatment in individuals with 22q11.2DS compared to individuals with idiopathic ADHD, and to explore effects of catechol-O-methyltransferase (COMT) genotype on 22q11.2DS response to stimulants and risk of side effects. Rates of stimulant use and methylphenidate equivalent exposure were compared among individuals with 22q11.2DS, between 51 with psychotic disorders and a control group of 57 22q11.2DS without psychotic disorders, from Tel Aviv and Geneva. In addition, 44 individuals with 22q11.2DS and ADHD from Tel Aviv who initiated stimulants before age 18Â years were compared to a control group of 35 age- and sex-matched controls with idiopathic ADHD, for treatment effectiveness (Clinical Global Impression Scale-Improvement), and rates of side effects. Stimulant use history and methylphenidate equivalent exposure did not differ among individuals with 22q11.2DS, between those with and without psychotic disorders. The long-term retrospective follow-up (5.3±4.1 years) of stimulant-treated individuals with 22q11.2DS showed a higher rate of significant clinical improvement of ADHD symptoms, compared to idiopathic ADHD individuals (p=0.013), and similar side effect rates. There was no effect of the COMT genotype on response to stimulants or on any side effects. This preliminary long-term retrospective analysis suggests that stimulant treatment in 22q11.2DS is apparently safe in terms of psychosis conversion and rates of side effects, and that it is effective in alleviating ADHD symptoms

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Eur Child Adolesc Psychiatry. 2022 Aug;31:1-12.

VITAMIN D LEVELS IN CHILDREN AND ADOLESCENTS WITH CHRONIC TIC DISORDERS: A MULTICENTRE STUDY.

Bond M, Moll N, Rosello A, et al.

This study investigated whether vitamin D is associated with the presence or severity of chronic tic disorders and their psychiatric comorbidities. This cross-sectional study compared serum 25-hydroxyvitamin D [25(OH)D] (ng/ml) levels among three groups: children and adolescents (3-16 years) with CTD (n = 327); first-degree relatives (3-10 years) of individuals with CTD who were assessed for a period of up to 7 years for possible onset of tics and developed tics within this period (n = 31); and first-degree relatives who did not develop tics and were ≥ 10 years old at their last assessment (n = 93). The relationship between 25(OH)D and the presence and severity of tics, as well as comorbid obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD), were analysed controlling for age, sex, season, centre, latitude, family relatedness, and comorbidities. When comparing the CTD cohort to the unaffected cohort, the observed result was contrary to the one expected: a 10 ng/ml increase in 25(OH)D was associated with higher odds of having CTD (OR 2.08, 95% CI 1.27-3.42, $p < 0.01$). There was no association between 25(OH)D and tic severity. However, a 10 ng/ml increase in 25(OH)D was associated with lower odds of having comorbid ADHD within the CTD cohort (OR 0.55, 95% CI 0.36-0.84, $p = 0.01$) and was inversely associated with ADHD symptom severity ($\beta = -2.52$, 95% CI - 4.16-0.88, $p < 0.01$). In conclusion, lower vitamin D levels were not associated with a higher presence or severity of tics but were associated with the presence and severity of comorbid ADHD in children and adolescents with CTD

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Eur Child Adolesc Psychiatry. 2022.

ABERRANT BRAIN DYNAMICS AND SPECTRAL POWER IN CHILDREN WITH ADHD AND ITS SUBTYPES.

Luo N, Luo X, Zheng S, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children, usually categorized as three subtypes, predominant inattention (ADHD-I), predominant hyperactivity-impulsivity (ADHD-HI), and a combined subtype (ADHD-C). Yet, common and unique abnormalities of

electroencephalogram (EEG) across different subtypes remain poorly understood. Here, we leveraged microstate characteristics and power features to investigate temporal and frequency abnormalities in ADHD and its subtypes using high-density EEG on 161 participants (54 ADHD-Is and 53 ADHD-Cs and 54 healthy controls). Four EEG microstates were identified. The coverage of salience network (state C) were decreased in ADHD compared to HC (p = 1.46e-3), while the duration and contribution of frontalΓÇôparietal network (state D) were increased (p = 1.57e-3; p = 1.26e-4). Frequency power analysis also indicated that higher delta power in the fronto-central area (p = 6.75e-4) and higher power of theta/beta ratio in the bilateral fronto-temporal area (p = 3.05e-3) were observed in ADHD. By contrast, remarkable subtype differences were found primarily on the visual network (state B), of which ADHD-C have higher occurrence and coverage than ADHD-I (p = 9.35e-5; p = 1.51e-8), suggesting that children with ADHD-C might exhibit impulsivity of opening their eyes in an eye-closed experiment, leading to hyper-activated visual network. Moreover, the top discriminative features selected from support vector machine model with recursive feature elimination (SVM-RFE) well replicated the above results, which achieved an accuracy of 72.7% and 73.8% separately in classifying ADHD and two subtypes. To conclude, this study highlights EEG microstate dynamics and frequency features may serve as sensitive measurements to detect the subtle differences in ADHD and its subtypes, providing a new window for better diagnosis of ADHD

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Eur Child Adolesc Psychiatry. 2022.

THE ASSOCIATION BETWEEN EARLY CHILDHOOD ONSET EPILEPSY AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) IN 3237 CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER (ASD): A HISTORICAL LONGITUDINAL COHORT DATA LINKAGE STUDY.

Carson L, Parlatini V, Safa T, et al.

Children and young people with Autism Spectrum Disorder (ASD) have an increased risk of comorbidities, such as epilepsy and Attention-Deficit/Hyperactivity Disorder (ADHD). However, little is known about the relationship between early childhood epilepsy (below age 7) and later ADHD diagnosis (at age 7 or above) in ASD. In this historical cohort study, we examined this relationship using an innovative data source, which included linked data from routinely collected acute hospital paediatric records and childhood community and inpatient psychiatric records. In a large sample of children and young people with ASD (N = 3237), we conducted a longitudinal analysis to examine early childhood epilepsy as a risk factor for ADHD diagnosis while adjusting for potential confounders, including socio-demographic characteristics, intellectual disability, family history of epilepsy and associated physical conditions. We found that ASD children and young people diagnosed with early childhood epilepsy had nearly a twofold increase in risk of developing ADHD later in life, an association which persisted after adjusting for potential confounders (adjusted OR = 1.72, CI95% = 1.13ΓÇô2.62). This study suggests that sensitive monitoring of ADHD symptoms in children with ASD who have a history of childhood epilepsy may be important to promote early detection and treatment. It also highlights how linked electronic health records can be used to examine potential risk factors over time for multimorbidity in neurodevelopmental conditions

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Eur Child Adolesc Psychiatry. 2022.

RELATIONSHIPS BETWEEN SENSORY INTEGRATION AND THE CORE SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE MEDIATING EFFECT OF EXECUTIVE FUNCTION.

Li J, Wang W, Cheng J, et al.

Attention-deficit/hyperactivity disorder (ADHD) is often accompanied by executive function deficits and functional alterations in sensory integration. The present study aimed to investigate the relationship between ADHD core symptoms, executive function, and sensory integration in children with ADHD. A total of 228 children with ADHD were recruited for our study. The Sensory Organization Test (SOT) and Child Sensory Integration Scale (CSIS) evaluated the sensory integration ability from lab-based and scaled-based perspectives, respectively. Three core components of executive functions (inhibition, working memory, and set-shifting) were assessed using both lab-based tests and the relevant factors from the behavior rating

inventory of executive function (BRIEF). Partial correlation analysis was performed to explore the correlation of sensory integration with EF and ADHD core symptoms. Based on the observed significant correlation, bootstrap analyses were further conducted to explore the potential mediating effect of EF on the relationship between sensory integration and ADHD core symptoms. ADHD symptoms and EF were significantly correlated with CSIS scores; no factors were significantly correlated with SOT performance. In detail, the vestibular-balance score was negatively correlated with both inattention and hyperactivity/impulsivity symptoms, while the hyper-sensory and proprioception scores were negatively correlated with only inattention symptoms. For the scaled-based EF, vestibular-balance was negatively correlated with inhibition and working memory, and the hyper-sensory score was negatively correlated with shift factor. No correlation was found for the lab-based EF tests. The subsequent mediation analysis found that inhibition partially mediated the relationship between vestibular balance and hyperactivity/impulsivity symptoms. Working memory completely mediated the relationship between vestibular-balance, hyper-sensory, proprioception, and inattention symptoms. These results were well validated in an independent sample. Our present findings demonstrated that the functional alteration in basic sensory integration might be associated with impairments of executive functions and then lead to the behavioral expression of ADHD. The present findings might provide a new perspective to understand the occurrence of ADHD symptoms and potential precise intervention methods

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Eur J Neurol. 2022;29:802.

MONOALLELIC CARRIERS OF WWOX MUTATIONS SHOW MILD INTELLECTUAL DISABILITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Iruzubieta P, Ondaro J, Equiza J, et al.

Background and aims: Mutations in the WWOX (WW domain-containing oxidoreductase) gene have been associated with different autosomal recessively inherited disorders including SCAR 12 (spinocerebellar ataxia type 12) and WOREE (WWOX-related epileptic encephalopathy). We show for the first time, that monoallelic carriers of WWOX mutations may present a phenotype characterized by mild intellectual disability, attention deficit hyperactivity disorder and increased CSF tau levels.

Methods: We collected clinical data from three monoallelic carriers. In one of them, studies were completed with neuropsychological evaluation, brain MRI and lumbar puncture. Moreover, we isolated skin-derived fibroblasts to measure WWOX levels through Western blotting.

Results: The proband is a 3-years old child with WOREE and two pathogenic mutations in WWOX (c.689A>C and c.136C>T). His older brother, his mother and his grandfather are all carriers of the variant c.689A>C (Figure 1). These carriers showed mild learning difficulties and attention problems. The grandfather consulted to our Neurology Department because of memory complaints. Neuropsychological evaluation showed a low limit IQ as a consequence of impaired working memory and sustained attention. Complementary studies showed a normal brain MRI and EEG and an increased tau (1558pg/ml; normal range<360pg/mL) and phospho-tau (105pg/ml; normal range: <61pg/mL) levels in CSF. Furthermore, we performed protein expression analyses from skin-derived fibroblasts showing WWOX haploinsufficiency (Figure 2)

Conclusion: Here, we expand the neurological phenotype associated to the c.689A>C WWOX mutation, showing a milder phenotype in monoallelic carriers

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Europ J Spec Needs Educ. 2022;37:617-31.

TEACHERS AS DISORDER-SPOTTERS: (IN)DECISIVENESS IN ASSIGNING A CHILD'S HYPERACTIVITY, IMPULSIVITY AND/OR INATTENTION TO ADHD AS THE UNDERLYING CAUSE.

Degroote E, Brault MC, Van Houtte M.

Their unique observational position in the classroom allows teachers to take on an informal role as disorder-spotter. By means of focus groups in four Flemish elementary schools, this study investigates teachers ΓÇÖ decisiveness in assigning a childΓÇÖs hyperactivity, impulsivity and/or inattention to Attention-Deficit/Hyperactivity Disorder (ADHD) as the underlying cause. Results show that, when teachers talked

about specific children who exhibited hyperactivity, impulsivity and/or inattention, they were, more often than not, decisive in their observation that ADHD was or was not the underlying cause of the childΓÇÖs behaviours. However, several child-related factors caused teachers to be indecisive about whether ADHD was indeed at the base of a specific child's hyperactivity, impulsivity and/or inattention

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Eur Neuropsychopharmacol. 2022;62:63-73.

POLYGENIC RISK SCORES FOR ANTISOCIAL BEHAVIOR IN RELATION TO AMYGDALA MORPHOLOGY ACROSS AN ATTENTION DEFICIT HYPERACTIVITY DISORDER CASE-CONTROL SAMPLE WITH AND WITHOUT DISRUPTIVE BEHAVIOR.

Kleine Deters R, Ruisch IH, Faraone SV, et al.

Antisocial and aggressive behaviors show considerable heritability and are central to disruptive behavior disorders (DBDs), but are also frequently observed in attention deficit hyperactivity disorder (ADHD). While the amygdala is implicated as a key neural structure, it remains unclear whether common genetic variants underlie this brain-behavior association. We hypothesized that polygenic (risk) scores for antisocial and aggressive behaviors (ASB-PRS) would be related to amygdala morphology. Using the Broad Antisocial Behavior Consortium genome-wide association study (GWAS; mostly population based cohorts), we calculated ASB-PRS in the NeuroIMAGE I ADHD case-control sample with varying levels of DBD symptomatology (n=679 from 379 families, aged 7 Γ Çô 29). We first investigated associations of several ASB-PRS p value thresholds with the presence of DBD symptoms and self-reported antisocial behavior (ASB) to determine the threshold for further analyses. This PRS was then related to amygdala volume and shape using regression and vertex-wise analyses. Our results showed associations of ASB-PRS with the presence of DBD symptoms, self-reported ASB, and left basolateral amygdala shape, independent of ADHD symptom severity and ADHD-PRS, with a relative outward displacement of the vertices. No associations of ASB-PRS, DBD symptoms or self-reported ASB with amygdala volume were found. Our results indicate that genetic risk for antisocial and aggressive behaviors is related to amygdala shape alterations, and point to genetic sharing across different DBD and ASB and aggression-related phenotypes as a spectrum of genetically related quantitative traits. Additionally, our findings support the utility of vertex-based shape analyses in genetic studies of ASB, aggression, and DBDs

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Expert Opin Drug Metab Toxicol. 2022 Jun;18:357-66.

EVALUATING THE PHARMACOKINETICS OF EXTENDED RELEASE VILOXAZINE IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress A, Burton S.

INTRODUCTION: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood and impacts function negatively in multiple settings. Current treatments include stimulants, which inhibit the reuptake of dopamine and norepinephrine, a nonstimulant norepinephrine reuptake inhibitor (NRI) atomoxetine, and alpha-2 agonists clonidine extended release (ER) and guanfacine ER. Despite the effectiveness of these medications some patients do not respond to available drugs or may experience tolerability issues that hinder their use.

AREAS COVERED: Viloxazine, a serotonin norepinephrine modulating agent, was used outside of the United States (U.S.) as an effective antidepressant for several decades, but its use fell out of favor due to the need for multiple daily dosing. An ER viloxazine formulation was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD. The efficacy, pharmacokinetics and metabolism of viloxazine and viloxazine ER are reviewed.

EXPERT OPINION: Viloxazine ER is the first nonstimulant approved to treat ADHD in more than a decade. Although they have not been directly compared, the effect size of viloxazine ER is less than has been observed for stimulants. However, its pharmacokinetic properties and tolerability make viloxazine ER a useful addition to the collection of FDA approved ADHD treatments

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Front Human Neurosci. 2022;16.

EXAMINING THE EFFECT OF TRANSCRANIAL ELECTRICAL STIMULATION AND COGNITIVE TRAINING ON PROCESSING SPEED IN PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PILOT STUDY.

Dakwar-Kawar O, Berger I, Barzilay S, et al.

Objective: Processing Speed (PS), the ability to perceive and react fast to stimuli in the environment, has been shown to be impaired in children with attention deficit hyperactivity disorder (ADHD). However, it is unclear whether PS can be improved following targeted treatments for ADHD. Here we examined potential changes in PS following application of transcranial electric stimulation (tES) combined with cognitive training (CT) in children with ADHD. Specifically, we examined changes in PS in the presence of different conditions of mental fatigue.

Methods: We used a randomized double-blind active-controlled crossover study of 19 unmedicated children with ADHD. Participants received either anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (dlPFC) or transcranial random noise stimulation (tRNS), while completing CT, and the administration order was counterbalanced. PS was assessed before and after treatment using the MOXO-CPT, which measures PS in the presence of various conditions of mental fatigue and cognitive load.

Results: tRNS combined with CT yielded larger improvements in PS compared to tDCS combined with CT, mainly under condition of increased mental fatigue. Further improvements in PS were also seen in a 1-week follow up testing.

Conclusion: This study provides initial support for the efficacy of tRNS combined with CT in improving PS in the presence of mental fatigue in pediatric ADHD

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Front Psychiatry. 2022;13.

PREVALENCE OF HIGH-RISK FOR OBSTRUCTIVE SLEEP APNEA IN ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN REFERRED TO PSYCHIATRY CLINIC AND IMPACT ON QUALITY OF LIFE.

Prajsuchanai T, Tanphaichitr A, Hosiri T, et al.

Objectives: To study the prevalence of high-risk obstructive sleep apnea (OSA) in attention deficit hyperactivity disorder (ADHD) children in a child and adolescent psychiatry clinic using the Thai version of the Pediatric Obstructive Sleep Apnea Screening Tool (POSAST) questionnaire. The secondary objective was to evaluate the quality of life and identify associated factors for high-risk OSA in ADHD children. Study design: Prospective cross-sectional study.

Material and method: Caregivers of pediatric patients aged 5ΓÇô18 years old and diagnosed with ADHD by child and adolescent psychiatrists were surveyed about their child's sleeping habits.

Results: Two hundred and seventy-four subjects were included. The patients' mean age was 10.4 -¦ 2.6 years, and 82.8% were males. There were 30 children (10.9%) diagnosed with obesity, 46 (16.8%) with chronic rhinitis, and 9 (3.3%) with asthma. The median duration of ADHD symptoms was 22.1 months. The prevalence of high-risk OSA was 18.2% and was associated with significantly reduced quality of life (adjusted OR = 4.46, 95% CI: 2.26-8.81, P < 0.001). A significant association between high-risk OSA and obesity also emerged (adjusted OR = 2.84, 95% CI: 1.17ΓÇô6.88, P = 0.021).

Conclusion: An elevated prevalence of high-risk OSA is present among Thai children with ADHD, and significantly impacts quality of life. A significant association between high-risk OSA and obesity is also detected in patients with ADHD. Therefore, screening for high-risk OSA in ADHD patients may likely facilitate early detection and treatment of OSA, and potentially prevent adverse consequences

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Front Psychiatry. 2022;13.

INDIVIDUAL DIFFERENCES IN SENSITIVITY TO POSITIVE HOME ENVIRONMENT AMONG CHILDREN "AT RISK" FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A REVIEW.

Einziger T, Berger A.

Although the evidence for the genetic basis of attention-deficit/hyperactivity disorder (ADHD) is strong, environmental factors, such as the quality of parenting or the home environment, may moderate such genetic

liability. The plausible negative effect of a low-quality home environment and negative parenting on child outcomes is well-established; however, the positive effect of a high-quality environment and positive parenting remained largely uninvestigated. Due to the presence of genetic, temperamental, or physiological factors, children who were traditionally considered at-risk for ADHD may be more sensitive to aspects of their environment compared to children who are not at such risk. Therefore, they would be more affected by their environmental experience, either for good or bad. Under supportive environmental conditions, such at-risk individuals might actually outperform their non-vulnerable peers, suggesting that these individual factors might be considered susceptibility factors rather than risk factors. Little is known regarding the positive effect of the environment in the ADHD literature, but it has been demonstrated in cognitive functions that are closely associated with ADHD, such as executive functions (EF). We review this literature and examine the extant empirical support for sensitivity to aspects of the home environment and parenting in the case of ADHD and EF. Moreover, we review factors that could help identify the specific aspects of the home environment and parenting that these children might be more susceptible to. Such knowledge could be valuable when designing preventive interventions and identifying those children that are especially sensitive and could benefit from such interventions. Recommendations for future studies are discussed as well

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Front Psychiatry. 2022;13.

THE ASSOCIATION BETWEEN HEIGHTENED ADHD SYMPTOMS AND CYTOKINE AND FATTY ACID CONCENTRATIONS DURING PREGNANCY.

Gustafsson HC, Dunn GA, Mitchell AJ, et al.

Objective: Previous research conducted with samples of children suggest that individuals with attention-deficit/hyperactivity disorder (ADHD) have altered fatty acid concentrations and may have increased systemic inflammation. Whether these differences are also apparent in other populations of individuals with heightened ADHD symptoms (e.g., pregnant adults) is unknown. The goal of the current study was to examine whether there are ADHD-associated differences in polyunsaturated fatty acid concentrations or pro-inflammatory cytokine concentrations during pregnancy, a developmental period when fatty acid concentrations and systemic inflammation have implications for the health of both the pregnant person and the developing child. We hypothesized that plasma levels of the ratio of omega-6s to omega-3s (n-6:n-3) and plasma inflammatory cytokine levels would be higher in individuals with heightened ADHD symptoms, consistent with previous findings in children with ADHD.

Methods: Data (N = 68) came from a prospective study of pregnant community volunteers who were oversampled for ADHD symptoms. During the 3rd trimester, plasma concentrations of fatty acids and the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-+¦) were assessed. Dietary intake was examined in the 3rd trimester using three 24-h recalls conducted by trained dietitians and by examining plasma levels of conjugated linoleic acid (n-6) and +¦-linolenic acid (n-3), essential fatty acids that must come from dietary intake.

Results: The group with heightened ADHD symptoms had higher n-6:n-3s (+¦ = 0.30, $p < 0.01$) and higher TNF-+¦ concentrations (+¦ = 0.35, $p < 0.001$) relative to controls. There were no group differences in dietary variables, as assessed by self-report and via plasma concentrations of essential fatty acids. IL-6 was not reliably associated with ADHD status in this sample.

Conclusion: Pregnant individuals with ADHD, on average, had higher plasma n-6:n-3s and higher TNF-+¦ concentrations relative to controls. A difference was not detected in their dietary intake of fatty acids or other relevant nutrients. Though these null findings are inconclusive, they are consistent with the hypothesis that ADHD-associated differences in plasma fatty acid concentrations are the result of ADHD-associated differences in fatty acid metabolism, rather than simply differences in dietary intake

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Front Psychiatry. 2022;13.

RESTING-STATE BRAIN VARIABILITY IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER .

Hong SB, Hwang S.

In this study, we sought to determine the nature of the abnormality in resting-state default mode network (DMN) activation and explore its correlation with functional connectivity in attention-deficit/hyperactivity disorder (ADHD). We obtained resting-state functional magnetic resonance images of youth with ADHD and typically developing counterparts from the publicly available ADHD-200 database. We used data from Peking University (232 scans) and New York University (172 scans); the scan repetition time was 2 s for both data collection sites. We applied generalized estimating equations to estimate the variability of the averaged blood-oxygen-level-dependent (BOLD) time series extracted from the DMN at rest. We performed network-based statistics to determine the association between the observed differences in BOLD signal variability and altered functional connectivity. We analyzed data from 105 youth with ADHD (age: mean 12.17, standard deviation 2.31, median 12.25; 15.2% female, 84.8% male) and 140 typically developing youth (age: mean 11.99, standard deviation 2.28, median 11.85; 47.1% female, 52.9% male), who aged 7ΓÇô17 years. The imaging data were cross-sectionally collected for each participant at one time point. We observed a greater number of significant BOLD signal changes and higher-order polynomial significant associations in youth with ADHD. Moreover, there were significant between-group differences in BOLD signal change after the first 140 s, which coincided with decreased resting-state functional connectivity within the DMN in youth with ADHD. Increased variability of neural signaling was intermittently observed in the brains of youth with ADHD at rest, thereby indicating their default mode state was more unstable than that of typically developing youth

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Genet Med. 2022 Aug;24:1774-80.

LOSS-OF-FUNCTION VARIANTS IN SRRM2 CAUSE A NEURODEVELOPMENTAL DISORDER.

Cuinat S, Nizon M, Isidor B, et al.

PURPOSE: SRRM2 encodes the SRm300 protein, a splicing factor of the SR-related protein family characterized by its serine- and arginine-enriched domains. It promotes interactions between messenger RNA and the spliceosome catalytic machinery. This gene, predicted to be highly intolerant to loss of function (LoF) and very conserved through evolution, has not been previously reported in constitutive human disease.
METHODS: Among the 1000 probands studied with developmental delay and intellectual disability in our database, we found 2 patients with de novo LoF variants in SRRM2. Additional families were identified through GeneMatcher.
RESULTS: Here, we report on 22 patients with LoF variants in SRRM2 and provide a description of the phenotype. Molecular analysis identified 12 frameshift variants, 8 nonsense variants, and 2 microdeletions of 66 kb and 270 kb. The patients presented with a mild developmental delay, predominant speech delay, autistic or attention-deficit/hyperactivity disorder features, overfriendliness, generalized hypotonia, overweight, and dysmorphic facial features. Intellectual disability was variable and mild when present.
CONCLUSION: We established SRRM2 as a gene responsible for a rare neurodevelopmental disease

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Health Econ. 2022 Sep;31:1926-53.

ADHD MISDIAGNOSIS: CAUSES AND MITIGATORS.

Furzer J, Dhuey E, Laporte A.

ADHD diagnoses increase discontinuously by a child's school starting age, with young-for-grade students having much higher ADHD diagnostic rates. Whether these higher rates reflect over-diagnosis or under-diagnosis remains unknown. To decompose this diagnostic discrepancy, we exploit differences in parent and teacher pre-diagnostic assessments within a regression discontinuity strategy based on school starting age. We show that being young-for-grade or male generates over-assessment of symptoms specifically from teacher assessment. However, under-assessments of the oldest students in a grade, especially the oldest females, account for a large part of the observed school starting age assessment gap. We argue that this difference by sex and higher school starting age effects in lower-income schools may exacerbate known

gaps in educational attainment by gender and socioeconomic status. Importantly, we fail to find evidence that teachers who receive special education training make such errors

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IEEE Trans Image Process. 2022;31:5025-37.

A Robust Movement Quantification Algorithm of Hyperactivity Detection for ADHD Children Based on 3D Depth Images.

He L, He F, Li Y, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood mental disorders. Hyperactivity is a typical symptom of ADHD in children. Clinicians diagnose this symptom by evaluating the children's activities based on subjective rating scales and clinical experience. In this work, an objective system is proposed to quantify the movements of children with ADHD automatically. This system presents a new movement detection and quantification method based on depth images. A novel salient object extraction method is proposed to segment body regions. In movement detection, we explore a new local search algorithm to detect any potential motions of children based on three newly designed evaluation metrics. In the movement quantification, two parameters are investigated to quantify the participation degree and the displacements of each body part in the movements. This system is tested by a depth dataset of children with ADHD. The movement detection results of this dataset mainly range from 91.0% to 95.0%. The movement quantification results of children are consistent with the clinical observations. The public MSR Action 3D dataset is tested to validate the performance of this system

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Indian Journal of Forensic Medicine and Toxicology. 2022;16:196-203.

Relationship between Parenting Stress and Risk of Attention Deficit Hyperactivity Disorder (ADHD) in Elementary School Children.

Setyanisa AR, Setiawati Y, Irwanto, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder during child development with three symptoms which are comprised of inattention, hyperactivity, and impulsiveness that may persist into adulthood. This condition can be a stressor for parents in performing parenting and may lead into a state of parenting stress.

Objective: To analyze the relationship between parenting stress and the risk of developing Attention Deficit Hyperactivity Disorder (ADHD) in elementary school children.

Methods: This research was conducted in Surabaya from November 2020 to January 2021 with respondents consisting of parents of elementary school children who have ADHD risk and agreed to participate in this study with a total of 55 samples selected using a purposive sampling technique. The research design was cross-sectional using demographic questionnaire, Abbreviated Conners Rating Scale (ACRS), and Parenting Stress Index-Short Form (PSI-SF) which were filled out by respondents through an online form. The data were processed and analyzed using One-Sample Chi-Square analysis test program with a p-value <0.05, considered statistically significant.

Results: The majority of parents experienced moderate parenting stress levels (58.2%). There was a significant relationship between each level of parenting stress and the risk of ADHD in children ($p < 0.001$).

Conclusions: There is a significant relationship between parenting stress and the risk of ADHD in children

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Innov Clin Neurosci. 2022;19:11-22.

Use of Repetitive Transcranial Magnetic Stimulation in Child Psychiatry.

Bejenaru AM, Malhi NK.

Objective: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive diagnostic and therapeutic technique that has showed benefits in various psychiatric disorders. Although there is a large body of literature available on its use in adult populations, existing research in pediatric populations is very limited.

Current research has primarily focused on its use in adolescent treatment-resistant depression. However, recently, rTMS has gained attention among researchers to find its utility in other neuropsychiatric disorders, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), tics, and psychosis. There is a lack of systematic data on the safety of rTMS in children and adolescents. The aim of this article was to present an overview of the existing literature on the use of rTMS in children and adolescents and examine the relevant safety considerations.
Methods: We conducted a literature review of the English literature in PubMed on TMS in children and adolescents, using comprehensive search terms and expanding our review to include sources cited by these reports. We reviewed the application of rTMS in psychiatric disorders in the pediatric population.
Results: rTMS has been used for depression and anxiety disorders, OCD, ADHD, Tourette syndrome/tics, ASD, and schizophrenia, with variable results.
Conclusion: rTMS is a promising treatment in children and adolescents with psychiatric disorders, although larger, sham-controlled, randomized, controlled trials (RCTs) will be required to definitely demonstrate efficacy, as well as to support a safety profile

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Int J Environ Res Public Health. 2022 Aug;19.
PARENTAL EFFICACY IN MANAGING SMARTPHONE USE OF ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PARENTAL AND ADOLESCENT RELATED FACTORS .
Chou WJ, Hsiao RC, Yen CF.
Parental management has an important role in preventing problematic smartphone use among adolescents with attention-deficit/hyperactivity disorder (ADHD). This study aimed to examine the parental factors (e.g., demographics, depressive symptoms and parenting styles) and adolescent factors (e.g., demographics, ADHD and oppositional defiant disorder [ODD] symptoms, and problematic smartphone use) related to parental efficacy in managing adolescent smartphone use (PEMASU) among 237 parents of adolescents with ADHD. PEMASU was measured by the Parental Smartphone Use Management Scale. Parental depressive symptoms and parenting styles (parental affection/care and overprotection) were measured by the Center for Epidemiologic Studies-Depression Scale and Parental Bonding Instrument, respectively. Adolescent ADHD and ODD symptoms and problematic smartphone use were measured by the Swanson, Nolan, and Pelham, version IV scale and Problematic Smartphone Use Questionnaire, respectively. Three models of hierarchical linear regression were performed to examine the parental and adolescent factors related to PEMASU. The results indicated that adolescent older age and more severe ODD symptoms and problematic smartphone use were significantly associated with lower PEMASU, whereas greater parental affection/care was significantly associated with higher PEMASU. This study demonstrated that both parental and adolescent factors contribute to PEMASU among parents of adolescents with ADHD. Intervention programs aiming to enhancing PEMASU need to take these related factors into consideration

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Int J Environ Res Public Health. 2022 Jul;19.
CLASSIFYING YOUNG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BASED ON CHILD, PARENT, AND FAMILY CHARACTERISTICS: A CROSS-VALIDATION STUDY.
Law E, Sideridis G, Alkhadim G, et al.
We aimed to identify subgroups of young children with differential risks for ADHD, and cross-validate these subgroups with an independent sample of children. All children in Study 1 (N = 120) underwent psychological assessments and were diagnosed with ADHD before age 7. Latent class analysis (LCA) classified children into risk subgroups. Study 2 (N = 168) included an independent sample of children under age 7. A predictive model from Study 1 was applied to Study 2. The latent class analyses in Study 1 indicated preference of a 3-class solution (BIC = 3807.70, p < 0.001). Maternal education, income-to-needs ratio, and family history of psychopathology, defined class membership more strongly than child factors. An almost identical LCA structure from Study 1 was replicated in Study 2 (BIC = 5108.01, p < 0.001). Indices of sensitivity (0.913, 95% C.I. 0.814-0.964) and specificity (0.788, 95% C.I. 0.692-0.861) were high across studies. It is concluded

that the classifications represent valid combinations of child, parent, and family characteristics that are predictive of ADHD in young children

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Int J Psychiatry Med. 2022.

COVID-19 VACCINE COMPLIANCE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shkalim Zemer V, Hoshen M, Gerstein M, et al.

Objective: To compare the rate of the administration of the PfizerΓÇôBioNTech COVID-19 vaccinations between adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) and non-ADHD subjects.

Method: A retrospective chart review was performed on all adolescents aged 12-17 years registered at a central district in Israel from January 1st 2021 to October 31st 2021.

Results: Of the 46,544 subjects included in the study, 8241 (17.7%) were diagnosed with ADHD. Of them, 3% were PCR-COVID-19 positive. Among the patients with ADHD, the older adolescents were more likely to be vaccinated: 48.8% of those aged 12-15 years were vaccinated versus 59.6% of patients aged 16-17 years. The ultra-orthodox Jewish and Arab adolescents in the ADHD group were far less likely to be vaccinated (22.9% and 34.6%, respectively), compared to the adolescents with ADHD in the general population (60.5%). Girls were also somewhat more likely to be vaccinated.

Conclusions: Adolescents diagnosed with ADHD had a higher COVID-19 vaccination rate compared to their non-ADHD counterparts. The vaccine uptake was lower amongst Arab and ultra-orthodox Jewish populations

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Iran J Psychiatr Behav Sci. 2014;8:7-11.

COMPARISON OF THERAPEUTIC EFFECTS OF OMEGA-3 AND METHYLPHENIDATE (RITALIN®) IN TREATING CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Dashti N, Hekmat H, Soltani HR, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is a fixed pattern of disregard and hyperactivity that is much more severe than what is normal in children of the same age. Multiple drugs are used for the treatment of children with ADHD; however, their side effects and efficacy are not clearly known. This study was designed to evaluate and compare the therapeutic effects of two drugs, that is, omega-3 and methylphenidate hydrochloride (Ritalin(®)), used to treat patients with ADHD.

Methods: In a randomized, placebo control clinical trial in Yazd, Iran, 85 ADHD children were divided into two experimental and one control groups. Thus, 29 subjects were treated with Ritalin(®), 28 subjects received omega-3, and the remaining 28 received placebo. The data collection tools used in this study consisted of the Conners' Parent Rating Scale and Teacher Rating Scale. The scores obtained from these questionnaires were analyzed using chi-square test and paired t-test in PASW Statistics.

Results: The average age of the population was 8.22 (± 1.65) years. Significant associations were observed between Ritalin(®) therapy and the changes before and after the treatment, and the omega-3 treatment and the changes before and after treatment ($p < 0.001$). There was no significant association between the placebo group and the changes before and after the treatment ($p > 0.050$). Omega-3 had considerable efficacy as well as Ritalin(®) ($P = 0.001$).

Conclusions: More attention should be given to screening, prevention, and treatment with omega-3 and its effective role in the development of the brain and mental health, and increasing children's attention span and thinking ability

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J Affect Disord. 2022 Oct;314:259-62.
SEASONALITY AND ADHD: SUMMER TIME IS ASSOCIATED WITH LESS SYMPTOMS OF INATTENTION AMONG CHILDREN AND ADOLESCENTS WITH ADHD.
Zeran-Rugerio MF, Alda JA, Carpio-Arias TV, et al.

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J Am Acad Child Adolesc Psychiatry. 2022 Aug;61:965-67.
EDITORIAL: CAN WE ACCURATELY SCREEN FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? MOVING TO A DIMENSIONAL, MULTISTEP PROCESS TO SUPPORT YOUTH DEVELOPMENT.
Karalunas SL.
Mental health concerns are a major source of health-related burden worldwide, including shortened life spans as a result of accidental injury, suicide, and secondary health complications.(1) Attention-deficit/hyperactivity disorder (ADHD) is emblematic in that it can be a serious concern in and of itself as well as an early-emerging risk factor for a variety of other serious physical and mental health outcomes.(2) While there remains a need for more effective treatment, especially for core ADHD symptoms,(3) many of the long-term negative outcomes associated with ADHD can be at least partially mitigated with early intervention.(4,5) Thus, cost-effective, accurate screening is a critical need for the field of child and adolescent psychiatry. The systematic review and meta-analysis of available ADHD screening tools by Mulraney etÂ al.(6) reflects an enormous effort to summarize the overall accuracy, sensitivity, and specificity of available screening measures. The results highlight both what we can and, critically, what we cannot yet achieve with current tools and suggest paths forward

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J Am Acad Child Adolesc Psychiatry. 2022 Sep;61:1141-54.
TRANSGENERATIONAL FACTORS ASSOCIATED WITH MILITARY SERVICE: COMPARISON OF CHILDREN OF VETERANS AND NONVETERANS IN A NATIONALLY REPRESENTATIVE SAMPLE.
Bommersbach TJ, Rosenheck R, Rhee TG.
OBJECTIVE: While the psychological effects of military service on the children of active-duty personnel have been studied extensively, little is known about the potential effects of military service for children of veterans after service has ended.
METHOD: Using nationally representative data from the 2018-2019 National Survey of Children's Health, school-age children of veteran families (n = 4,028) were compared with children of nonveteran families (n = 38,228). Owing to large sample sizes, effect sizes (relative risk and Cohen's d), rather than p values, were used to identify substantial differences in caregiver-reported sociodemographic, clinical, and school performance factors between children and caregivers in families with and without a veteran caregiver. Multivariate analyses were used to adjust for socioeconomic factors that could increase health service use.
RESULTS: Children of veteran families were more likely to have higher family incomes, health insurance, and married caregivers, but were also reported to have higher rates of clinically recognized externalizing behavioral conditions (attention-deficit disorder/attention-deficit/hyperactivity disorder or conduct disorder) (17.6% vs 12.7%; relative risk 1.42; 95% CI 1.21-1.66) and adverse childhood experiences; no substantial differences were reported in clinically recognized anxiety or depression. After adjustment for potentially confounding factors, children in veteran families were still more likely to be reported to have externalizing problems (odds ratio 1.34; 95% CI 1.02-1.77).
CONCLUSION: After adjustment for socioeconomic advantages that may increase health service use, children of veteran families demonstrate substantially higher rates of clinically recognized externalizing problems. While explanations for this require further study, service systems working with veterans may consider integrating child-focused screening/services

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J Atten Disord. 2022 Oct;26:1631-39.

NEUROPSYCHOLOGICAL CHARACTERISTICS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SLUGGISH COGNITIVE TEMPO.

Wu ZM, Liu J, Wang P, et al.

OBJECTIVE: The present study aims to explore the neuropsychological features of children with Attention-Deficit/Hyperactivity Disorder (ADHD) and Sluggish Cognitive Tempo (SCT).

METHODS: Fifty-eight children with ADHD+SCT, 480 children with ADHD-SCT, and 105 healthy controls (HC) were recruited. Neuropsychological tests and the Behavior Rating Inventory of Executive Function (BRIEF) were used.

RESULTS: The ADHD+SCT group performed worse than the HC in processing speed ($p = .005$), set-shifting ($p = .0003$), interference control ($p = .00014$), and visual memory ($p = .007$), while the ADHD-SCT group performed worse than the HC in sustained attention measurements (all $p < .0001$). The ADHD+SCT group scored higher than the ADHD-SCT group in the following factors from BRIEF: plan/organize ($p = .00083$), working memory ($p < .001$), and shift ($p = .0054$).

CONCLUSION: Our results indicated that SCT symptoms are associated with worse executive function in children with ADHD except for sustained attention

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J Atten Disord. 2022 Oct;26:1605-21.

CORTISOL REACTIVITY AND OBSERVED PARENTING AMONG MOTHERS OF CHILDREN WITH AND WITHOUT ADHD.

Thomas SR, Woods KE, Mazursky-Horowitz H, et al.

OBJECTIVE: Neurobiological models suggest links between maternal cortisol reactivity and parenting; however, no studies have examined cortisol reactivity and parenting in mothers of school-age children with ADHD.

METHOD: We examined the relationship between observed parenting and maternal cortisol reactivity in two laboratory contexts: the Trier Social Stress Task (TSST) and parenting-child interaction (PCI). Mothers of children with ($N = 24$) and without ($N = 36$) ADHD participated.

RESULTS: During the TSST, greater cortisol output and increase were associated with decreased positive and increased negative parenting. However, during the PCI, cortisol output was associated with increased self-reported and observed positive parenting, and decreased observed negative parenting. Cortisol change during the PCI was associated with decreased observed positive parenting and increased self-reported negative parenting. Among mothers of children with ADHD, cortisol output during the PCI was negatively associated with negative, inconsistent parenting. Change in cortisol predicted more inconsistent discipline and corporal punishment.

CONCLUSION: Findings contribute to an integrative biological, psychological, and cognitive process model of parenting in families of children with ADHD

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J Atten Disord. 2022 Oct;26:1535-48.

FACTORS ASSOCIATED WITH BULLYING VICTIMIZATION AND BULLYING PERPETRATION IN CHILDREN AND ADOLESCENTS WITH ADHD: 2016 TO 2017 NATIONAL SURVEY OF CHILDREN'S HEALTH.

Cuba BC, Adams RE, Claussen AH, et al.

OBJECTIVE: To identify characteristics associated with bullying involvement in pediatric ADHD.

METHODS: Data from the 2016 to 2017 National Survey of Children's Health for children aged 6 to 17 years with ADHD were evaluated to assess the association between parent-reported bullying victimization or perpetration and the following potential predictors: demographic characteristics, family factors, school factors, and child conditions/behaviors.

RESULTS: Among children with ADHD, 46.9% were bullying victims and 16.2% were perpetrators. Factors associated with victimization included having family financial strain, developmental delay or intellectual disability, friendship difficulties, and school reports about problems. Factors linked to perpetration included

being male, receiving government assistance, lack of school engagement, school reports about problems, and having difficulties with friendships, staying calm, and arguing.
CONCLUSIONS: Children with ADHD frequently were bullying victims and sometimes bullying perpetrators. Factors related to family financial strain, developmental disabilities, emotional regulation, peer relationships, and school functioning may help to identify risk for bullying and opportunities for anti-bullying interventions

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J Atten Disord. 2022 Oct;26:1576-90.
THE ASSOCIATIONS BETWEEN SLUGGISH COGNITIVE TEMPO, INTERNALIZING SYMPTOMS, AND ACADEMIC PERFORMANCE IN CHILDREN WITH READING DISORDER: A LONGITUDINAL COHORT STUDY.
Hossain B, Bent S, Parenteau C, et al.
OBJECTIVE: To investigate whether sluggish cognitive tempo (SCT) was associated with anxiety, depression, and academic performance (AP) in children with reading disorder (RD), and whether ADHD-Inattention (ADHD-IN) moderated these relationships.
METHOD: Parents and teachers of children with RD (N = 147, ages 6-18) completed evaluations of SCT, ADHD, anxiety, depression, and AP, every 3 months for 18 months. Baseline and longitudinal associations between SCT and outcomes, and effect moderation of ADHD-IN, were assessed.
RESULTS: Teacher-rated SCT was positively associated with teacher-rated anxiety ($p < .001$) and negatively associated with AP ($p < .001$) cross-sectionally and longitudinally, with significant effect modification by ADHD-IN for both outcomes. SCT was not associated with depression in adjusted cross-sectional and longitudinal analyses. There were no significant findings for any parent-reported measures.
CONCLUSION: SCT has negative effects on anxiety and AP in children with RD among individuals with low ADHD-IN according to teacher report. Targeted treatment of SCT may provide substantial benefits

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J Atten Disord. 2022 Oct;26:1549-62.
VERBAL MEMORY INTERFERENCE IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A META-ANALYTIC REVIEW.
Orban SA, Festini SB, Yuen EK, et al.
OBJECTIVE: Interference control is used to overcome conflict among competing memory representations and may contribute to memory difficulties in ADHD. This meta-analytic review examined memory interference to evaluate susceptibility to proactive, retroactive, and memory control interference among those with ADHD.
METHOD: Twenty studies (1987-2019) examining verbal memory interference in ADHD met inclusion criteria (age: 8-36 years). Proactive and retroactive interference indices were extracted from list-learning tasks, and memory control indices were extracted from experimental paradigms (e.g., directed-forgetting).
RESULTS: Children with ADHD were less affected by proactive interference (g=-0.53, 95% CI [-0.75, -0.31]), whereas no significant differences were found in adults (g=0.13, 95% CI [-0.02, 0.28]). Adults and children with ADHD exhibited more retroactive interference (g=0.17, 95% CI [0.05, 0.29]) and performed worse on memory control tasks (g=0.35, 95% CI [0.08, 0.62]) relative to controls.
CONCLUSION: Differences in verbal memory interference control in ADHD were observed but effects were different depending upon interference type and participant age

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J Atten Disord. 2022 Oct;26:1563-75.
LOCAL FUNCTIONAL CONNECTIVITY AS A PARSIMONIOUS EXPLANATION OF THE MAIN FRAMEWORKS FOR ADHD IN MEDICATION-NAÏVE ADULTS.
Marcos-Vidal L, et al.
OBJECTIVE: Neuroimaging studies in children with ADHD indicate that their brain exhibits an atypical functional connectivity pattern characterized by increased local connectivity and decreased distant connectivity. We aim to evaluate if the local and distant distribution of functional connectivity is also altered in adult samples with ADHD who have never received medication before.

METHODS: We compared local and distant functional connectivity between 31 medication-naïve adults with ADHD and 31 healthy controls and tested whether this pattern was associated with symptoms severity scores.
RESULTS: ADHD sample showed increased local connectivity in the dACC and the SFG and decreased local connectivity in the PCC.
CONCLUSION: Results parallel those obtained in children samples suggesting a deficient integration within the DMN and segregation between DMN, FPN, and VAN. These results are consistent with the three main frameworks that explain ADHD: the neurodevelopmental delay hypothesis, the DMN interference hypothesis and multi-network models

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J Atten Disord. 2022 Oct;26:1668-81.
NEURAL ACTIVITY AND EMOTION SOCIALIZATION AS PREDICTORS OF LATER EMOTION REGULATION DIFFICULTIES IN CHILDREN WITH AND WITHOUT HYPERACTIVITY/IMPULSIVITY.
Gair SL, Brown HR, Breaux R, et al.
OBJECTIVE: This study examined emotion socialization and neural activity during frustration as predictors of emotion regulation (ER) difficulties, and the interplay of emotion socialization and neural activity, in children with and without hyperactivity/impulsivity (H/I).
METHOD: At Time 1, neural activity (P1, N2, P3) during a frustration task, H/I symptoms, and emotion socialization were assessed in 68 children (aged 4-7 years old). At Time 2 (1.5-2 years later), child-report, maternal-report, and observation measures of ER difficulties were assessed.
RESULTS: H/I symptoms moderated the relation between predictors and ER difficulties; there were significant relations for children with high, but not low, levels of H/I. Further, as emotion socialization quality increased, relations between event-related potentials and later ER difficulties became weaker.
CONCLUSION: The processes underlying ER difficulties differ for children with H/I symptoms. High quality emotion socialization may have a protective effect for children whose neural patterns indicate risk for later ER difficulties

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J Atten Disord. 2022 Oct;26:1653-67.
IS PARENTS' ADHD SYMPTOMATOLOGY ASSOCIATED WITH THE CLINICAL FEASIBILITY OR EFFECTIVENESS OF A PSYCHOEDUCATIONAL PROGRAM TARGETING THEIR CHILDREN'S ADHD?
Lindstram T, Kierkegaard SA, Forster M, et al.
OBJECTIVE: To examine if the clinical feasibility and effectiveness of a psychoeducational program targeting children's ADHD differ between parents with varying ADHD symptom severities.
METHOD: An open trial analyzed data from 549 parents of children with ADHD aged 3 to 17 years, who participated in psychoeducation at an outpatient habilitation/disability clinic. In all analyses, parents were stratified into three symptom severity groups (low/middle/high) based on scores on an ADHD screening scale.
RESULTS: Parental ADHD symptom severity was not associated with results on any outcome, although the odds of having incomplete data were higher in parents reporting higher symptom severity. Across the entire sample, we observed high program completion rates, positive acceptability ratings and large increases in parental knowledge.
CONCLUSIONS: Psychoeducation may be beneficial regardless of the participating parent's ADHD symptomatology. Further research is needed to examine whether these results are generalizable to parents diagnosed with ADHD, an underrepresented group in our study

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J Child Adolesc Psychopharmacol. 2022 Aug;32:337-48.

IMPACT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMORBIDITY ON PHENOMENOLOGY AND TREATMENT OUTCOMES OF PEDIATRIC OBSESSIVE-COMPULSIVE DISORDER.

Efe A, Kaba D, CanlÄ± M, et al.

Objective: This study, with a case-control design, investigates the impact of attention-deficit/hyperactivity disorder (ADHD) comorbidity on the phenomenology and treatment outcomes in a clinical sample of pediatric obsessive-compulsive disorder (OCD).

Methods: The data were derived from an evaluation of the sociodemographic and clinical characteristics of 364 children with OCD who were regularly followed up over a 4-year period. Between-group analyses of psychiatric scales were used to compare patients with ADHD comorbidity (n=144, 39.5%) with their ADHD-free opponents. The clinical course and treatment outcomes of each patient were evaluated based on 4-year clinical follow-up data.

Results: Substantial clinical variations in pediatric OCD caused by ADHD comorbidity were identified, including a male preponderance, higher rates of concurrent conduct problems, tic disorders, and learning disabilities, as well as prolonged symptom and treatment durations accompanied by poor response to first-line treatments and higher rates of treatment resistance. Contrary to previous findings, ADHD comorbidity had no impact on the age of OCD onset, and the severity of OCD symptoms was lower in ADHD. With ADHD comorbidity, the OCD symptom course tended to be chronically stable, which may have resulted in complaints persisting into adulthood. In ADHD-free patients, contamination, doubt, religious, somatic obsessions, and cleaning were all more common than in those with ADHD. There was a positive correlation between compulsion scores and the severity of ADHD symptoms, which may be related to increased compulsive coping in ADHD. Impulsivity or compulsivity dominance in the symptom presentation of OCD-ADHD comorbidity may determine phenomenological distinctions such as whether concurrent traits are more prone to tics, conduct problems, or internalizing problems. The primordial associations for clinical characteristics, which were independently associated with ADHD comorbidity, were adjusted using multivariate logistic regression analysis. Clinical variables such as being male, absence of cleaning compulsion, the existence of concurrent conduct problems, tic disorders, and dyslexia, as well as longer treatment duration and poorer treatment response, were all independent predictors of ADHD comorbidity. With an 80.8% accurate classification and relatively fine goodness-of-fit model, the regression model consisting of those predictors had good predictiveness for ADHD comorbidity (R(2)=0.543).

Conclusions: The close association between pediatric OCD, ADHD, and tic disorders can be defined as a specific subtype of pediatric OCD, characterized by more conduct problems, a chronically stable course of OCD symptoms, and poorer treatment outcomes. Correlational analyses in a longitudinal design and the inclusion of an impulsivity scale would be beneficial for further research to interpret the impulsivity-related correlates in the findings on tic and conduct problems

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J Child Adolesc Psychopharmacol. 2022 Aug;32:328-36.

ASSOCIATION OF COEXISTING CONDITIONS, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDICATION CHOICE, AND LIKELIHOOD OF IMPROVEMENT IN PRESCHOOL-AGE CHILDREN: A DEVELOPMENTAL BEHAVIORAL PEDIATRICS RESEARCH NETWORK STUDY.

Deavenport-Saman A, Vanderbilt DL, Harstad E, et al.

Objectives: To determine whether conditions coexisting with attention-deficit/hyperactivity disorder (ADHD) in preschool-age children are associated with choice of stimulants or alpha-2 adrenergic agonists (A2As) and/or likelihood of improvement in ADHD symptoms.

Methods: A retrospective electronic health record review of 497 children from 7 Developmental Behavioral Pediatrics Research Network (DBPNet) sites. Children were <72 months when treated with medication for ADHD from January 1, 2013 to July 1, 2017. We abstracted coexisting conditions, initial medication prescribed, and whether the medication was associated with improvement in symptoms. Analysis of improvement was adjusted for clustering by clinician and site.

Results: The median (interquartile range) child age at the time of initiation of ADHD medication was 62 (54-67) months. The most common coexisting conditions included language disorders (40%), sleep disorders (28%), disruptive behavior disorders (22.7%), autism spectrum disorder (ASD; 21.8%), and motor disorders

(19.9%). No coexisting conditions were present in 17.1%; 1 in 36.8%, 2 in 26.8%, and 3 in 19.3%. Stimulants were initially prescribed for 322 (64.8%) and A2A for 175 (35.2%) children. Children prescribed stimulants were more likely to have no coexisting conditions than those prescribed A2A (22.3% vs. 7.4%; p<0.001). Coexisting ASD and sleep disorder were associated with increased likelihood of starting A2As versus stimulants (p<0.0005; p=0.002). The association between medication treatment and improvement varied by number of coexisting conditions for 0, 1, 2, or 3, respectively (84.7%, 73.8%, 72.9%, 64.6%; p=0.031). Children with 3 coexisting conditions were less likely to respond to stimulants than children with no coexisting conditions (67.4% vs. 79.9%; p=0.037).
Conclusions: Among preschool-age children with ADHD, those with 3 coexisting conditions were less likely to respond to stimulants than those with no coexisting conditions. This was not found for A2A, but further research is needed as very few children with no coexisting conditions were treated with A2A

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J Child Psychol Psychiatry. 2022 Sep;63:1057-67.
ALTERED THETA-BETA RATIO IN INFANCY ASSOCIATES WITH FAMILY HISTORY OF ADHD AND LATER ADHD-RELEVANT TEMPERAMENTAL TRAITS.
Begum-Ali J, Goodwin A, Mason L, et al.
BACKGROUND: Uncovering the neural mechanisms that underlie symptoms of attention deficit hyperactivity disorder (ADHD) requires studying brain development prior to the emergence of behavioural difficulties. One new approach to this is prospective studies of infants with an elevated likelihood of developing ADHD.
METHODS: We used a prospective design to examine an oscillatory electroencephalography profile that has been widely studied in both children and adults with A

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J Child Psychol Psychiatry. 2022 Sep;63:1046-56.
MENTAL DISORDERS IN PREADOLESCENT CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER - A FOUR-YEAR FOLLOW-UP STUDY: THE DANISH HIGH RISK AND RESILIENCE STUDY, VIA 11: THE DANISH HIGH RISK AND RESILIENCE STUDY, VIA 11.
Gregersen M, et al.
Background: Children at familial high-risk of schizophrenia and bipolar disorder have an elevated prevalence of mental disorders but studies of children within a narrow age range are lacking and there are few conjoint studies of these two groups. Knowledge on their mental health is important for prevention and early intervention.
Methods: The authors examined mental disorders and global functioning in children at familial high-risk of schizophrenia (FHR-SZ) and bipolar disorder (FHR-BP) compared with population-based controls. In a longitudinal cohort study, 450 children (FHR-SZ, n = 171; FHR-BP, n = 104; controls, n = 175), were assessed for Axis I disorders at baseline and four-year follow-up (mean age 11.9, SD 0.2) with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children and for global functioning with Children's Global Assessment Scale.
Results: Cumulative incidence of Any Axis I disorder was elevated by age 11 in children at FHR-SZ (54.4%, OR 3.0, 95% CI 1.9-4.7, p < .001) and children at FHR-BP (52.9%, OR 2.8, 95% CI 1.7-4.7, p < .001) compared with controls (28.6%). Children at FHR-SZ and FHR-BP had higher rates of affective disorders (OR 4.4, 95% CI 1.4-13.5, p = .009; OR 5.1, 95% CI 1.6-16.4, p = .007), anxiety disorders (OR 2.1, 95% CI 1.1-4.0, p = .02; OR 3.0, 95% CI 1.5-6.1, p = .002), and stress and adjustment disorders (OR 3.3, 95% CI 1.4-7.5, p = .006; OR 5.3, 95% CI 2.2-12.4, p < .001). Disruptive behavior disorders (OR 2.8, 95% CI 1.0-7.3, p = .04) and ADHD (OR 2.9, 95% CI 1.6-5.3, p < .001) were elevated in children at FHR-SZ. Both FHR groups had lower global functioning than controls. Cumulative incidence of disorders increased equally across the three groups from early childhood to preadolescence and level of functioning did not change differentially.
Conclusions: Children at FHR-SZ and FHR-BP have an elevated prevalence of mental disorders and poorer functioning than controls. Vulnerability in children at FHR manifests early and remains stable throughout

childhood. Early attention toward their mental health and identification of those in need of intervention is warranted

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J Child Psychol Psychiatry. 2022 Sep;63:1017-26.

A SYMPTOM LEVEL PERSPECTIVE ON REACTIVE AND PROACTIVE AGGRESSIVE BEHAVIOURS AND ADHD SYMPTOMS IN CHILDHOOD.

Speyer LG, Eisner M, Ribeaud D, et al.

OBJECTIVE: Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent childhood disorders, affecting around 3.4% of children worldwide. A common and impairing correlate of ADHD is aggressive behaviour. ADHD symptoms and aggression are both heterogeneous and it has been speculated that certain symptoms of ADHD might be more important in aggressive behaviours of different types than others. This study uses a symptom-level analysis to investigate the concurrent and temporal links between ADHD symptoms and aggressive behaviours.

METHODS: Using Gaussian Graphical Models and Graphical Vector Autoregression Models, longitudinal and cross-sectional networks of ADHD symptoms and aggressive behaviours, measured using parent-reported Social Behaviour Questionnaires, were estimated. Participants included 1,246 children taking part in the longitudinal Swiss z-proso cohort study at ages 7, 9 and 11.

RESULTS: The longitudinal network highlighted that ADHD symptoms and aggressive behaviours share a multitude of reciprocal temporal relations, with inattentive ADHD symptoms preceding both reactive and proactive aggression. Cross-sectional networks suggested that hyperactive/impulsive symptoms were predominantly connected to reactive aggressive behaviours but also to a form of proactive aggression, namely dominating other children.

CONCLUSION: Findings provide preliminary evidence which specific symptoms are the most promising targets for reducing aggressive behaviours in children with ADHD. They also highlight the potential importance of targeting feedback loops resulting from aggressive behaviours. Future research is needed to better understand the mechanisms through which ADHD and aggressive behaviours become linked

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J Child Psychol Psychiatry. 2022 Sep;63:984-91.

DEPRESSION IN 3/6-YEAR-OLD CHILDREN: CLINICAL AND PSYCHOSOCIAL OUTCOMES IN LATER CHILDHOOD AND ADOLESCENCE.

Silver J, Olino TM, Carlson GA, et al.

BACKGROUND: In recent years, epidemiological and clinical studies have revealed that depressive disorders can present in early childhood. To clarify the validity and prognostic significance of early childhood-onset depression, we investigated diagnostic and functional outcomes in later childhood and adolescence.

METHODS: A community sample (N=516) was assessed for psychopathology at ages 3 and 6 using the Preschool Age Psychiatric Assessment. When participants were 9, 12, and 15 years old, children and parents completed the Kiddie Schedule for Affective Disorders and Schizophrenia and measures of symptoms and functioning.

RESULTS: In models adjusting for covariates, depressed 3/6-year-old children were more likely to experience subsequent episodes of depressive disorders and exhibited significantly higher rates of later anxiety disorder, attention deficit hyperactivity disorder, and suicidality compared to children without depressive disorders at age 3/6. Early childhood depression was also associated with higher levels of mother, but not child, reported depressive symptoms at age 15 compared to children without depressive disorders at age 3/6. Finally, depression at age 3/6 predicted lower levels of global and interpersonal functioning and higher rates of treatment at age 15 compared to children without depressive disorders at age 3/6.

CONCLUSIONS: Results support the clinical significance of depression in 3/6-year-old children, although further studies with larger samples are needed

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J Child Psychol Psychiatry. 2022 Sep;63:1089-91.

COMMENTARY: SUICIDE RISK IS HIGH, BUT OFTEN OVERLOOKED, IN AUTISTIC SPECTRUM DISORDER POPULATIONS.

Curtis L.

Self-Harm Significantly Higher in Populations with ADHD, Anxiety, ASD, Depression, and Eating Disorders. I appreciated your recent paper on the large and well-matched studies on nonfatal self-harm and suicide among adolescents in the UK Clinical Practice Research Datalink (Cybulski etÂ al. 2021). This large study involved 56,008 self-harm cases and 1,399,356 controls aged 10-19â€‰years and reported that many diagnoses were associated with significantly higher rates of self-harm. Compared to controls, the risk of self-harm was significantly higher in attention-deficit/hyperactivity disorder (ADHD) (OR 3.3, 95% CI 3.1-3.4), anxiety disorder (OR 3.8, 95% CI 3.7-3.9), autism spectrum disorder (ASD) (OR 2.4, 95% CI 2.3-2.6), depression (OR 7.9, 95% CI 7.8-8.2), and eating disorders (OR 3.1, 95% CI 3.0-3.2) (Cybulski et al. 2021)

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J Clin Sleep Med. 2022 Aug;18:2029-39.

THE ASSOCIATIONS OF INSOMNIA SYMPTOMS WITH DAYTIME BEHAVIOR AND COGNITIVE FUNCTIONING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Li X, Shea KSC, Chiu WV, et al.

STUDY OBJECTIVES: The current study aimed to examine the association of insomnia symptoms with daytime behavior and cognitive functioning in children with attention-deficit/hyperactivity disorder (ADHD).

METHODS: Thirty-six children with ADHD and insomnia symptoms, 27 children with ADHD without insomnia symptoms, and 21 age-matched healthy controls were recruited in this study (age range: 6-12 years, 70% male). They were assessed by parent-report questionnaires on insomnia symptoms (Children's Sleep Habits Questionnaire) and ADHD symptoms (Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale [SWAN]), and completed a battery of cognitive tests including the Continuous Performance Test (CPT) for sustained attention, Letter-digit test for processing speed, Digit Span forward test and N-back task for working memory, Tower of London (TOL) test for planning skills and Bergs Card Sorting Test (BCST) for set-shifting ability.

RESULTS: Children with ADHD and insomnia symptoms had the highest scores on SWAN total and inattention and hyperactivity subscales, followed by children with ADHD without insomnia and healthy controls (all $P < .05$). After controlling for potential confounders, children with ADHD and insomnia symptoms showed poorer performance on the CPT and Letter-digit test as compared with children with ADHD without insomnia and healthy controls (all $P < .05$).

CONCLUSIONS: Insomnia symptoms are associated with more severe ADHD symptoms and cognitive impairments in children with ADHD, especially deficits in sustained attention and processing speed. Future longitudinal studies are needed to explore the long-term impacts of insomnia symptoms and the effects of sleep-focused intervention on cognitive functioning in children with ADHD.

CITATION: Li X, Shea KSC, Chiu WV, et al. The associations of insomnia symptoms with daytime behavior and cognitive functioning in children with attention-deficit/hyperactivity disorder

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J Genet Couns. 2022 Aug;31:1008-15.

LEVERAGING ELECTRONIC HEALTH RECORDS TO INFORM GENETIC COUNSELING PRACTICE SURROUNDING PSYCHIATRIC DISORDERS.

Richter LD, Morley TJ, Hooker GW, et al.

Since nearly one-fifth of US adults have a psychiatric disorder, genetic counselors (GCs) will see many patients with these indications. However, GCs' reports of inadequate preparation and low confidence in providing care for patients with psychiatric disorders can limit their ability to meet patient's needs. How frequently psychiatric disorders present in GC sessions is currently unclear. Here, we used deidentified electronic health records (EHR) to estimate the prevalence of 16 psychiatric disorders. In 7,155 GC patients, 34% had a diagnostic code associated with a psychiatric disorder; 23% with anxiety/phobic disorders; 21% with mood disorder/depression; 5% with attention deficit hyperactivity disorder (ADHD); and 1% with

psychotic disorders. Compared to 415,709 demographically matched controls, GC patients showed a significantly higher prevalence of psychiatric disorders (GC prevalence: 34%, matched prevalence: 30%, p-value < 0.0001) driven predominantly by anxiety disorder, major depressive disorder, generalized anxiety disorder, and ADHD. Within GC specialties (prenatal: nÂ =Â 2,674, cancer: n = 1,474, pediatric: n = 465), only pediatric GC patients showed a significant increase in psychiatric disorder prevalence overall (pediatric GC prevalence: 28%, matched prevalence: 13%, p-value <Â 0.0001). However, significant evidence of increased prevalence existed for generalized anxiety disorder (prenatal GC prevalence 6.4%, matched prevalence: 4.9%, p-value < 0.0001), anxiety disorders (cancer GC prevalence: 26%, matched prevalence: 21%, p-value < 0.0001 and pediatric GC prevalence: 12%, matched prevalence: 5.5%), and ADHD (pediatric GC prevalence: 18%, matched prevalence: 7.9%, p-valueÂ < 0.0001). These results highlight the need for additional guidance around care for patients with psychiatric disorders and the value of EHR-based research in genetic counseling

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J Neurodev Disord. 2022 Aug;14:45.

A FRAMEWORK FOR CHARACTERIZING HETEROGENEITY IN NEURODEVELOPMENTAL DATA USING LATENT PROFILE ANALYSIS IN A SAMPLE OF CHILDREN WITH ADHD.

Arnett AB, Flaherty BP.

BACKGROUND: Heterogeneity in neurodevelopmental disorders, and attention deficit hyperactivity disorder (ADHD) in particular, is increasingly identified as a barrier to identifying biomarkers and developing standards for clinical care. Clustering analytic methods have previously been used across a variety of data types with the goal of identifying meaningful subgroups of individuals with ADHD. However, these analyses have often relied on algorithmic approaches which assume no error in group membership and have not made associations between patterns of behavioral, neurocognitive, and genetic indicators. More sophisticated latent classification models are often not utilized in neurodevelopmental research due to the difficulty of working with these models in small sample sizes.

METHODS: In the current study, we propose a framework for evaluating mixture models in sample sizes typical of neurodevelopmental research. We describe a combination of qualitative and quantitative model fit evaluation procedures. We test our framework using latent profile analysis (LPA) in a case study of 120 children with and without ADHD, starting with well-understood neuropsychological indicators, and building toward integration of electroencephalogram (EEG) measures.

RESULTS: We identified a stable five-class LPA model using seven neuropsychological indicators. Although we were not able to identify a stable multimethod indicator model, we did successfully extrapolate results of the neuropsychological model to identify distinct patterns of resting EEG power across five frequency bands.

CONCLUSIONS: Our approach, which emphasizes theoretical as well as empirical evaluation of mixture models, could make these models more accessible to clinical researchers and may be a useful approach to parsing heterogeneity in neurodevelopmental disorders

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J Neurol. 2022 Sep;269:4997-5007.

SCHOOL PERFORMANCE AND PSYCHIATRIC COMORBIDITY IN JUVENILE ABSENCE EPILEPSY AND JUVENILE MYOCLONIC EPILEPSY: A DANISH POPULATION-BASED COHORT STUDY.

Boesen MS, et al.

Background: We aimed to determine school performance and psychiatric comorbidity in juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures (GTCS) alone.

Methods: All children (< 18 years) fulfilled International League Against Epilepsy criteria after review of their medical records. Control groups were the pediatric background population or children with non-neurological chronic disease. Outcomes were on school performance and psychiatric comorbidity. We compared mean grade point averages using linear regression and estimated hazard ratios using Cox regression in the remaining analyses. We adjusted for the child's sex, age, and year of birth; and parental highest education, receipt of cash benefits or early retirement.

Results: We included 92 JAE, 190 JME, 27 GTCS alone, 15,084 non-neurological chronic disease controls, and population controls. JAE had two times increased hazard for special needs education compared with age-matched population controls (hazard ratio 2.2, 95% CI = 1.1–4.6, p = 0.03); this was not seen in JME. Compared with population controls, both JAE and JME had lower grade point average in secondary and high school (JME: 9th grade: - 0.5 points, 95% CI = -0.9 to -0.06, p = 0.03; high school: - 0.6 points, 95% CI = -1.3 to -0.1, p = 0.04), and 8% fewer JME and 15% fewer JAE attended high school. Both JME and JAE had higher hazard for redeeming sleep medication compared with non-neurological chronic disease; additionally, JAE had increased hazard for ADHD medicine redemptions.
Conclusions: Both JAE and JME had marginally poorer school performance; performance seemed worse in JAE than in JME. Both JAE and JME had increased use of sleep medication

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J Pediatr Gastroenterol Nutr. 2022 Sep;75:286-92.
IMPACT OF NEURODEVELOPMENTAL DISORDERS ON BOWEL MANAGEMENT OUTCOMES IN CHILDREN WITH FUNCTIONAL CONSTIPATION.
Seidler GR, Knaus ME, Beyene TJ, et al.
OBJECTIVES: Patients experiencing functional constipation (FC) can participate in structured bowel management programs (BMPs) to manage constipation or fecal incontinence when standard management fails. We sought to evaluate the efficacy of BMPs for children with FC with and without neurodevelopmental disorders.
METHODS: We performed a retrospective review of children with FC who participated in our BMP from 2014 to 2021. Stool/urinary continence, bowel regimen, surgical history, parent-reported outcomes measures (PROMs: Cleveland Clinic Constipation Score, Baylor Continence Scale, Vancouver Symptom Score for Dysfunctional Elimination), and Pediatric Quality of Life Inventory (PedsQL) were assessed pre- and at least 9 months post-BMP.
RESULTS: The cohort included 156 patients with a median age of 9 years and follow-up of 627 days (IQR: 389-808 days). Two sub-cohorts included patients with FC only (69%) and FC plus a neurodevelopmental disorder (31%): 59% attention-deficit/hyperactivity disorder, 33% autism spectrum disorder, and 8% obsessive-compulsive disorder. Both groups had significantly improved follow-up bowel movement frequency and continence (39%-90% neurodevelopmental, 44%-82% FC only, $P < 0.001$) and urinary continence (65%-90% neurodevelopmental, 69%-91% FC only, $P < 0.02$). There was a significant improvement in most of the PROMs at follow-up. Both groups experienced a clinically meaningful improvement in overall PedsQL scores (pre- and postBMP difference of >4.5).
CONCLUSIONS: Patients with FC with and without a neurodevelopmental disorder had significant improvement in stool and urinary continence after undergoing a BMP. Further studies are needed to see if this improvement is durable over a longer period of time in this challenging cohort

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J Pediatr Psychol. 2022 Aug;47:892-904.
INDIVIDUAL DIFFERENCES IN GERM SPREADING BEHAVIORS AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE ROLE OF EXECUTIVE FUNCTIONING.
Hernandez ML, Spiegel JA, Coxe S, et al.
Objective: Infectious diseases, such as coronavirus disease 2019 (COVID-19), are commonly transmitted by respiratory droplets and contact with contaminated surfaces. Individuals with attention-deficit/hyperactivity disorder (ADHD) are more likely to be infected with COVID-19 and experience more hospitalizations than individuals without ADHD. The current study investigated the role of ADHD symptomatology and executive functioning (EF) in germ spreading behavior frequency among young children with and without ADHD and parenting responses to these behaviors.
Methods: Participants included 53 children diagnosed with ADHD and 47 typically developing (TD) children between the ages of 4-5 years (76% male; Mage = 4.62; 86% Hispanic/Latinx). Parents and teachers reported on children's ADHD symptomatology and children completed three EF tasks. Germ spreading

behavior frequency (direct contact of hand to face and toy in mouth) and parenting responses (verbal and nonverbal behaviors) were observed during a 5-min parent-child play situation.
Results: Negative binomial regression analyses indicated that both ADHD diagnostic status and poor metacognition predicted both higher rates of toy to mouth (β = 1.94, p < .001; β = 0.03, p = .004) and face touching frequency (β = 0.60, p = .03; β = 0.03, p = .004), respectively. Additionally, poor attention and worse cognitive flexibility only predicted higher rates of toy to mouth frequency (β = 0.09, p < .001; β = -0.04, p = .001), respectively.
Conclusions: Young children with ADHD are at high risk for spreading germs via putting toys in their mouth and touching their face. Particularly, high levels of inattention and poor EF appear to be associated with higher rates of germ spreading behaviors

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JACCP Journal of the American College of Clinical Pharmacy. 2022;5:772-73.
RISK FOR SUICIDAL IDEATION WITH ATOMOXETINE AND BUPROPION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A COHORT STUDY.
Coon S, Tabulov C, Garcia A.
Introduction: Atomoxetine and bupropion are used for attention-deficit/ hyperactivity disorder (ADHD) and both carry a black box warning for suicidal ideation (SI). Little is known about the effect this combination has on SI in patients with ADHD. Research Question or Hypothesis: What is the incidence of SI in patients with ADHD? Does the combination of atomoxetine and bupropion increase risk for SI compared to atomoxetine in patients with ADHD? Study
Design: Retrospective cohort study and time-to-event analysis
Methods: A retrospective cohort study was conducted using the TriNetX electronic health records network. The primary cohort included patients (6-24 years old) with ADHD from Jan. 1, 2016-Dec. 31, 2020. Additional cohorts were created from the primary cohort, varying based on treatment exposure. For the primary analysis, patients with ADHD prescribed atomoxetine and bupropion (Cohort ATX+BUP) were compared to a matched control prescribed atomoxetine (Cohort ATX). The index event was the first instance in which both diagnosis and medication criteria were met.
Data Analysis: The incidence of SI was calculated for all cohorts. Cohorts ATX+BUP and ATX were balanced using a matched 1:1 propensity score algorithm. Covariates included: age, sex, race, medications (CN600, CN700), and ICD-10 codes (R45.85, Z81; Z91; T50.902; S00-T88; F30-F39; F10-F19). The incidence of SI was estimated and compared via Kaplan-Meier analysis and log-rank test, respectively. Hazard ratios and 95% confidence intervals were calculated via proportional hazard model.
Results: The incidence of SI varied, with the lowest rate in the pharmacotherapy-excluded cohort (0.0182 cases/person-year; n=206,320) and highest in the atomoxetine and bupropion cohort (0.0876 cases/person-year; n=1,740). At 60 months, SI occurred in 334/1,739 of the post-match Cohort ATX+BUP and 289/1,739 of the post-match Cohort ATX, HR 1.196 (95%CI 1.022,1.4, p=0.0257).
Conclusion: The incidence of SI was high in patients with ADHD and was highest among those receiving atomoxetine and bupropion. The addition of bupropion to atomoxetine increased risk for SI

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J Affective Disord. 2022;313:27-31.
A PLANT-BASED DIETARY SCORE AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN IRANIAN CHILDREN: A CASE-CONTROL STUDY.
Darand M, Hassanizadeh S, Martami F, et al.
Objective: Attention-deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder with a prevalence of 5 % among children and adolescents worldwide. Plant foods have a protective effect against inflammation and oxidative stress which both are involved in psychiatric disorders pathophysiology including ADHD. Accordingly, we investigated the association between plant-based diet (PDI) and ADHD.
Methods: This case-control study was conducted on 345children and adolescents 7-13 years old in Yazd, Iran. Subjects were categorized into the case (n = 113) and control groups (n = 232) based on matching age

and sex. To diagnose ADHD, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMIV-TR) was used. Food frequency questionnaire was used to measure food intake. The association of PDI with ADHD was examined by logistic regression.
Results: Children in the highest quartile of PDI compared to the lowest quartile had a higher energy and macronutrient intake, calcium, zinc, iron, vitamin B12, B6, and folic acid. After adjusting for potential confounders, a significant decreasing trend in the odds of ADHD across increasing quartiles of the PDI (P-trend = 0.001) was observed. In addition, children in the fourth quartile of PDI had 68 % lower odds of ADHD than the first quartile. This association remained significant after further adjustment for BMI (OR: 0.32;95 % CI: 0.13-0.79; P for trend: 0.001).
Conclusion: We found that PDI is associated with lower risk of ADHD in children. Cohort and clinical studies are necessary to approve our results

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Journal of Child and Adolescent Trauma. 2022.
AN EXPLORATORY INVESTIGATION OF CHILDHOOD SEXUAL ABUSE AND OTHER THEORY-DRIVEN PREDICTORS OF SEX WORK AMONG WOMEN WITH AND WITHOUT CHILDHOOD ADHD.
Halkett A, et al.
Limited research has identified prospective risk factors for young-adult sex work or examined overlapping predictors concurrently. We investigated childhood sexual abuse (CSA), along with other theory-driven predictors of sex work, among a well-characterized sample of girls with and without childhood diagnoses of attention/deficit-hyperactivity disorder (ADHD). Methods: Participants were a racially and socioeconomically diverse sample of 140 girls with rigorously diagnosed ADHD (47 Inattentive [ADHD-I], 93 Combined [ADHD-C]), and 88 age- and ethnicity-matched comparison girls, all followed longitudinally into adulthood. Self-report data on young-adult occupations revealed a subsample of 7 participants reporting engagement in ΓÇ£sex workΓÇØ or ΓÇ£prostitution.ΓÇØ Logistic regressions tested whether CSA, measured both dichotomously and by discrete age ranges, predicted later sex work, accounting for other risk factors. Results: A lifetime history of CSA was positively associated with sex work in initial analyses (+¦ = 1.51, p =.045), but not after adjusting for additional risk factors. When examined by age ranges, only CSA occurring between ages 9-15 significantly predicted sex work (+¦ = 2.84, p =.043), even after adjusting for additional risk factors. Childhood ADHD-C also emerged as a significant predictor (+¦ = 4.94, p =.015). ADHD-related medication and years of education were protective factors only when CSA was considered dichotomously. Conclusions: Findings from this exploratory study underscore the need for longitudinal research that (a) considers the developmental timing of CSA and (b) accounts for impulsivity and inattention as risk factors for sex work among young-adult women. Implications for clinical practice are briefly discussed

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J Child Fam Stud. 2022 Aug;31:2077-90.
EVALUATION OF AN INTEGRATED PARENTING INTERVENTION TARGETING MATERNAL DEPRESSION: EFFECTS ON PARENT ATTRIBUTIONS OF CHILD BEHAVIORS.
Novick DR, Lorenzo NE, Danko CM, et al.
More than half of mothers of children with ADHD have a lifetime history of major depressive disorder. Prior research has thus examined treatments integrating behavioral parent training (BPT) and cognitive-behavioral therapy (CBT) to target parent depressive symptoms that may contribute to negative parent/child behaviors. However, little is known about whether such interventions affect depressogenic cognitions of child behaviors and pathways by which these cognitions impact parenting. This study examined effects of the integrated parenting intervention for ADHD (IPI-A; a combination of group CBT for depression with BPT), and standard BPT on post-treatment child-blaming and child-crediting attributions, and maternal expectations of child compliance. We hypothesized that randomization to IPI-A would predict greater reductions in depressogenic cognitions of child behavior, relative to BPT. The current study also explored maternal attributions as mechanisms of change in observed parenting outcomes. Participants were 98 children (Mage = 8.78; 66% Male) with ADHD and their biological mothers with at least a mild level of depressive symptoms. Mothers in

IPI-A reported significantly more post-treatment child-crediting attributions relative to those in BPT. Treatment group was not associated with post-treatment child-blaming attributions or expectations for child compliance. Exploratory mediation analyses demonstrated that post-treatment child-crediting attributions mediated the association between treatment condition and observed negative parenting at post-treatment. Specifically, mothers in IPI-A (vs. BPT) exhibited less negative parenting at post-treatment via more child-crediting attributions. These findings indicate that integrating CBT skills in BPT for child ADHD enhances outcomes on child-crediting attributions for mothers with elevated depressive symptoms

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Journal of Clinical Medicine. 2022;11.

METHYLPHENIDATE USE FOR EMOTIONAL DYSREGULATION IN CHILDREN AND ADOLESCENTS WITH ADHD AND ADHD AND ASD: A NATURALISTIC STUDY.

Ventura P, de Giambattista C, Trerotoli P, et al.

Emotional dysregulation (ED) is common in attention-deficit/hyperactivity disorder (ADHD). Nonetheless, research on ADHD in children with autism spectrum disorder (ASD) and ADHD is still ongoing. Several studies suggest that methylphenidate (MPH) may be effective for ED in ADHD, while there is not enough evidence about its use in ASD with comorbid ADHD. This naturalistic study aims to investigate the effectiveness of immediate-and extended-release MPH in the treatment of ED in 70 children and adolescents (6ΓÇô18 years), with a diagnosis of ADHD (n = 41) and of ASD with comorbid ADHD (n = 29), using the Child Behavior Checklist-Attention/Aggressive/Anxious (CBCL-AAA). Their parents completed the CBCL twice-first during the summer medication-free period, that is, at least one month after drug interruption; and again after three months of treatment restart. Results demonstrate that MPH is associated with a statistically significant reduction in ED in ADHD and ASD, without substantial adverse events, supporting the use of psychostimulants for the treatment of ED in these neurodevelopmental disorders

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Journal of Clinical Psychology in Medical Settings. 2022.

EFFECTIVENESS OF CLINIC-BASED BRIEF BEHAVIORAL INTERVENTION (BBI) IN LONG-TERM REDUCTION OF ADHD SYMPTOMS AMONG PRESCHOOLERS.

Teasdale AE, Duran PA, Axelrad ME.

Preschoolers commonly experience symptoms of ADHD and disruptive behavior problems. Behavioral parent management training (PMT) is an evidence-based intervention for addressing both ADHD and disruptive behaviors in this population; however, many PMT programs are burdensome in length and have limited data regarding long-term effectiveness for ADHD specific outcomes. This study examined outcomes up to 1-áyear following completion of a brief behavioral intervention (M = 6.51 sessions) for preschoolers. Participants were children aged 2ΓÇô6-áyears with clinically significant disruptive behaviors and their parents. Results demonstrated significant improvements in parent-reported child hyperactivity and inattention from pre-to-post intervention, with sustained improvement at 6-ámonths and 1-áyear post intervention. Teacher-reported hyperactivity and inattention also showed significant improvements from pre-to-post intervention, which were maintained across time points. These results were also found among a subset of participants with clinically significant ADHD symptoms at baseline. This study highlights the long-term effectiveness of a brief PMT program to address symptoms of ADHD and disruptive behaviors in preschoolers. Findings support the recommendation to offer PMT as a first-line intervention for preschoolers with ADHD symptoms to reduce the need for early intervention with stimulant medication and address comorbid disruptive behaviors

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J Cogn Dev. 2022.

REWARDS CAN FOSTER RESPONSE EXECUTION AND RESPONSE INHIBITION IN YOUNG CHILDREN DIAGNOSED WITH ADHD.

Sader A, Walg M, Ferdinand NK.

Children with ADHD show deficits in executive functioning, especially the ability to inhibit inadequate responses, and deficits in motivational processes due to dopaminergic dysfunctions. There is evidence that rewards can foster inhibition in children with ADHD. However, most studies examined a wide age range of children above 7 years of age, so almost nothing is known about inhibition and reward effects on inhibition in younger children. The primary goals of the present study were a) to examine response inhibition in young children with ADHD in a relatively narrow age range (5-8 years) in comparison to children without ADHD b) to investigate whether performance in an inhibition task can be fostered by rewards in this young age group. For this purpose, children with ADHD (n=20) and control children (n=20) were recruited from schools as well as pediatric, psychiatric, and psychological practices in North Rhine-Westphalia, Germany. Children conducted a Go/NoGo task under a non-rewarded and a rewarded condition. Our findings demonstrate a generally decreased response inhibition in ADHD as compared to control children. Rewards led to improvements in response inhibition in both groups of children. However, in contrast to control children whose ability to inhibit increased with practice in both conditions, children with ADHD inhibition decreased over the course of the non-rewarded condition but was raised by the prospect of a reward at the start of the reward condition. Thus, it seems that already at this young age, German children without ADHD are better able to keep their inhibition ability up over time than children with ADHD

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Journal of Medical Signals and Sensors. 2022;12:254-62.

DETECTION OF ADHD FROM EOG SIGNALS USING APPROXIMATE ENTROPY AND PETROSAIN'S FRACTAL DIMENSION.

Sho'ouri N .

Background: Previous research has shown that eye movements are different in patients with attention deficit hyperactivity disorder (ADHD) and healthy people. As a result, electrooculogram (EOG) signals may also differ between the two groups. Therefore, the aim of this study was to investigate the recorded EOG signals of 30 ADHD children and 30 healthy children (control group) while performing an attention-related task.

Methods: Two features of approximate entropy (ApEn) and Petrosian's fractal dimension (Pet's FD) of EOG signals were calculated for the two groups. Then, the two groups were classified using the vector derived from two features and two support vector machine (SVM) and neural gas (NG) classifiers.

Results: Statistical analysis showed that the values of both features were significantly lower in the ADHD group compared to the control group. Moreover, the SVM classifier (accuracy: 84.6% -¦ 4.4%, sensitivity: 85.2% -¦ 4.9%, specificity: 78.8% -¦ 6.5%) was more successful in separating the two groups than the NG (78.1% -¦ 1.1%, sensitivity: 80.1% -¦ 6.2%, specificity: 72.2% -¦ 9.2%).

Conclusion: The decrease in ApEn and Pet's FD values in the EOG signals of the ADHD group showed that their eye movements were slower than the control group and this difference was due to their attention deficit. The results of this study can be used to design an EOG biofeedback training course to reduce the symptoms of ADHD patients

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Journal of Nephrology. 2022.

UTILITY OF CONTINUOUS PERFORMANCE TEST (MOXO-CPT) IN CHILDREN WITH PRE-DIALYSIS CHRONIC KIDNEY DISEASE, DIALYSIS AND KIDNEY TRANSPLANTATION.

Ekim M, et al.

Background: Children with chronic kidney disease and on kidney replacement therapy may have neurocognitive and psychosocial disorders. Although kidney transplantation improves quality of life, psychological problems may exist in children who undergo kidney transplantation. Herein, we aimed to investigate attention-deficit hyperactivity disorder-like symptoms with MOXO-continuous performance test in children with pre-dialysis chronic kidney disease, dialysis and kidney transplantation.

Methods: The MOXO-continuous performance test measures four domains of attention-deficit hyperactivity disorder-like symptoms, including attention, timeliness, hyperactivity and impulsivity. Patients with at least three scores < -1.5 standard deviations were considered as-ápositive to MOXO-continuous performance test. Test scores of the pre-dialysis chronic kidney disease, dialysis (divided into-áperitoneal dialysis and hemodialysis subgroups) and kidney transplantation groups were compared. Correlations of test scores with the patient's clinical and laboratory-ácharacteristics and effects of hospitalizations and schooling were assessed.
Results: Seventy-two patients aged 13.3 -¦ 3.4 years (23 with kidney transplantation, 23 on dialysis and 26 with-pre-dialysis chronic kidney disease) were evaluated. Overall MOXO-continuous performance test positivity was 29%. No differences were detected between the three groups concerning total or z scores. Attention and timeliness z scores were significantly higher in females (p = 0.004 and p = 0.008, respectively). Age was positively correlated to attention and timeliness total scores (p = 0.000, r = 0.445 and p = 0.004, r = 0.243, respectively), and inversely correlated to hyperactivity total scores (p = 0.000, r = -0.415).
Conclusions: Prevalence of attention-deficit hyperactivity disorder-like symptoms in the study population was much higher than that of pediatric attention-deficit hyperactivity disorder. We believe that the MOXO-continuous performance test is a valid supportive measure for evaluation of attention-deficit hyperactivity disorder diagnosis in children with various stages of chronic kidney disease or on kidney replacement therapy. Graphical abstract: [Figure not available: see fulltext.]

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J Neursurg Pediatr. 2022;30:188-94.

PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND INTELLECTUAL DISABILITY AMONG CHILDREN WITH HYDROCEPHALUS.

Maleknia P, Chalamalla AR, Arynchyna-Smith A, et al.

OBJECTIVE Little is known about the prevalence of attention-deficit/hyperactivity disorder (ADHD) in children with hydrocephalus. In this study, the authors assessed the prevalence of ADHD and its association with clinical and demographic factors, including intellectual disability (ID), a potential factor that can confound the diagnosis of ADHD.

METHODS The authors conducted a cross-sectional study of children 6ΓÇô12 years of age with hydrocephalus using parent telephone surveys. The Child and Adolescent Intellectual Disability Screening Questionnaire (CAIDS-Q) and the National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale were used to screen for ID and ADHD, respectively. Among children without ID, the authors identified those with ADHD and calculated a prevalence estimate and 95% confidence interval (Wald method). Logistic regression analysis was conducted to compare children with ADHD with those without ADHD based on demographics, family income, parental educational, etiology of hydrocephalus, and primary treatment. As a secondary analysis, the authors compared subjects with ID with those without using the same variables. Multivariable analysis was used to identify factors with independent association with ADHD and ID.

RESULTS A total of 147 primary caregivers responded to the telephone questionnaire. Seventy-two children (49%) met the cutoff score for ID (CAIDS-Q). The presence of ID was significantly associated with lower family income (p < 0.001). Hydrocephalus etiology (p = 0.051) and initial treatment (p = 0.06) approached significance. Of children without ID (n = 75), 25 demonstrated a likely diagnosis of ADHD on the NICHQ, yielding a prevalence estimate of 0.33 (95% CI 0.22-0.44). No clinical or demographic variable showed significant association with ADHD.

CONCLUSIONS These data indicate that the prevalence of ADHD among children with hydrocephalus (33%) is higher than among the general population (estimated prevalence in Alabama is 12.5%). ID is also common (49%). Routine screening for ADHD and ID in children with hydrocephalus may help to ensure that adequate resources are provided to optimize functional outcomes across development

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Journal of Obstetrics and Gynaecology Canada. 2022;44:608.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN BORN TO PATIENTS WITH INFERTILITY: A POPULATION-BASED COHORT STUDY.

Fine A, Dayan N, Djerboua M, et al.

Objectives: Long-term neurodevelopmental outcomes in children conceived to mothers requiring infertility treatment are unknown. We investigated the association between infertility, infertility treatment, and risk of childhood attention deficit disorder (ADHD).

Methods: This population-based cohort study included infants born at ΓëÑ 24 weeks gestation across all of Ontario, 2006-2014. The study exposure was conception type: i) unassisted conception (referent), ii) subfertility (an infertility consult < 2 years prior to conception without subsequent infertility treatment), iii) ovulation induction or intrauterine insemination (OI/IUI), and iv) in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI). Cox proportional-hazards models generated hazard ratios (HR) for the association between each exposure category and the risk of ADHD diagnosed at age 6 years or later, adjusting for maternal demographics, substance use, and pre-existing conditions including mental illness.

Results: 922 383 children were born to 661 072 mothers: 87.0% following unassisted conception; 10.2% with subfertility, 1.3% OI/IUI, and 1.5% IVF/ICSI. Starting at age 6 years, children were followed for a median of 4 years (IQR 2ΓÇô6) thereafter. Relative to the offspring in the unassisted conception group (5.9%), the risk of ADHD was highest in the subfertility group (6.1% an adjusted HR of 1.16 [95% CI 1.13ΓÇô1.19]). OI/IUI was not associated with ADHD (5.5%; HR 1.07 [95% CI 0.99-1.17]), or IVF/ICSI (4.5%; HR 0.99 [95% CI 0.91ΓÇô1.08]).

Conclusions: In the absence of receiving infertility treatment, maternal subfertility alone may be an unrealized risk factor for ADHD in the offspring. The reason for why this is so warrants further study.

Keywords: ADHD; infertility treatment; subfertility; IVF; pregnancy

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J Psychiatr Res. 2022;152:201-18.

A SYSTEMATIC REVIEW OF INTERVENTIONS TO ENHANCE ADHERENCE AND PERSISTENCE WITH ADHD PHARMACOTHERAPY.

Parkin R, Nicholas FM, Hayden JC.

Although high rates of poor adherence/persistence have been documented in ADHD, there is limited research targeting the problem. This systematic review evaluated interventions to address poor adherence/persistence to ADHD pharmacotherapy, with the aim of guiding the development of future interventions. An extensive search was conducted from January 1980 until January 2021. Thirteen studies were identified involving interventions based on psychoeducation, behavioural therapy, combined psychoeducation/behavioural therapy, technology-based interventions, written informed consent and a nursing support line. All 13 studies (including five RCTs) reported improvement in adherence/persistence and five studies (including four RCTs) also reported improvement in ADHD symptomatology. Almost all studies involved interventions utilising some form of education. Three RCTs of psychoeducation alone were included, with two of the three studies reporting adherence benefits at three and 12 months respectively. The third RCT was terminated early due to poor recruitment. A behavioural intervention RCT reported improved adherence six months post intervention (but not at 12 months), although a substantial drop-out rate was observed. A final included RCT used a Smartphone Application and reported a short term increase in adherence. The authors of the studies in this review make salient attempts at improving adherence and provide insight for future intervention development. We believe future interventions should involve combinations of strategies, have a theoretical framework and target the most common reasons for non-adherence. Interventions should also be integratable into routine care and include patient input to maximise sustainability

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J Psychiatr Res. 2022;155:49-67.

EXAMINING THE IMPACT OF ADHD POLYGENIC RISK SCORES ON ADHD AND ASSOCIATED OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Green A, Baroud E, DiSalvo M, et al.

Early identification of attention-deficit/hyperactivity disorder (ADHD) is critical for mitigating the many negative functional outcomes associated with its diagnosis. Because of the strong genetic basis of ADHD, the use of polygenic risk scores (PRS) could potentially aid in the early identification of ADHD and associated outcomes. Therefore, a systematic search of the literature on the association between ADHD and PRS in pediatric populations was conducted. All articles were screened for a priori inclusion and exclusion criteria, and, after careful review, 33 studies were included in our systematic review and 16 studies with extractable data were included in our meta-analysis. The results of the review were categorized into three common themes: the associations between ADHD-PRS with 1) the diagnosis of ADHD and ADHD symptoms 2) comorbid psychopathology and 3) cognitive and educational outcomes. Higher ADHD-PRS were associated with increased odds of having a diagnosis (OR = 1.37; p<0.001) and more symptoms of ADHD (+¦ = 0.06; p<0.001). While ADHD-PRS were associated with a persistent diagnostic trajectory over time in the systematic review, the meta-analysis did not confirm these findings (OR = 1.09; p = 0.62). Findings showed that ADHD-PRS were associated with increased odds for comorbid psychopathology such as anxiety/depression (OR = 1.16; p<0.001) and irritability/emotional dysregulation (OR = 1.14; p<0.001). Finally, while the systematic review showed that ADHD-PRS were associated with a variety of negative cognitive outcomes, the meta-analysis showed no significant association (+¦ = 0.08; p = 0.07). Our review of the available literature suggests that ADHD-PRS, together with risk factors, may contribute to the early identification of children with suspected ADHD and associated disorders

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J Psychopathol Behav Assess. 2022.

DOES CHILD ANXIETY EXACERBATE OR PROTECT AGAINST PARENTΓÇôCHILD RELATIONSHIP DIFFICULTIES IN CHILDREN WITH ELEVATED ADHD SYMPTOMS?

Chan ESM, Maclas M, Kofler MJ.

Pediatric ADHD is associated with parent child relationship difficulties. However, the extent to which these relations are attributable to specific ADHD symptom clusters (i.e., inattentive vs. hyperactive/impulsive), and the extent to which child anxiety symptoms may exacerbate or protect against these difficulties, remains unclear. To address these gaps in the literature, the current study combined multi-informant measures (parent, teacher, child) with a clinically-evaluated and carefully-phenotyped sample of 188 children with and without ADHD and anxiety (ages 8ΓÇô13; 63 girls). Results indicated that child-reported anxiety (+¦ =.46) and teacher-reported inattentive (+¦ =.71) symptoms, and their interaction (+¦ = -1.06), along with child age and IQ (+¦ = -.14 to -.15), predict the extent to which parents perceive themselves as confident and competent parents (all p <.05). In contrast, only comorbid oppositional-defiant disorder conferred risk for increased parent-reported relational frustration, and we were unable to detect any reliable child-level demographic, diagnostic, or behavioral predictors of parent-reported discipline practices. These findings were robust to control for child demographic characteristics, clinical diagnoses, and intellectual functioning, with sensitivity analyses highlighting the importance of assessing ADHD inattentive vs. hyperactive/impulsive symptoms separately for understanding parenting outcomes. Taken together, the current findings suggest that child ADHD and anxiety symptoms may influence specific rather than broad-based aspects of the parentΓÇôchild relationship, and produce differently valenced outcomes in the presence vs. absence of the other condition. Interestingly, it appears that the combination of greater child inattention and anxiety, rather than elevations in either symptom domain independently, predict adverse parenting outcomes in terms of reduced parental confidence

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J Am Acad Child Adolesc Psychiatry. 2022.

EFFICACY AND SAFETY OF LISDEXAMFETAMINE IN PRESCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Lloyd E, Jacobsen L, et al.

Objective: To evaluate the acute efficacy, safety, and tolerability of lisdexamfetamine dimesylate (LDX) vs placebo (PBO) in preschool-aged children with attention-deficit/hyperactivity disorder (ADHD). Method: This phase 3, double-blind, fixed-dose study randomly assigned children (aged 4-5 years) with ADHD to 6 weeks of LDX (5, 10, 20, 30 mg) or PBO. The prespecified primary (change from baseline at week 6 in ADHD Rating Scale IV, Preschool version, total score [ADHD-RS-IV-PS-TS]) and key secondary (Clinical Global Impression Improvement [CGI-I] score at week 6) efficacy endpoints were assessed using linear mixed-effects models for repeated measures. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and changes in pulse and blood pressure (BP).

Results: The study comprised 199 participants randomly asigned 5:5:5:5:6 to receive 5, 10, 20, 30 mg LDX or PBO, respectively. Least squares (LS) mean (95% CI) treatment difference at week 6 between pooled LDX (10, 20, 30 mg) and PBO was statistically significant for ADHD-RS-IV-PS-TS change (5.9 [11.01, 0.78], p = .0242; effect size [ES], 0.43). CGI-I scores improved (ie, 1-2 on CGI-I) in 41.7% for pooled LDX and 24.3% for PBO (p = .0857). The LS mean (95% CI) treatment difference between pooled LDX and PBO for CGI-I score at week 6 was 0.6 (ΓÇô1.03, 0.16; p = .0074; ES, 0.52). Frequency of TEAEs was 46.6% across all 4 LDX doses vs 42.2% with PBO; the most frequent TEAEs were decreased appetite (13.7% vs 8.9%, respectively) and irritability (9.6% vs 0%). Discontinuations because of TEAEs were 5.5% for all LDX doses and 4.4% for PBO. Mean -¦ SD pulse/BP changes from baseline at week 6/early termination were numerically greater with LDX vs PBO (pulse beats/min: 2.7 -¦ 10.79 vs 1.2 -¦ 9.90; systolic BP, mm Hg: 1.0 -¦ 7.51 vs 0.3 -¦ 6.06; diastolic BP, mm Hg: 1.7 -¦ 5.90 vs 0.0 -¦ 6.88).

Conclusion: In children aged 4 to 5 years with ADHD, LDX was more efficacious than PBO in reducing symptoms. The observed ES for change in ADHD-RS-IV-PS-TS appears to be smaller in magnitude than has been reported for studies of LDX conducted in older children and adolescents. LDX was generally well tolerated, and no new safety signals were identified.

Clinical trials registry information: Safety and Efficacy Study in Preschool Children Aged 4ΓÇô5 Years With Attention-Deficit/Hyperactivity Disorder; http://www.clinicaltrials.gov; NCT03260205

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L'Encéphale: Revue de psychiatrie clinique biologique et thérapeutique. 2022 Jun;48:354-58.

ADAPTING A PARENT TRAINING PROGRAM TO THE COVID-19 CRISIS IN A MENTAL HEALTH CARE SETTING IN FRANCE.

Maurice V, Didillon A, Purper-Ouakil D, et al.

In the event of the COVID-19 outbreak in France and the consequent lockdown established by the French Government in March 2020, care delivery had to be adapted in many French mental health settings in order to ensure continuing access to mental health care according to patients' needs since face-to-face support was no longer possible. Léo is an 8-year-old boy who was diagnosed with ADHD in October 2019 in our unit. His parents had previously participated in the face-to-face BPT program at the end of 2019.In summary, Léo's parents started by organizing a daily 'special moment' with Léo alone. In this article, we describe how the BPT program was adapted to an online group format at Saint Eloi Hospital of Montpellier, to ensure continuity of care for parents of school aged children with a diagnosis of ADHD in the context of the Covid-19 crisis, a setting that is suggested to cause worsening of ADHD symptoms and behavioral disturbances. In conclusion, the Online-BPT seems to allow continuity of care while being compatible and complementary with existing health care services and would be maintained after the health crisis

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Lancet Psychiatry. 2022 Sep;9:715-24.

NEUROPSYCHIATRIC RISK IN CHILDREN WITH INTELLECTUAL DISABILITY OF GENETIC ORIGIN: IMAGINE, A UK NATIONAL COHORT STUDY.

Wolstencroft J, Wicks F, Srinivasan R, et al.

BACKGROUND: Children with intellectual disability frequently have multiple co-morbid neuropsychiatric conditions and poor physical health. Genomic testing is increasingly recommended as a first-line investigation for these children. We aim to determine the effect of genomics, inheritance, and socioeconomic deprivation on neuropsychiatric risk in children with intellectual disability of genetic origin as compared with the general population.

METHODS: IMAGINE is a prospective cohort study using online mental health and medical assessments in a cohort of 3407 UK participants with intellectual disability and pathogenic genomic variants as identified by the UK's National Health Service (NHS). Our study is on a subset of these participants, including all children aged 4-19 years. We collected diagnostic genomic reports from NHS records and asked primary caregivers to provide an assessment of their child using the Development and Well-Being Assessment (DAWBA), the Strengths and Difficulties Questionnaire (SDQ), the Adaptive Behaviour Assessment System 3 (ABAS-3), and a medical history questionnaire. Each child was assigned a rank based on their postcode using the index of multiple deprivation (IMD). We compared the IMAGINE cohort with the 2017 National Survey of Children's Mental Health in England. The main outcomes of interest were mental health and neurodevelopment according to the DAWBA and SDQ.

FINDINGS: We recruited 2770 children from the IMAGINE study between Oct 1, 2014 and June 30, 2019, of whom 2397 (86·5%) had a basic assessment of their mental health completed by their families and 1277 (46·1%) completed a medical history questionnaire. The mean age of participants was 9·2 years (SD 3·9); 1339 (55·9%) were boys and 1058 (44·1%) were girls. 355 (27·8%) of 1277 reported a seizure disorder and 814 (63·7%) reported movement or co-ordination problems. 1771 (73·9%) of 2397 participants had a pathogenic copy number variant (CNV) and 626 (26·1%) had a pathogenic single nucleotide variant (SNV). Participants were representative of the socioeconomic spectrum of the UK general population. The relative risk (RR) of co-occurring neuropsychiatric diagnoses, compared with the English national population, was high: autism spectrum disorder RR 29·2 (95% CI 23·9-36·5), ADHD RR 13·5 (95% CI 11·1-16·3). In children with a CNV, those with a familial variant tended to live in more socioeconomically deprived areas than those with a de novo variant. Both inheritance and socioeconomic deprivation contributed to neuropsychiatric risk in those with a CNV.

INTERPRETATION: Children with genomic variants and intellectual disability are at an increased risk of neuropsychiatric difficulties. CNV variant inheritance and socioeconomic deprivation also contribute to the risk. Early genomic investigations of children with intellectual disability could facilitate the identification of the most vulnerable children. Additionally, harnessing parental expertise using online DAWBA assessments could rapidly identify children with exceptional needs to child mental health services. FUNDING: UK Medical Research Council and Medical Research Foundation

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Malawi Med J. 2022 Jun;34:105-10.

PREVALENCE AND CORRELATES OF COMMON MENTAL DISORDERS AMONG CHILDREN AND ADOLESCENTS IN BLANTYRE-URBAN, MALAWI.

Matandika I, Mategula D, Kasenda S, et al.

BACKGROUND: The high global prevalence of mental disorders justifies the need to quantify their burden in the sub-Saharan Africa where there is a dearth of information. These mental disorders are linked to different socio-demographic factors.

OBJECTIVE: To determine the prevalence of, and factors associated with mental disorders among children and adolescents in Blantyre City, Malawi. METHODS: Children and adolescents aged 6 to 17 years were interviewed to determine their socio-demographic characteristics and assess their mental health status using the Strengths and Difficulties Questionnaire (SDQ) and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Associations between mental disorders and socio-demographic characteristics were tested using Chi-square and logistic regression analysis.

RESULTS: The prevalence of symptoms of psychopathology on the SDQ was 7.3% (95%CI 4.8-10.5%) while for the K-SADS was 5.9% (95% CI 3.7%-8.9%). The prevalence of mental disorders across the age ranges of 6 to 12 years and 13 to 17 years was 5.4% and 7.9 % respectively. Males had a higher prevalence (7.1%) compared to females (4.7%). Conduct disorder was most prevalent (3.4%), followed by either type of ADHD-Attention Deficit Hyperactive Disorders (2.0%). Having a single parent (p<0.001), staying with a non-biological guardian (p<0.030), engaging in paid work (p<0.039), not attending school (p<0.019) and having teacher difficulties(p<0.028) were positively associated with a mental disorder.
CONCLUSION: The socio-demographic factors associated with the risk of developing mental disorders may be important targets for mental health intervention programs

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MedEdPORTAL. 2022;18:11270.
MENTAL HEALTH IN THE MEDICAL HOME: A LONGITUDINAL CURRICULUM FOR PEDIATRIC RESIDENTS ON BEHAVIORAL AND MENTAL HEALTH CARE.
Meyers N, Maletz B, Berger-Jenkins E, et al.
INTRODUCTION: Currently, a pediatric mental and behavioral health crisis exists, driven by increasing stressors among children coupled with a paucity of psychiatric providers who treat children. Pediatric primary care providers can play a critical role in filling this gap, yet trainees feel uncomfortable screening for, identifying, and managing mental and behavioral health conditions among their patients. Thus, expanding training for pediatricians in this domain is critical.
METHODS: We created a longitudinal integrated mental and behavioral health curriculum for pediatric residents at NewYork-Presbyterian/Columbia University Irving Medical Center with a logic model contextualizing outpatient pediatric care as a framework for the development and planned evaluation. We devised a comprehensive set of materials, with presentations on topics including attention deficit hyperactivity disorder and anxiety disorders. Workflows and escalation pathways promoting collaboration among interdisciplinary providers were implemented. We evaluated residents' and faculty members' participation in the curriculum and their perception of curricular gaps.
RESULTS: Approximately 155 pediatric residents participated in the curriculum from 2017 to 2021, reflecting robust curricular exposure. Few residents and no preceptors perceived mental and behavioral health as a curricular gap.
DISCUSSION: Our curriculum is feasible and can be adapted to a variety of educational settings. Its use of a logic model for development, implementation, and ongoing evaluation grounds the curriculum in educational theory and can address curricular gaps. The framework can be adapted to suit the needs of other institutions' educational and practice settings and equip pediatric trainees with the skills to promote patient mental health and well-being

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Medicine Today. 2022;23:39-44.
ADHD IN CHILDREN WHAT THE GP CAN DO.
Poulton A, Kramer J.
Although treatment of attention deficit hyperactivity disorder (ADHD) usually involves specialist input, the GP plays an important role in assessment and arranging nonpharmacological treatment while waiting for a paediatric appointment. Assessment of a child showing typical ADHD features of inattention, hyperactivity or impulsivity focuses on whether the behaviour is out of proportion to his or her developmental level and whether it is causing functional impairment

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Mental Health and Physical Activity. 2022;23.

ACUTE EFFECTS OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTION IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Sibbick E, Boat R, Sarkar M, et al.

Attention-deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders in children and adolescents, is typically managed with medications which are associated with negative side effects. Therefore, non-pharmacological treatments, such as physical activity, are an attractive option. The aim of this meta-analysis was to explore the effects of acute physical activity on cognition in children and adolescents with ADHD. A comprehensive search of three literature databases yielded 14 studies for inclusion. An overall meta-analysis was conducted alongside sub-group analyses for cognitive domain, physical activity characteristics, and timing of cognitive measurements. Results revealed a small beneficial effect of physical activity on cognitive function (SMD = 0.18, [0.12,0.25], p < 0.01). Sub-group analyses revealed beneficial effects of physical activity on the domains of cognitive flexibility (SMD = 0.21, [0.09,0.32], p < 0.01), attention (SMD = 0.20, [0.09,0.32], p = 0.001), and inhibitory control (SMD = 0.18, [0.03,0.33], p = 0.02), but not memory (p = 0.87). Cognitive benefits also differed depending on physical activity duration (<10 min, p = 0.27; 11ΓÇô20 min, SMD = 0.23, [0.14,0.31], p < 0.01; >20 min, SMD = 0.13, [-0.00,0.26], p = 0.05), and modality (running, SMD = 0.21, [0.12,0.29], p < 0.01; ΓÇÿotherΓÇÖ, SMD = 0.39, [0.18,0.61], p < 0.01; cycling, p = 0.35), and the timing of cognitive measurement following physical activity (immediately, SMD = 0.17, [-0.01,0.35], p = 0.06; 2ΓÇô10 min, SMD = 0.21, [0.12,0.30], p < 0.01; >10 min, SMD = 0.19, [-0.09,0.47], p = 0.19). Overall, physical activity has a positive acute effect on subsequent cognition in children and adolescents with ADHD, though effects may be domain specific and influenced by the duration and modality of physical activity. These findings have practical implications for those interested in using physical activity to enhance cognition in children and adolescents with ADHD

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Modern Rheumatology Case Reports. 2022;6:55-58.

DEVELOPMENT OF GRAVES' DISEASE DURING DRUG-FREE REMISSION OF JUVENILE DERMATOMYOSITIS.

Kobayashi I, Shimomura M, Ueki M, et al.

We report a Japanese boy with Graves' disease (GD) which developed during drug-free remission of juvenile dermatomyositis (JDM). He had been diagnosed with JDM at the age of 6 years by typical skin rashes, muscle weakness, elevated serum transaminase levels, and typical findings of both magnetic resonance imaging and muscle biopsy. Although anti-melanoma differentiation antigen 5 autoantibody was positive, there was no complication of interstitial lung disease. He showed good response to methylprednisolone pulse therapy followed by oral prednisolone in combination with weekly methotrexate (MTX) and achieved drug-free remission after 3.5 years of treatment. Nevertheless, serum levels of soluble interleukin-2 receptor (sIL-2R) gradually elevated to 3185 U/ml despite no signs of relapse or malignancy. Hyperactivity and attention deficit was also noted. One year and 3 months after the cessation of MTX, he presented with abdominal pain, tachycardia, and apparent goitre. Laboratory tests showed elevated free triiodothyronine, undetectable thyroid stimulating hormone (TSH), and positive anti-TSH receptor antibodies. 99mTc scintigraphy showed high levels of thyroid uptake. He was diagnosed with GD and treated with 15 mg/day of thiamazole. Although transient drug eruption was observed, his thyroid functions are currently well-controlled on 5 mg/day of thiamazole. In conclusion, to our knowledge, this is the first report in English literature describing complication of GD with JDM. Unexpected elevation of sIL-2R could be a clue to the diagnosis of GD during the follow-up of JDM

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Nat Genet. 2022 Aug;54:1117-24.

DIFFERENCES IN THE GENETIC ARCHITECTURE OF COMMON AND RARE VARIANTS IN CHILDHOOD, PERSISTENT AND LATE-DIAGNOSED ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Rajagopal VM, Duan J, Vilar-RibÃ³ L, et al.

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with onset in childhood (childhood ADHD); two-thirds of affected individuals continue to have ADHD in adulthood (persistent ADHD), and sometimes ADHD is diagnosed in adulthood (late-diagnosed ADHD). We evaluated genetic differences among childhood (n=14,878), persistent (n=1,473) and late-diagnosed (n=6,961) ADHD cases alongside 38,303 controls, and rare variant differences in 7,650 ADHD cases and 8,649 controls. We identified four genome-wide significant loci for childhood ADHD and one for late-diagnosed ADHD. We found increased polygenic scores for ADHD in persistent ADHD compared with the other two groups. Childhood ADHD had higher genetic overlap with hyperactivity and autism compared with late-diagnosed ADHD and the highest burden of rare protein-truncating variants in evolutionarily constrained genes. Late-diagnosed ADHD had a larger genetic overlap with depression than childhood ADHD and no increased burden in rare protein-truncating variants. Overall, these results suggest a genetic influence on age at first ADHD diagnosis, persistence of ADHD and the different comorbidity patterns among the groups

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Neuroimage Clin. 2022;35:103141.

BRAIN STRUCTURAL CHANGES AND THE DEVELOPMENT OF INTERFERENCE CONTROL IN CHILDREN WITH ADHD: THE PREDICTIVE VALUE OF PHYSICAL ACTIVITY AND BODY MASS INDEX.

Ludyga S, Ishihara T.

BACKGROUND: Children with ADHD face deficits in interference control due to abnormalities in brain structure. A low body mass index and high physical activity are factors promoting brain health and may have the potential to reduce ADHD-related cognitive deficits. We aimed to investigate the predictive values of ADHD, body mass index and physical activity for interference control and the potential mediation of these associations by brain structure.

METHOD: At 9 and 11Â years, 4576 children with ADHD and neurotypical peers from the ABCD-cohort completed a Flanker task, anthropometric assessments and reported physical activity. Additionally, T1- and T2-weighted magnet resonance images were collected at both measurement time points.

RESULTS: ADHD, lower physical activity and higher body mass index at baseline predicted lower interference control. Gray matter volume, surface area and gray-white matter ratio contributed to interference control. The longitudinal association between body mass index and interference control was mediated by gray-white-matter ratio. This mediating effect was stronger for children with ADHD than neurotypical peers and mainly restricted to regions associated with cognitive control.

CONCLUSION: The maintenance of a lower body mass index contributes to interference control by a tendency to normalize regional alterations in grey-white-matter ratio. Being compliant with physical activity also promises higher interference control, but brain structure does not seem to underlie this association

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Neuropsychologia. 2022;174.

SEVERE DEVELOPMENTAL TOPOGRAPHICAL DISORIENTATION ASSOCIATED WITH ADHD AND DYSCALCULIA: A CASE REPORT.

Descloux V, Ruffieux N, Gasser AI, et al.

We report the clinical case of AB, a right-handed 19-year-old woman who presents severe developmental topographical disorientation, a relatively rare syndrome, leading to difficulties in navigating in familiar (and novel) environments. This symptomatology appears without acquired cerebral damage (MRI described as normal) nor more global cognitive disability (high degree of education achieved). An extensive assessment of spatial cognition with different aspects of underlying cognitive processes is first presented. Second, the patient's preserved cognitive abilities and her major difficulties in calculation, as well as her attention deficit, as seen in a detailed neuropsychological assessment, are reported. For the first time to our knowledge, we

show that developmental topographical disorientation can be associated with other developmental cognitive disorders affecting number processing (dyscalculia) and attention (Attention Deficit-Hyperactivity Disorder (ADHD)). We discuss the links between these different cognitive processes in relation to visuo-spatial working memory and magnitude representation, which could represent common denominators for all these syndromes. This case report highlights the importance of thoroughly assessing potentially associated neurocognitive disorders in developmental topographical disorientation. In addition, it highlights the necessity to keep in mind the prevalence of spatial difficulties in the assessment of children and adolescents with other neurodevelopmental syndromes. Finally, this case study raises a new question about the nosology of developmental disorders affecting the visuo-spatial and spatial domains

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NeuroQuantology. 2022;20:6467-74.

KNOWLEDGE AND ATTITUDE OF SAUDI PRIMARY TEACHERS TOWARDS STUDENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ALBAHA REGION.

Almilaibary A.

Background: Attention deficit hyperactivity disorder (ADHD) is among the most frequent psychiatric disorder in children, and it has a detrimental impact on the child's social, familial, and familial functioning. Teachers are frequently the first to suspect attention ADHD in their students since they are with them for the most of the day and are familiar with how normal students behave in the classroom.
Aims & Objective: this study aims to identify and measure the awareness and attitude of primary teachers towards the diagnosis and management of students with ADHD.
Subjects and methods: This cross-sectional study was conducted at a primary school in the AlBaha area of Saudi Arabia from January 18 to April 24, 2022. Data were collected using a written questionnaire in Arabic language and simple vocabulary. Data was statistically analyzed using SPSS (version 25).
Results: Around 361 participants completed the questionnaire; worked in AlBaha. Therefore, they were included in the analysis. Most of the teachers were female (N = 226, 62.6%) and had bachelor's as their highest qualification (N = 296, 81.9 %). For most of the questions, the teachers had inadequate or poor knowledge, around 66.5% of teachers had more than ten years of work experience.
Conclusions: The study emphasized the lack of understanding of ADHD among primary and kindergarten school teachers in AlBaha city. This information gap raises severe concerns about the screening of ADHD at the school level in Suadia Arabia

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Neurosci Biobehav Rev. 2022 Sep;140:104798.

PSYCHOLOGICAL DISORDERS, ADVERSE CHILDHOOD EXPERIENCES AND PARENTAL PSYCHIATRIC DISORDERS IN CHILDREN AFFECTED BY HEADACHE: A SYSTEMATIC REVIEW.

Polese D, Belli A, Esposito D, et al.

BACKGROUND: Pediatric headaches have been linked to adverse life events or psychological factors in children and their families, with a complex and bidirectional association. Moreover, it is well-known that psychological stress can trigger headaches.
METHODS: We searched three databases for studies focusing on headaches and adverse events or psychological factors in children up to 12 years old or in their caregivers.
RESULTS: We included 28 studies. Child psychological factors, including internal and external symptoms, were commonly associated with all types of headaches. Sleep disturbances showed a positive association with headaches in 3 out of 5 studies. Family conflict and unhappiness were frequently found in children suffering with headaches, while single-parent families and divorce were not associated. Stressful environments and adverse life events, particularly bullying, were also found to be linked with headaches.

CONCLUSIONS: Childhood headaches represent an alarm bell for clinicians to investigate and treat psychological or psychiatric disorders in children and their family. Further studies are needed to elucidate the role of early-life adverse events in children and their families

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Nord J Psychiatry. 2022.

INVESTIGATING THE EFFECTS OF AGE, IQ, DOSING, AND ANTHROPOMETRIC MEASURES ON THE TREATMENT PERSISTENCE IN LONG-TERM METHYLPHENIDATE USE.

Tuncturk M, Ermis C, Buyuktaskin D, et al.

Objectives: This study aimed to determine anthropometric and clinical correlates of persistence to methylphenidate (MPH) treatment in Turkish youth with attention-deficit hyperactivity disorder (ADHD).

Methods: Data from medical records of 518 children and adolescents with ADHD were recorded between March 2012 and January 2022. Clinical variables of patients persistent to MPH 2 years were compared with those of the non-persistent group. Children and adolescent age groups were compared using Kaplan Meier estimates for treatment drop-outs. Cox regression analysis until the treatment drop-out was implemented to calculate hazard ratios (HRs) for gender, age, full-scale IQ, and anthropometric measures. Weight, height, and body mass index (BMI) z-scores were calculated per national guidelines.

Results: Persistent and non-persistent study groups had similar full-scale IQ, weight, height, and BMI z-scores at treatment onset. The mean MPH dose was significantly higher in the persistent group compared to the non-persistent counterparts (31.43 -¦ 10.70 vs. 24.28 -¦ 9.60 mg/d, $p < 0.001$, $d = 0.70$). Compared to children, the adolescents showed earlier treatment drop-outs in males ($p < 0.001$) but not in females ($p = 0.110$). Younger age showed a positive effect on treatment persistence. Conversely, baseline BMI and IQ scores were not associated with long-term persistence.

Discussion: Our study demonstrated lower daily doses and older age-onset were associated with early drop-outs in MPH treatment. These findings supported the notion that effective dosing strategies at younger ages could increase the sustainability of the treatment with MPH in the Turkish population

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Nutr Hosp. 2022 Aug;39:8-15.

Characterization, epidemiology and trends of eating disorders.

Arija V, V, Santi Cano MJ, Novalbos Ruiz JP, et al.

Background: eating disorders are a group of conditions in which negative beliefs about food, body shape, and body weight together with behaviors such as restricted food intake, binge eating, excessive exercise, self-induced vomiting, and use of laxatives. They can become serious, affect quality of life, and lead to multiple physical and even psychiatric complications with a fatal outcome. The purpose of this chapter is to describe the characteristics, epidemiology, and trends of eating disorders with updated information based on the most recent publications.

Methods: we conducted a systematic literature search in Medline, EMBASE, Cochrane, and Web of Science. The search terms were "anorexia nervosa", "bulimia nervosa", "binge eating disorders" and "epidemiology" both in titles and in abstracts.

Results and conclusions: EDs generally occur in adolescents and young adults. The best characterized TCAs are anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (TA). Prevalence studies indicate wide differences by age group and sex, much higher in young women (NA, 0.1-2 %; BN, 0.37-2.98 %; BED, 0.62-4.45 %). The prevalence of EDs is 2.2 % (0.2-13.1 %) in Europe, 3.5 % (0.6-7.8 %) in Asia, and 4.6 % (2.0-13.5 %) in America. Comorbidity is high with psychiatric problems such as depression, anxiety, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and personality disorders

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Pediatr Int. 2022 Jan;64:e15209.

BIFIDOBACTERIUM BREVE DURING INFANCY ATTENUATES MOBILITY IN LOW BIRTHWEIGHT RATS .

Itoh A, Tanaka N, Fukunaga S, et al.

BACKGROUND: Children with low birthweight (LBW) have a higher risk for developing attention-deficit/hyperactivity disorder, for which no prophylactic measure exists. The gut microbiota in infants with LBW is different from that in infants with normal birthweight and is associated with attention-deficit/hyperactivity disorder. Oral supplementation with Bifidobacterium has several health benefits, such as suppressing inflammation.

METHODS: We examined the effect of gavage supplementation with Bifidobacterium breve M-16V from postnatal days 1-21 in a rat model of intrauterine hypoperfusion.

RESULTS: The open-field test at 5 weeks of age (equivalent to human pubertal age) showed that rats in the LBW-vehicle group were marginally hyperactive compared with rats in the sham group, while rats in the LBW-B.breve group were significantly hypoactive compared with rats in the LBW-vehicle group. The gut microbiota in the LBW-vehicle group exhibited a profile significantly different from that in the sham group, whereas the gut microbiota in the LBW-B.breve group did not exhibit a significant difference from that in the sham group. Anatomical/histological evaluation at 6 weeks of age demonstrated that the brain weight and the cerebral areas on coronal sections were reduced in the LBW groups compared with the sham group. Probiotic supplementation did not ameliorate these morphological brain anomalies in LBW animals. The percentage of Iba-1(+) cells in the brain was not different among the LBW-B.breve, LBW-vehicle, and sham groups.

CONCLUSION: Bifidobacterium breve supplementation during early life is suggested to have the potential to help children with LBW attenuate hypermobility in adolescence

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Pediatrics. 2022;149.

PARENTAL BIRTH OUTSIDE THE UNITED STATES AS A PREDICTOR OF ADHD DIAGNOSIS IN CHILDREN.

Rosenthal HE, Mehta S, O'Connor M, et al.

Background: Children of immigrants face unique challenges due to environmental, cultural, and physical factors that may adversely impact their development. Immigration-related linguistic isolation, parental education and employment, socioeconomic status, and cultural attitudes are known to result in differing educational and health outcomes. The CDC reported that Attention-Deficit/Hyperactivity Disorder (ADHD) affects 10% of United States (US) children, but the condition is often underdiagnosed and undertreated. The extent to which immigration-related challenges may adversely affect early diagnosis and treatment of ADHD is unknown. This study uses a nationally representative sample to examine associations between parental birth outside the US and ADHD diagnosis in children.

Methods: Secondary analysis of a combined 2016-2019 National Survey of Children's Health (NSCH) dataset was completed using logistic regression models. The predictor variable was parental birth outside of the US with the response variable being rates of ADHD, Autism Spectrum Disorder (ASD), diabetes, asthma, and heart conditions in children aged 3-17. The reference group included children with US-born parents. Adjusted Odds Ratio (aOR) and P-values were computed, adjusted for the child's age, race, household income, highest level of education of adults in the household, insurance coverage, and primary language spoken in the household.

Results: Among the five conditions considered for the analysis, Duy Pham, BA; Claudia Hatef, n/a; Allison Lin, BS; Nelson Chow; children with ADHD were the least likely to come from a household with both parents being born outside of the United States (aOR=0.341, p-value<0.001) (Figure 2). The odds ratio increases with one (aOR=0.452, p-value<0.001) and two parents (aOR=0.452, p-value<0.001) being born in the United States, respectively. Notably, the trend holds for all other conditions studied in this analysis.

Conclusion: Parental birth outside the US was found to be a strong predictor of reduced rates of ADHD diagnosis in children. Although lower rates of diagnosis for the other studied conditions were all strongly predicted by parental birth outside the US, ADHD had the lowest likelihood of diagnosis, even after adjustment. Therefore, ADHD diagnosis in children of immigrants is of special concern. Language/educational barriers, cultural attitudes, and access to medical resources should be considered when identifying potential ADHD presentation. Use of rating scales should also be evaluated for utility/robustness/cultural relevance in diagnosing children of immigrants. Pediatricians should be aware that

immigration-related challenges can preclude proper diagnosis of ADHD and employ early interventions in these communities. Proper identification and treatment of behavioral challenges in children of immigrants is needed to ensure healthy development

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Pharmacol Biochem Behav. 2022 Jul;218:173424.

PREPUBERTAL METHYLPHENIDATE LEADS TO SEX-DEPENDENT DIFFERENCES IN PROBABILISTIC DISCOUNTING.

Kelly G, Bezenah JC, Tejada AN, et al.

Prescription psychostimulants, such as methylphenidate (MPH), have served as a first line treatment for ADHD and associated developmental disorders since 1961. Psychostimulants has been shown to improve attention, response inhibition, and reduce hyperactivity in patients with ADHD, as well as in non-clinical human populations and animals. While there is a considerable amount of preclinical research investigating the effects of stimulant medications on reward sensitivity and basic learning in male rats, less is understood about their effects in females. Further, there are competing theories on the long-term cognitive impact of MPH, specifically in children who do not have ADHD. To this end, Long-Evans female and male rats were exposed to methylphenidate (0, 2.5, 5Â mg/kg, BID, IP) for 20 days during early development (PD10-29). After discontinuation of MPH into adulthood, rats (beginning PD 60) were trained and tested for risk-preference using a 2-choice probabilistic discounting task. For this task, rats were given an option between a 'large-risky' choice (3 sugar pellets delivered on a probabilistic VR schedule) and 'small-certain' choice (1 sugar pellet delivered on a FR schedule). Rats were subsequently tested on an open field conflict test. The results demonstrate that prepubertal exposure to MPH can have lasting effects on decision-making. Specifically, female rats treated with 2.5 mg/kg MPH displayed a decrease in preference for the risky option, whereas male rats treated with the same dose showed an overall increase in preference compared to sex-matched controls. Irrespective of sex, rats treated with 2.5 mg/kg MPH also demonstrated a decrease in anxiety/inhibitory behavior on the modified open field test compared to controls. These results were not due to differences in locomotor behavior. Overall, the study contributes to the growing body of evidence to suggest that MPH exposure early in development can have a sex-dependent impact on decision-making in adulthood

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PLoS ONE. 2022;17:e0267773.

EXPERIENCES AND CHALLENGES OF PARENTS CARING FOR CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A QUALITATIVE STUDY IN DAR ES SALAAM, TANZANIA.

Ching'oma CD, Mkoka DA, Ambikile JS, et al.

BACKGROUND: Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioral childhood disorder. Children with ADHD are difficult to handle due to the symptoms causing great impairments such as inattention, hyperactivity compared to other childhood mental disorders. Having a child with ADHD is a stressful situation as it impacts the whole family. However, little is known about the experiences and challenges of parents caring for children with ADHD in low and middle-income countries such as Tanzania. Thus, this study explored the experiences and challenges of parents caring for children with ADHD in Dar es Salaam, Tanzania.

METHODS: We conducted a qualitative descriptive study involving 16 parents of children with ADHD at Muhimbili National Hospital (MNH). We used the purposive sampling technique to obtain the participants. In-depth interviews, using a semi-structured interview guide, were used to collect data. Audio-recorded data were transcribed, translated, and analysed using qualitative content analysis.

RESULTS: Parents experienced difficulties in handling the children whose level of functioning was impaired due to abnormal and disruptive behaviour such as not being able to follow parental instructions. Psychological problems were also experienced due to caring demands exacerbated by lack of support and stigma from the community. Moreover, there were disruptions in family functioning and social interactions among family members due to the children's behaviour. Lastly, too much time and family resources spent to

fulfil the needs of these children culminated into disruption in economic activities that negatively affected everyday life.
CONCLUSION: Parents struggle to meet and cope with care demands posed by children with ADHD. The disruptive nature of ADHD symptoms presents a unique caring challenge different from those experienced with other childhood mental illnesses. To address these challenges, a collaborative approach among key stakeholders such as the government, health care professionals, and non-governmental organizations, is needed

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PLoS ONE. 2022;17:e0272121.

EFFECT OF GAME-BASED HIGH-INTENSITY INTERVAL TRAINING PROGRAM ON THE EXECUTIVE FUNCTION OF CHILDREN WITH ADHD: PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL.

Sun F, Chow GC, Yu CC, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a common developmental disorder in childhood, with a 5%-6% worldwide prevalence. Children with ADHD often demonstrate impaired executive function, which is closely related to the development of the commonly observed behavioral problems such as inattention, impaired inhibition, and hyperactivity. The purpose of this study is to examine whether a game-based high-intensity interval training (HIIT) program can improve the executive function of children with ADHD, compared with a traditional structured aerobic exercise program and a non-treatment control group.
METHODS/DESIGN: A total of 42 children with ADHD will be recruited to participate in this three-arm school-based randomized controlled trial. An 8-week specially designed game-based HIIT (GameHIIT) program and a traditional game-based structured aerobic exercise (GameSAE) program will be delivered to those children randomly assigned to these two intervention groups, while the children in the control group will maintain their regular physical activity over the same period. A number of outcome measures including executive function, cerebral hemodynamic response, physical activity, physical fitness, and enjoyment and adherence to the intervention will be assessed for both groups at baseline (T0), immediately after the intervention period (T1), and after the follow-up period (T2).
DISCUSSION: HIIT has recently emerged as a feasible and efficacious strategy for increasing physical health outcomes and cognitive function, including executive function, in healthy young people. However, research has yet to investigate whether the executive function of children with ADHD can be effectively enhanced through HIIT. If, as hypothesized, GameHIIT program improves outcomes for children with ADHD, the present research will inform the development of targeted exercise programs that can be more broadly used with this particular population

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Prev Sci. 2022 Aug;23:996-1006.

EFFECTS OF THE TARGETED INTERVENTION FOR FIVE- TO SIX-YEAR-OLD CHILDREN AFFECTED BY ATTENTIONAL AND CONCENTRATION DEVELOPMENTAL RISKS: RESULTS OF A DYNAMIC PROSPECTIVE COHORT STUDY CONDUCTED IN SOCIALLY DEPRIVED REGIONS IN GERMANY.

Franze M, Biermann J, KÃ¤stner A, et al.

Epidemiological data reveal that there is a need for prevention measures specifically targeted at children with low SES. In the German federal state Mecklenburg-Western Pomerania preschools in socially deprived regions can apply for additional funds to support children with developmental risks. Mandatory criteria for obtaining these funds involve an annual assessment of all children using the "Dortmunder Developmental Screening for Preschools (DESK 3-6 R)." This instrument can detect and monitor developmental risks in the domains fine motor skills, gross motor skills, language, cognition, and social development. In this study, we examine the domain "Attention and concentration," which is included for the 5 to 6-year-old age group, using data from two consecutive survey waves (sw). Research questions: (1) Does the prevalence rate ratio (PRR) improve over time? (2) Is the rate of improvements (developmental risk at sw1, no developmental risk at sw2) higher than the rate of deteriorations (no developmental risk at sw1, developmental risk at sw2)? Prospective cohort analysis (nâ€‰=â€‰940). The prevalence rate of a developmental risk in this DESK

domain decreases over time (PRRâ€‰=â€‰0.78; pâ€‰=â€‰0.019). The ratio of the rate of improvements is 8.47 times higher than the rate of deteriorations. The results provide evidence of the effectiveness of targeted intervention measures in preschools focusing on skills that improve attention and concentration. This is significant considering the small-time interval and the categorization method of DESK scores. Nevertheless, over the same time period, the DESK results of some children deteriorated. Therefore, preschools also have to be aware that it is natural for some children to show modest declines in their skills over time. German Clinical Trials Register, ID: DRKS00015134, Registered on 29 October 2018, retrospectively registered

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Primary Care Companion for CNS Disorders. 2021;23.
ADHD MASQUERADING AS CAUTOPYREIOPHAGIA EXACERBATED BY RISPERIDONE AND IMPROVED WITH METHYLPHENIDATE IN A PRESCHOOLER.
Naguy A.

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Primary Care Companion for CNS Disorders. 2022;24.
Sluggish Cognitive Tempo and ADHD: La Même Chose?
Naguy A.

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2022;119.
IS THERE A PLACE FOR DIETETIC INTERVENTIONS IN ADULT ADHD?
Breda V, Cerqueira RO, Ceolin G, et al.
Current treatments for Attention-Deficit/Hyperactivity Disorder (ADHD) in adults are limited by lack of response and side effects in about one third of the individuals. Changes towards a healthier lifestyle could have a positive impact beyond the relief of specific symptoms. However, it is not clear if nutritional interventions influence mental health and cognition. The objective of this study was to summarize the available literature addressing the impact of different diets in ADHD. The most promising dietetic approaches in ADHD are diets considered to be healthy (Mediterranean-type; DASH) and the Few-Foods Diet for children. Studies should take into account the presence of multiple confounders, biases associated with difficulties in blinding participants and researchers, and search for possible mechanisms of action, so we can have better evidence to guide clinical mental care of adults with ADHD

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Psychiatr Pol. 2022;56:535-49.
ATTACHMENT IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND OPPOSITIONAL DEFIANT DISORDER.
Kamierczak-Mytkowska A, Butwicka A, Lucci KD, et al.
Objectives. To assess attachment styles among adolescents (13–16 years) with ADHD or ADHD and oppositional defiant disorders (ODD).
Material and methods. The Parents and Peers Attachment (IPPA) and the Parent Bonding Questionnaire (PBI) were used in three groups of teenagers raised in biological families: (1) ADHD/ODD group (n = 40), (2) ADHD group (n = 40) and (3) K (control) group of teenagers (n = 40) who have not benefited from psychological or psychiatric care in the past or at present.
Results. Parental attachment styles in the area of “Trust”, “Communication” and “Aliena-tion” (IPPA), and “Care” and “Control” (PBI) in the ADHD/ODD group differ significantly compared to the control group. Teens from the ADHD/ODD group report to have experienced significantly less “Trust” and “Communication” (IPPA),

and “Care” (PBI) in relationships with parents and more “Alienation” (IPPA) and “Control” (PBI) than adolescents in the ADHD group. Attachment patterns with peers in both clinical and control groups differ significantly. The ADHD/ODD group is dominated by the anxious-avoidant style of attachment to the mother and father, in the ADHD group, a secure style in relation to the mother and anxious-avoidant in relation to the father. In relations with peers in the ADHD/ODD group and the ADHD group, the anxious-avoidant style dominates.
Conclusions. The attachment style is significantly different in adolescents diagnosed with ADHD and ODD than in adolescents with only ADHD. In the ADHD/ODD group and the ADHD group, unlike in the group of adolescents without a psychiatric diagnosis, insecure attachment styles for parents and peers dominate (mainly anxious-avoidant style).

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Psychiatry and Clinical Psychopharmacology. 2017;27:102.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DUE TO CORPUS CALLOSUM AGENESIS: A CASE REPORT.
Doaru H.
Attention-deficit/hyperactivity disorder (ADHD), characterized by attention deficit, extreme mobility and impulsivity is a neuropsychiatric disorder in which findings usually start around 3-years of age. This disorder puts the child into a social, academic, emotional, and cognitive turmoil. Incidence of ADHD in school-age children varies between 5-7%. The etiology of ADHD is not explained clearly but various genetic, environmental factors are considered responsible for the disruption in the early development phase. A 4 year-old, presented to the outpatient clinic with complaints of sudden attacks of rage, hyperactivity, restlessness, talkativeness, digging around all the time. On exam distractibility, mobility, talkativeness, inability to sustain attention were evident. After taking the history, it has been learned that the development of the patient's gait and speech started late. In the nursery form, the teacher stated that the patient was always on the move, had difficulty paying attention, and fought too often with his friends. The Corpus Callosum, indicates one of the most common structural abnormalities in the brain. These children might present with growth retardation, microcephaly, epilepsy and mental retardation. The condition virtually might not cause any problem at all. Damage in this area may disrupt the cognitive skills, attention, language, learning, and fields such as impulse control mechanism. Sometimes patients may present with attention deficit, just as in this case. The effect of the structural change in the brain over the course of patient's clinic is not well understood in ADHD but a neurodevelopmental disruption is obvious. Thus, neuroradiological tools are of great importance especially in cases with developmental delay to rule out corpus callosum agenesis

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Psychiatry and Clinical Psychopharmacology. 2017;27:118.
COMPULSIONS AFTER ATOMOXETINE TREATMENT: A CASE REPORT.
Doaru H.
Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder incidence of which is 5-10% in childhood. Although stimulants are particularly preferred as effective drugs for this group, in the presence of comorbidities like anxiety disorders atomoxetine is usually preferred. A 12-year-old boy with a known history of ADHD and anxiety co-existence presented to Child and Adolescent Psychiatry clinic with complaints of excessive talking, distractibility and restlessness. As a result of a complete psychiatric exam reinforced with psychometric tests and taking history ADHD and mild level mental retardation were diagnosed and atomoxetine treatment was initiated with a daily dose of 0.5 mg/kg. Keeping in mind the mental retardation, the dosage was slowly increased until the desired therapeutic dose is achieved (1.2 mg/kg/day) at the 3rd month of treatment. However, on the last scheduled appointment his mother stated that he began to continuously wash his hands, collect individual hairs from the ground and constantly tidy up seat coverings. During the follow up, it has been observed that attention, distractibility and anxiety complaints have improved significantly but atomoxetine aggravated compulsive behaviors which were sufficiently severe to cause a significant disruption in functionality. Risperidone was initiated and titrated up until 0.75 mg/day. After 2

months of therapeutic dose his compulsions subsided. Comorbid anxiety disorders can be seen in 25-35% of ADHD patients. This comorbidity state displays more aggressive prognostic features (less compliance with treatment, more adverse effect) than ADHD alone. Mild intellectual disability as in this case might expose the patient to a higher potential risk of additional sensitivity to adverse effects. Clinicians must be careful about this potential neurodevelopmental risk in the co-existence of ADHD and mental retardation

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Psychiatry and Clinical Psychopharmacology. 2017;27:155.

DOSE-DEPENDENT HEADACHE DUE TO ATOMOXETINE TREATMENT IN A PATIENT WITH AUTISM: A CASE REPORT.

Doaru H.

ASD is a group of complex neurological disorders. These disorders affect behavior, development and communication. With the release of the Diagnostic and Statistical Manual of Mental Disorders, The American Psychiatric Association states that the two conditions can occur together. In a review of studies looking at the comorbidity of ADHD and ASD, researchers found that between 30 to 50 percent of people with ADHD also have symptoms of ASD. Pharmacotherapy of ADHD symptoms in ASDs is often problematic, with unexpected responses, generally poorer tolerability, and less impressive average benefit. In such cases atomoxetine treatment is considered safer. Atomoxetine is a non-stimulant ADHD treatment that increases norepinephrine levels in the presynaptic cleft by blocking the action of the norepinephrine transporter. A 13 years-old boy presented to our clinic with lack of concentration, over activity and getting bored, losing his stuff, lack of concern or inability to react to other people's emotions or feelings, repetitive movement, such as twisting, bothering his class mates during lectures, not completing his homework and tasks, and forgetfulness complaints. Symptoms started at pre-school period and increased with time, especially during school time. Even though many ASD related studies emphasize a better tolerability for atomoxetine than methylphenidate. The neurodevelopmental structure in individuals with autism might be more fragile than pure ADHD patients and might have different sensitivity to drugs. Autism and ADHD are neurodevelopmental diseases. Especially in cases of these diseases seen as comorbid forms the drug dose should be titrated more slowly than usual. Otherwise, drug related side effects might appear much easier. The resulting side effects such as headache might be dose dependent and can regress with reducing the dose again

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Psychiatry and Clinical Psychopharmacology. 2017;27:160.

MULTIPLE COMPLEX DEVELOPMENTAL DISORDER: TWO REPRESENTATIVE CASES AND DIAGNOSTIC DIFFICULTIES.

Karabucak B, et al.

Multiple complex developmental disorder (MCDD) is a little-known disorder used to be labeled as 'childhood schizophrenia' and 'borderline syndrome of childhood' in the past and as 'childhood schizotypal disorder' or 'schizoid personality' more recently. Although the combination of early onset impairment in affect regulation, high levels of anxiety, disturbed social relationships, and periods of thought problems has been recognized by child psychiatrists throughout the past five decades and is not a rare phenomenon, neither the classification system of ICD-10 nor the DSM-5 lists MCDD as an independent disorder. Cohen, Paul, and Volkmar (1986) suggested the term multiple complex developmental disorder (MCDD) for which they proposed a specific set of diagnostic criteria. They emphasized that the social impairment seen in these children was suggestive of autism, and therefore considered MCDD as belonging to the group of pervasive developmental disorders (PDDs). In this article we aimed to focus on some special features and differential diagnosis of this disorder. Two eleven-years-old male patients admitted in our outpatient clinic with social difficulties, maladjustment and anxiety complaints. They had academic failure, behavioral problems in school, magical thinking and impairment in reality testing was defined as 'odd thinking' in teachers' reports. Both applied to other psychiatry clinics earlier, diagnosed with ADHD because of their distractibility and lack of interest in the class; treated with methylphenidate, both children manifested anger outbursts and suicidal

thoughts after pharmacotherapy was initiated. These two cases having similar atypical developmental trajectories and recent complaints will be discussed in terms of differential diagnosis and treatment

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Psychiatry and Clinical Psychopharmacology. 2017;27:31-32.

SLEEP AND QUALITY OF LIFE IN CHILDREN WITH TRAUMATIC BRAIN INJURY AND ADHD: A COMPARISON WITH PRIMARY ADHD.

Ekinci U, et al.

Objective: Attention problems are common in children who sustain a traumatic brain injury (TBI). The differential features of TBI-related Attention-Deficit/Hyperactivity Disorder (ADHD) and primary ADHD are largely unknown. This study aimed to compare sleep problems and quality of life between children with TBI and ADHD and children with primary ADHD.

Methods: Twenty children with TBI (mean age=12.7-¦3.1 years) who had clinically significant ADHD symptoms according to the structured diagnostic interview and rating scales; and a control group with primary ADHD (n=20) were included. Parents completed Children's Sleep Habits Questionnaire (CSHQ) and the Children's Quality of Life Questionnaire (Kinder-Lebensqualit+ñtsfragebogen, or KINDL-R). Neurology clinic charts were reviewed for TBI-related variables.

Results: When compared to children with primary ADHD; the Total score and Sleep Onset Delay, Daytime Sleepiness, Parasomnias and Sleep Disordered Breathing subscores of CSHQ were found to be higher in children with TBI-related ADHD. The Total Score and Emotional Well-Being and Self-Esteem subscores of the KINDL-R were found to be lower (poorer) in children with TBI-related ADHD. The Total score and certain subcores of KINDL-R were found to be lower in TBI patients with a CSHQ>56 (corresponds to significant sleep problems) when compared to those with a CSHQ<56. CSHQ Total score was negatively correlated with age.

Conclusions: Children with TBI-related ADHD symptoms were found to have a poorer sleep quality and quality of life then children with primary ADHD. ADHD in TBI may be considered as a highly impairing condition which must be diagnosed and treated earlier

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Psychiatry and Clinical Psychopharmacology. 2017;27:51-52.

INCIDENCE OF INTERNET ADDICTION IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mutluer BT, Yener Orum TG, Sahan E, et al.

Objective: In this study, we aimed to determine the internet use features of adult attention-deficit/hyperactivity disorder (ADHD) patients who were regularly followed-up at the Haydarpasa Numune Research and Training Hospital Psychiatry Department's ADHD Outpatient Clinic.

Methods: This study included 30 patients who were diagnosed with adult ADHD aged between 18-31 years. Participants rated their ADHD symptoms in childhood retrospectively, using short version of Wender Utah Rating Scale which consisting of 25-items on a five-point Likert-scale. Participants rated current adult ADHD symptoms with the Adult ADHD DSM-IV-Based Diagnostic Screening and Rating Scale and severity of symptoms measured by the Adult ADHD Self-Report Scale (ASRS). Internet addiction was assessed with Young's Internet Addiction Scale.

Results: We determined that none of 30 Adult ADHD patients have been diagnosed with Internet Addiction. 29 of patient have moderate internet use although 1 of patients have risky internet use. The results revealed that total ASRS scores (p=0.020), total Adult ADHD DSM-IV-Based Diagnostic Screening and Rating Scale scores (p=0.036), and the Attention Deficit related properties subscale scores (p=0.042) were significantly correlated with the internet addiction scale total score. Subscale of the self report scales including; failing to finish schoolworks, chores, or duties at workplace, difficulty of following through on instructions (p=0.017), restlessness; impaired inhibitory performance (p=0.017), feeling not confident (p=0.017), difficulty of managing time (p=0.047), failing to give close attention to details or making careless mistakes (p=0.037) were significantly correlated with the Internet Addiction Scale total score.

Conclusions: Clinical features, which are characteristic of Adult ADHD could have same shared etiology with Internet Addiction. Furthermore, ADHD patients are more likely to have an internet addiction diagnosis. However we thought that this result had to be supported with studies with larger samples

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Psychiatry and Clinical Psychopharmacology. 2017;27:13.

ELEVATED SERUM HEPCIDIN LEVELS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yazici KU, Yazici IP, Ustundag B.

Objective: Hepcidin regulates cellular iron release through interacting with ferroportin and it is accepted as the main regulatory hormone of systemic iron balance. Hepcidin is known to reduce body iron amount through inhibiting iron absorption from duodenum, iron release to plasma from macrophages, iron mobilization from hepatic stores. In this study, we aimed to compare attention-deficit/hyperactivity disorder (ADHD) patients and control subjects with regard to serum hepcidin levels and to examine whether there is a relationship between serum hepcidin level and ADHD symptom severity.

Methods: Seventy ADHD patients aged between 7-15 years and 69 healthy controls were included in the study. A semi-structured interview, "Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)" was administered for diagnosis. Intelligence quoitent was evaluated using Wechsler Intelligence Scale for Children-Revised (WISC-R). Child Behavior Checklist/4-18, Teachers Report Form, Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (Parent and Teacher), Conners Parent/Teacher Rating Scale-Revised Long Version were used for clinical assessment. The patients whose WISC-R scores were below 80, who had comorbid psychiatric disorders according to K-SADS-PL, history of previous psychotropic medication use, acute or chronic systemic diseases, who had an infections within the past month, who used iron preparation within the past year and whose Hb < 12 mg/dl were all excluded from the study.

Results: No significant difference was detected between groups with regard to socio-demographic characteristics. Serum hepcidin level was found significantly higher in ADHD cases compared to healthy controls. A positive correlation was found between hyperactivity-impulsivity symptom severity and serum hepcidin levels ($r=0.438$, $p<0.001$).

Conclusions: In our study, hepcidin levels were found significantly higher in ADHD cases compared to controls. Elevated hepcidin levels observed in ADHD cases are not known to have a cause-and-effect relationship. Further larger scale studies are required to elucidate this relationship

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Psychiatry and Clinical Psychopharmacology. 2017;27:10.

THE PREVALANCE AND RISK FACTORS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG ELEMENTARY SCHOOL CHILDREN IN ESKISEHIR PROVINCE.

Yalva A, Fidan T.

Objective: Attention Deficit and Hyperactivity Disorder (ADHD) is most seen and known as highly heritable childhood disorder, but non-inherited risk factors also are important for its etiology as well. Epidemiologic data are essential for planning health services and implementing strategies of detection and early intervention, with possible substantial benefits on public health. In this study, we aimed to identify the possible risk factors that might predict ADHD and its subtypes and determine the prevalences in primary school age children in Eskisehir Province.

Methods: A total of 3,230 students from 10 primary schools and 8 secondary schools were recruited for the study. Socio-demographic data form and the DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale were administered. SPSS Version 21 for Windows was used for statistical analyses. $p<0.05$ was considered statistically significant for all analyses.

Results: ADHD prevalence rate was found 4.4% among 3,329 children and adolescents included in the study. The prevalence of the subtypes were; 2.3% for ADHD-I (inattentive type), 1.3% for ADHD-HI (hyperactive-impulsive type), and 0.8% for ADHD-C (combined type). Male gender was found as a significant risk factor for ADHD and its subtypes. In addition, having a housewife mother and a single parent, history of

smoking during pregnancy, history of influenza/other respiratory tract infection, history of mental illness, presence of a chronic disease in the child, and having comorbid epilepsy or asthma were also risk factors for ADHD and its subtypes.
Conclusions: The prevalence rate of ADHD in Eskisehir province was found to be the least in Turkey. According to Turkish Statistical Institute data (2013), Eskisehir province having more literacy rate in women, might be a protective factor for ADHD in their children. According to our findings, encouraging mothers for working, avoiding smoking and prevention from infection during pregnancy are essential in reducing the environmental risk factors of ADHD. The relatively high risk of ADHD in children with chronic diseases such as epilepsy or asthma should also be kept in mind

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Psychiatry and Clinical Psychopharmacology. 2017;27:52.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND IMPULSIVITY IN FEMALE PATIENTS WITH FIBROMYALGIA.
Yilmaz E, Tamam L.
Objective: Data indicating greater role of central nervous system in the etiology of fibromyalgia is increasing. Neurotransmitters like dopamine and norepinephrine are shown to be common factors both in the etiology of fibromyalgia and attention-deficit/hyperactivity disorder (ADHD). Impulsivity is not a well-studied subject yet. The goal of the present study is to determine the link between fibromyalgia and ADHD and also to reveal the relevance of impulsivity dimension.
Methods: The study sample is comprised of 78 female with fibromyalgia who presented to The Physical Medicine and Rehabilitation Outpatient Clinic in Ceyhan State Hospital and 54 healty female controls. The diagnosis of fibromyalgia was made by an experienced physical medicine and rehabilitation specialist through consideration of American Romatology Association Diagnostic Criteria (1990). The diagnosis of ADHD was made by an experienced psychiatrist using the DSM-5 criteria. The Adult Attention Deficit Hyperactivity Disorder Self-report Scale, the Wender-Utah Rating Scale (WURS), the Barrat Impulsiveness Scale (BIS)-Short Form.
Results: Mean age of fibromyalgia group and control group was 40.3-¦9.39 and 38.9-¦8.,92, respectively. ADHD was diagnosed in 29.5% of fibromyalgia group, and 7.4% of control group; childhood and adolescent ADHD ratios were 33.3%and 11.1%, respectively. These findings were statistically significant (p=0.002, p=0.003). Fibromyalgia group scores was found to be significantly higher than control group scores of WURS; ADHD self-report scale, attention subscale, hyperactivity-impulsivity subscale; BIS non-planning and attentional impulsivity (p<0.05, p<0.01, p<0.01, p<0.05, p<0.01, p<0.05; respectively).
Conclusions: Present study has shown that both adult and childhood ADHD is pretty common occurence in female fibromyalgia patients. There was a link between fibromyalgia and impulsivity. We concluded that certain subtpyes of fibromylagia and attention-deficit/hyperactivity disorder might have shared common etiological pathways

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Psychiatry and Clinical Psychopharmacology. 2017;27:10-11.
DEFENSE MECHANISMS AND METHODS FOR COPING WITH STRESS OF MOTHERS WHOSE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Sari BA, et al.
Objective: In our study, it was aimed to examine anger and the ways of expressing anger, ways of coping with stress and defense mechanisms in the mothers of children with ADHD.
Methods: The study included 61 mothers of children with ADHD and 55 mothers without known psychiatric disorders in their own and in their children. Participants completed Socio-demographic Form, The Defense Style Questionnaire, Conners Teacher Rating Scale was completed for the children with ADHD.
Results: In our study, there was no difference between the mothers with ADHD and control group mothers in terms of anger levels and anger expression styles. However, when the duration of ADHD increased, the anger scores in the mothers increased and the defense mechanism scores decreased. In the presence of comorbid disease in children with ADHD, the scores of the controlled anger expression styles in the mothers

of the patient group were higher (r=0.272, p=0.03), the scores of somatization defense mechanism were higher (r=0.269, p=0.036), the behavioral nullity scores as a method of coping with stress were found to be higher (r=0.193, p=0.05).
Conclusions: In our study, there were no differences between the mothers with ADHD and control group mothers in terms of anger levels. However, when the duration of ADHD increased, the anger scores in the mothers increased. This suggested that early diagnosis and treatment of the disease would be beneficial in terms of preventing the mother from raising the level of anger and being able to cope with the disease. In the presence of a comorbid psychiatric disorder in children with ADHD, anger levels in the mother were increasing and somatization was more frequently used. This finding showed us how difficult it was for families to deal with ADHD

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Psychiatry and Clinical Psychopharmacology. 2017;27:278-80.
DIAGNOSIS AND TREATMENT OF ADHD IN COLLEGE STUDENTS.
Kili U.
Individuals with ADHD face substantial difficulties in academic performance, relationships, and self-esteem in college and across the life span. Estimated rates of ADHD in college are reported 2-8% in studies carried out in USA and these rates are based on studies that utilized self-reported symptoms or diagnostic status from convenience samples of students at individual campuses but not comprehensive assessment conducted with nationally representative samples1. College health care providers feel discomfort in diagnosing and treating ADHD and this could represent a barrier to care for college students2. The overarching goal of this presentation is to provide a clinically useful review of the available evidence that practicing clinicians can use to aid in the diagnostic assessment and treatment of ADHD in college students. Diagnosis of ADHD in college students Symptoms of ADHD in adulthood may not be as clear as in childhood. Despite recommendations regarding the diagnosis of emerging adults, there is not a strong consensus regarding the ideal method for diagnosing ADHD, additionally research on the diagnostics and follow up of ADHD in this population is limited. According to a recent study by Dyvorsky et al, rating scales can be used effectively to evaluate ADHD on college campuses if both parent and student rate childhood symptoms. The authors concluded collecting parent ratings helps against possible student malingering to obtain ADHD medications or accommodations and parent ratings of childhood ADHD symptoms of inattention were the strongest predictors of current diagnostic status of ADHD3. Another study in college students explored the association between level of impairment and the DSM-5 threshold of symptoms and suggested that DSM-V threshold of five symptoms for ages 17 years and older is not necessarily predictive of ADHD-related impairment in college students and may not be preferable to other thresholds4. Criteria to diagnose ADHD in adults were emphasized by other authors. These were: (1) confirmation of at least 4 inattentive and/or hyperactive impulsive symptoms which contributed to current impairment, (2) evidence of ADHD symptoms prior to 12 years of age that had an impact on impairment in multiple domains across the lifespan, (3) third party corroboration of symptoms and impairment, (4) the confirmation that impairment is not due to another disorder5. Outcome monitoring and assessment for comorbid conditions such as substance use, mood and anxiety disorders to properly treat these students. Treatment of ADHD in college students ADHD is one of the most referred disorders by college counselling centers for medication evaluation and treatment along with depressive and anxiety disorders6. Dopaminergic and noradrenergic deficits in the frontal cortex or regions projecting into that area have been implicated in the inattentiveness and/or hyperactivity associated with ADHD. Pharmacotherapy for adult ADHD often targets core symptom reduction, Current standard and first-line pharmacotherapy for adult ADHD is stimulant medication7. Psychostimulants relieve symptoms by increasing intra-synaptic dopamine, norepinephrine and serotonin. There are two classes of psychostimulants which are amphetamine-based and methylphenidate-based psychostimulants. Atomoxetine is a non-stimulant ADHD medication that is currently available for use in Turkey. Atomoxetine, inhibits norepinephrine transport and has also been approved for ADHD treatment as first-line pharmacotherapy in many countries8. Meta-analyses have provided evidence for the efficacy of stimulants9 and beneficial effects of atomoxetine in ADHD in adults10. Among alternative compounds, amphetamines (mixed amphetamine salts and lisdexamfetamine) have the most robust evidence of efficacy, but they may be associated with serious side effects (e.g., psychotic symptoms or hypertension). They are not currently

available in Turkey. Noradrenaline or dopamine enhancer antidepressants have an evidence of efficacy however not appropriate for patients with comorbid bipolar disorder11. Extended-release guanfacine and extended-release clonidine are two non-stimulant medications licensed for use in USA. Atypical antipsychotics are not indicated for treatment of core ADHD symptoms. According to a recent meta-analysis, stimulant drugs should be preffered over non-stimulant drugs due to superior efficacy. The efficacy of pharmacological treatment should be monitored over time because it may decrease progressively12. For adults with ADHD who continue to experience clinically significant symptoms following first-line medication treatment at the maximum tolerated dose, discontinuation of stimulant therapy and initiating non-stimulants like atomoxetine and bupropion is recommended. Although medication therapy has the most empirical support as treatments for ADHD in adults, many adults with ADHD continue to experience significant residual symptoms. Research evidence most strongly supports the use of cognitive-behavioral therapy (CBT) targeting deficits in executive function as well as the comorbid symptoms of anxiety and depression that tend to be present in these patients. Other psychological treatments consist CBT-oriented coaching13 and social skills training. Adapted Dialectical behavior therapy for adult ADHD addresses emotional awareness and regulation, mindfulness, organization, behavior analysis, stress management, interpersonal effectiveness, depression, and substance use disorders however there is little evidence from randomized trials to support the efficacy of DBT in adults with ADHD14,15. Available data support the use of structured, skills-based psychosocial interventions as a viable treatment for adults with residual symptoms of ADHD. These treatments, however, require further study for replication, extension and refinement16. There are no trials comparing psychotherapies with adult ADHD, treatment selection could be guided by availability, the clinical features of the patient's presentation, and existing evidence. For patients with prominent symptom clusters or deficit areas (e.g., executive dysfunction, emotional dysregulation, or impulsivity), it is suggested that a psychotherapy targeting that cluster or area be used. The presence of a co-occurring disorder treatable by psychotherapy will also influence the treatment provided. Adults with ADHD and with prominent deficits in executive function, augmentation of medication with cognitive behavioral therapy (CBT) that targets executive dysfunction seems more efficacious rather than other nonpharmacologic treatments or medication alone. In conclusion, there is no single test that can reliably diagnose ADHD. The diagnosis of ADHD in college students is based on a comprehensive clinical assessment. This presentation will mention several structured diagnostic interviews (The Adult ADHD Clinical Diagnostic Scale (Adult ACDS), ADHD Lifespan Functioning Interview (ALFI), Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID), Diagnostic Interview of ADHD in Adults (DIVA), Structured Clinical Interview for DSM-5 (SCID-5)-Adult ADHD Module, symptom measures to evaluate Adult ADHD in college students. The available Turkish versions of the interviews and measures and their practical application will be highlighted. How ADHD is best managed across the lifespan and across key transition periods such as in college needs much more investigation17 however the optimal medication and psychosocial treatment strategies will be discussed considering the current literature

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Psychiatry and Clinical Psychopharmacology. 2017;27:8.

EFFECT OF PRESENCE OF MATERNAL PSYCHIATRIC DISORDERS ON ATTACHMENT TO PARENTS AND PEERS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Doan H, et al.

Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity, which is observed in 3-7% of the children at school age. It is associated with significant disruption in developmental, cognitive, and academic domains. In recent years, intensive research has been conducted on the topic of Woman's Mental Health. Psychiatric disorders significantly affect individual and interpersonal relationships at all stages of individual's life.

Methods: 50 patients aged 11-17 years who were diagnosed as ADHD were enrolled to the study. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) interview and Wechsler Intelligence Scale for Children-Revised (WISC-R), Relationship Scale Questionnaire (RSQ), and Inventory of Parent and Peer Attachment (IPPA) were administered to all cases included.

Results: Mean age was 12.78-¦1.67 in patient group. Frequency of psychiatric disorder was 14% among mothers of the patients with ADHD. It was found that mean score for attachment to mother was 69, whereas mean score for attachment to father was 66. In peer attachment, highest mean score was found for disinterested attachment by 4.41-¦1.19. When attachment was assessed by maternal psychiatric disorder status, no significant differences were found in parent attachment, while a significant difference was found in favor of obsessive attachment to peer ($p<0.05$).
Conclusions: In our study, mean scores for obsessive attachment was found to be significantly higher in children in whom maternal psychiatric disorder was present. It was found that mothers of children with ADHD promoted less interaction with their children; that they were less responsive to positive and neutral interactions promoted by children; and that they used more negative, more reactive, more authoritative and more controlling but less positive parenting strategies. Previous studies reported that mothers of children with ADHD experienced more burn-out and have higher exhaustion levels when compared controls

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Psychiatry and Clinical Psychopharmacology. 2017;27:270-72.
TIC DISORDERS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Doan H.
Attention deficit hyperactivity disorder (ADHD) is the most common comorbidity seen in tic disorders (TDs). It has been reported that combined type ADHD is more common in tic disorders. Presence of TDs in association with ADHD doesn't affect the symptoms ADHD; however, it aggravates tic-related symptoms. Even in such condition, it should be taken into account that ADHD diagnosis is more important for long-term dysfunction. There are other comorbidities in majority of cases having these two diagnoses (70%). In addition, comorbid ADHD increases risk for development other comorbidities in TDs1. In population-based studies, comorbid ADHD was observed in 38% of cases with TDs. In clinical samples, ADHD was observed in 60% of children and 40% of adults with TDs. It is particularly observed in male patients. Mostly, ADHD symptoms are firstly recognized at 3-5 years of age, appearing 2-3 years before onset of tics2. Thus, debates whether drugs used for treatment of ADHD trigger tics in children and adolescents could be affected by onset of complaints. In general, it is accepted that disruptive behavior disorders and aggression could be increased in the presence of comorbid ADHD diagnosis with TDs and that self-perception and anger control are associated with ability to focus in these children. Comorbid ADHD diagnosis increases risk for additional psychopathologies in TDs and worsens their course. In fact, in a study on 5247 cases, it was reported that obsessive-compulsive disorder (OCD) was increased by 1.4 folds whereas specific learning disorder by 3.7 folds, mood disorders by 1.9 folds, anxiety disorders by 1.2 folds, conduct disorder and oppositional-defiant disorder by 6.1 folds, sleep disorders by 1.7 folds and anger control problems by 3.2 folds in children with association of TDs and ADHD when compared to those with TD alone. Again, in the same sample, both self-harming behavior and coprolalia/copropraxia were increased by 1.6 fold in the association of TDs and ADHD. It was also reported that problems related to social skills were observed 3.3 folds more frequently in these cases1. In adult patients with association of TDs and ADHD (n=1628), it was seen that the most common comorbidities were obsessive-compulsive disorders and mood disorder (Odds Ratio, OR: 1.5 and 1.3, respectively); in addition, anger control problems (OR: 2.8) and problems related to social skills (OR: 2.2) were maintained. In adult tic disorders, association with ADHD can be missed and assessment regarding ADHD is recommended1. Tic Disorders and Obsessive Compulsive Disorder Obsessive compulsive disorder and sub-threshold symptomatology may be added to TDs as well as tics may be present in cases with OCD. In fact, prevalence of TDs and tics has been reported as 7% and 20% in cases with OCB, respectively3. OCD is second most common comorbidity in TDs and it is generally accepted that it has a hereditary association with tic disorders. Threat perception related to obsessions is less clear in the association of TDs/chronic motor and vocal tic disorder (CMVTD) and OCD1. Again, compulsions and "exact localization rituals" are prominent in such cases. Thus, it may be difficult to distinguish compulsions and rituals from complex tics. In addition, sexual, religious and somatic obsessions involving violence, counting rituals, tic-like compulsions and saving are frequent in these patients. It has been reported that OCD accompanied by tics has an earlier onset and fluctuating but persistent course and that it is more prevalent among male patients2. This association increases risk for other psychopathologies and worsens prognosis of TD. In children with TDs, trichotillomania, scratching skin, nose picking, finger cracking, teeth grinding while awake,

self-harming, sniffing, splitting and opposite impulse phenomenon are more frequently seen in the presence of comorbid OCD. Among comorbidities in TDs, OCD is linked to perinatal problems, intrauterine alcohol/nicotine/caffeine exposure. In cases with TD/CMVTD, the diagnosis and symptoms of OCD may be more important for dysfunction. In these cases, OCB may not improve over time unlike tics. It is thought that cases without saving and obsessive compulsive personality traits which show early response to therapy have better prognosis1. Tic Disorders and Aggression In an international study, it was found that point and lifetime prevalence of anger control problem/aggression were 25% and 37% among cases with TDs, respectively. Aggression seen in TDs is mostly reactive and associated to ADHD symptoms. In such cases, oppositional defiant disorder (ODD), affective disorder (AD) and OCD diagnoses may be increased; however, it is thought that ADHD has primary importance for aggression. It has been reported that executive function disorders (EFDs) may promote aggression in cases with TDs. Aggression worsens prognosis and increases risk for additional psychopathology in patients with TDs1. Tic Disorders and Other Anxiety Disorders Anxiety disorders are one of the most commonly seen psychopathologies in children and adolescents. These disorders are most frequently associated to other anxiety disorders. Available data suggest that prevalence of anxiety disorders show no marked increase in children with TDs. For example, in the study by Specht et al., ADHD, social anxiety disorder, generalized anxiety disorder and OCD were found in 26%, 21%, 20% and 19% of children with CMVTD, respectively. In children with TD, anxiety disorders are also linked to sleep problems, acute alterations in mood and trichotillomania. Based on available data, it may be suggested that comorbid anxiety disorder is present in TB and should be evaluated systematically1. Tic Disorders and Affective Disorders It has been reported that affective disorders, primarily major depressive disorder (MDD) and persistent depressive disorder (dysthymia in DSM-IV-TR), can be frequently associated to TDs; however, these diagnoses are commonly missed. In general, it is accepted that there is interplay between affective disorders and TDs, and both disorders may aggravate each other. Regardless of diagnosis of affective disorder, temporary sub-threshold depressive state and passive suicidal thoughts may be present in periods where tics are increased. It was reported that such complaints and findings can appear as a response to sensation of failure and social challenges caused by loss of control on tics; however, each case should be assessed in details for a potential underlying affective disorder. Lifetime anxiety disorder was reported by 75% whereas ADHD by 0-57% and ODD/AD by 0-79% in cases with association of TDs and affective disorder1. Tic Disorders and Other Comorbidities Specific Learning Disorder The prevalence of comorbid specific learning disorder (SLD) is found as 22% in TDS while its prevalence has been reported as 15-20% in general population. Thus, it may be suggested that TDs doesn't increase risk for SLD specifically. Especially, comorbid ADHD may mediate to SLD seen in association with TDs. However, SLD subtypes differ when they accompanied to TDs. Reading disorder is more common SLD in general population while mathematics and written expression disorders are primarily seen SLDs in association with TDs. In individuals with TDs, social responsiveness and other communication functions can be affected in the presence of comorbid SLD, worsening prognosis4. Self-Harming Behaviors Prevalence of self-harming behavior can range from 17% to 53%. Some authors reported that self-harming behaviors are associated to motor tics while Kurlan advocated these behaviors are independent from tic severity. It has been reported that self-harming behaviors seen in TDs are independent from intelligence level; can be a marker for underlying depressive disorders; and obsessionality may mediate this symptom2. Autism Spectrum Disorders TDs frequently accompany to autism spectrum disorders (ASD) and this association creates specific challenges in terms of diagnosis. It was suggested that tics such as hand clapping and sniffing make diagnosis in particular. In some cases, OCD and TDs can occur during adolescence1,2,5. Mental Retardation There is a simplex relationship between TDs and mental retardation (MR). TD prevalence is increased in cases with MR but vice versa isn't true. Additional challenges may be present in the diagnosis as stereotypes are frequently seen in cases with MR. It has been reported that diagnosis is challenging in cases with moderate-to-severe MR1. Developmental Coordination Disorder, Trichotillomania, Substance Use Disorder Developmental coordination disorder (DCD) accompanies to TDs especially in the presence of comorbid ADHD and academic problems. It may increase risk for development of psychopathologies over time and this impact may be mediated by social and academic problems. SLD and speech disorders may be seen commonly in these cases1. Trichotillomania is increased in TDs. In particular, it is more common among women with TDs and may increase risk for anxiety disorders. Substance use disorders alone don't increase risk for TDs. The group with association of TDs and ADHD are particularly at increased risk for development

of substance use disorders. In these cases, it was reported substance use could aim self-medication and to control tics1,2

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Psychiatry and Clinical Psychopharmacology. 2017;27:286-87.

ADHD AND CRIME.

Semerci B.

Most of the literature tries to explore the relationship between mental illness and juvenile delinquency; however, there lies a gap in the literature on how mental illness affects severity of the committed crimes. Some psychiatric disorders, such as presence of conduct disorder and childhood ADHD emerge as predictors of more violent crimes1. Adolescent ADHD is also more likely to get in trouble with the law. Adolescents with co-morbid ADHD and CD/ODD appear to have higher levels of impulsivity and delinquency. The risk of committing crimes increases with age, and shows higher prevalence in children displaying co-morbidity with neuro-psychological deficits like low IQ scores and learning difficulties. Aggressive behavior, although not an adequate diagnostic criterion for ADHD, is displayed by more than 50% of the patients; and in childhood, it is found to be associated with ADHD, addiction to drugs and other antisocial behavior patterns and criminality2,3. In comparison to children with pure conduct disorder (CD), antisocial behavior and disposition to criminality are more prevalent in children with comorbid ADHD and CD4. Virtually all constructs of ADHD, such as impulsiveness, hyperactivity, restlessness, not considering consequences before acting, poor ability to plan ahead, low sense of control, risk taking and poor ability to delay gratification, measured in different ways, are persistently associated with offending5. It is crucial to spend more effort to diagnose and treat ADHD in order to prevent delinquency in children and adolescents

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Psychiatry and Clinical Psychopharmacology. 2017;27:102-03.

HALLUCINATION AS A SIDE EFFECT IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gaksua M, et al.

Methylphenidate and atomoxetine are frequently used in the treatment of ADHD. With the use of methylphenidate and atomoxetine, side effects such as abdominal pain, decreased appetite are common, while hallucination is a relatively rare side effect. A 4-year-old girl was referred to our outpatient clinic with her family for the complaint of masturbation. The child, who has limited eye contact, lack of empathy, difficulty in initiation, was clinically evaluated as autism spectrum disorder. The child, who applied with the complaint of hyperactivity on the 1st grade of elementary school, was treated with 10 mg methylphenidate daily regarding additional attention-deficit/hyperactivity disorder diagnosis. A few days later, she stated that she was seeing a lot of black images around her that were ambiguous. These images were evaluated as visual hallucinations and hallucinations passed immediately after the drug discontinuation. Subsequently, 18 mg of atomoxetine daily was started for the treatment of ADHD and 25 mg daily dose was reached after 10 days. Shortly after the atomoxetine dose was increased, the child started to shout that she heard some voices and her family reported that she talking and shouting to herself. These symptoms were considered as auditory hallucination and atomoxetine was also cut off. It is known that there are hallucinations at toxic doses and parenteral methylphenidate administration. There are also limited number of case reports reporting hallucinations, with the use of atomoxetine in therapeutic doses. Clinicians should be aware of the rare side effects of methylphenidate and atomoxetine, such as hallucinations, and should be more cautious when using medication in patients with developmental disorders who reported side effects before. Family history of psychosis, familial drug side effects such as hallucinations, and specific neurological tendencies of children diagnosed with social communication disorders should be considered carefully

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Psychiatry and Clinical Psychopharmacology. 2017;27:27.

AUTISTIC SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH CONGENITAL ADRENAL HYPERPLASIA.

Grenef H, et al.

Objective: Androgen exposure is hypothesized to play a role in the development of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) or their subclinical symptoms. The aim of this cross-sectional study was to examine the ASD and ADHD symptoms in children with congenital adrenal hyperplasia (CAH), a natural cause of prenatal androgen excess.

Methods: Forty-five children and adolescents (27 females, 18 males) with CAH and their 30 unaffected siblings (16 female, 14 male) were included in the study. Parents completed the Social Communication Questionnaire (SCQ) to measure ASD symptoms and the Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S) to assess ADHD symptoms.

Results: In this study, subjects with CAH reported by their parents to have more autistic symptoms in SCQ-Communication subscale and, although not statistically significant, in SCQ-Total scores. Children and adolescents with CAH had higher scores in terms of Inattention, Hyperactivity, Oppositional Defiant Disorder. and Conduct Disorder symptoms in T-DSM-IV-S compared to their unaffected siblings; however, these differences did not reach to statistical significance.

Conclusions: Our study supports the hypothesis that prenatal androgens are involved in the development of ASD but failed to provide significant evidence for an increase in ADHD symptoms in individuals with CAH. Further research with larger samples are needed to clarify the associations between CAH, ASD, and ADHD symptoms

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Psychiatry and Clinical Psychopharmacology. 2017;27:13-14.

HOMOCYSTEINE, PYRIDOXINE, FOLATE AND VITAMIN B12 LEVELS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Altun H, et al.

Objectives: Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurobehavioral disorder of which the pathophysiology is complex and yet unclear. Neurochemical, neuroanatomical, genetic, and environmental factors are considered in its etiology. Homocysteine is produced during the metabolism of methionine, which is an essential amino acid and plays several important roles in human physiology. Homocysteine metabolism depends on the level of piridoksine, folate and vitamin B12. It is known that elevated serum homocysteine, decreased folate and vitamin B12 serum levels are associated with cognitive impairment, neurodegenerative diseases and various psychiatric symptoms including autism, psychosis, affective, depression and other psychiatric disorders. The aim of this study is to evaluate the serum levels of homocysteine, pyridoxine, folate, and vitamin B12 in children with ADHD.

Methods: 30 patients with ADHD and 30 healthy controls were included in the study. The diagnosis of ADHD was made according to DSM-5 criteria. Children and adolescents were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Lifetime Version (KSAD-S) and the WISC-R. Homocysteine, pyridoxine, folate, and vitamin B12 levels were measured with enzyme-linked immunosorbent assay.

Results: There were no statistically significant differences between the groups in terms of age and gender ($p>0.05$). Homocysteine, pyridoxine, folate, and vitamin B12 levels were significantly lower in children with ADHD compared to the controls ($p<0.05$).

Conclusions: To the best of our knowledge, this is the first study to examine the association between serum homocysteine level and ADHD in children. In this study, contrary to other psychiatric disorders, homocysteine levels were found to be lower. However, similar to our study, only one study have reported that low serum homocysteine levels were reported in adults with ADHD. In addition, our study suggests that serum pyridoxine, folate, and vitamin B12 levels were significantly reduced in children with ADHD

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Psychiatry and Clinical Psychopharmacology. 2017;27:51.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WHO UNDERWENT LIVER TRANSPLANTATION.

Marangoz Y, Sari BA, Baris Z, et al.

Objective: We planned to examine the frequency of ADHD in children with liver transplantation and the possible causes of this disorder.

Methods: Sixty-two children aged between 6 and 18 years, who had liver transplantation between 2003 and 2015 in Baskent University Medical School Hospital was participated in the study. Primary diagnoses, age of transplantation, duration of pre-transplantation illness, duration of hospitalization and intensive care unit stay before and after transplantation, Child Pugh and PELD scores, donor type, prematurity, history of low birth weight, convulsion, familial epilepsy, and maternal smoking during pregnancy were all recorded. K-SADS (Schedule for Affective Disorders and Schizophrenia for School Aged Children-Kiddie-SADS-Present and Lifetime Version) were administered on all children and their parents by the clinical interviewer who is a specialist in child and adolescent mental health and DSM-IV Axis I diagnoses were determined. Patients were evaluated with Conners' Parent-Teacher Rating Scale (CPRS-CPTS).

Results: Six of the 62 patients (9.7%) were diagnosed with ADHD. 4% of the girls in the sample (1/25); 13.5% of men (5/37) were diagnosed with ADHD. The only patient who was diagnosed with inattentive type of ADHD was female, while the other five were male. The only patient who was diagnosed with inattentive type of ADHD was female, while the other five were male.

Conclusions: In our study the rate of ADHD was slightly higher than the proportion of community-based studies and lower than studies conducted with children with liver transplants. This suggested the effects of hepatic transplantation on cognitive function and attention. To the best ofour knowledge, this study is the first study to examine ADHD in children with liver transplants in Turkey

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Psychiatry and Clinical Psychopharmacology. 2017;27:105.

AN ADOLESCENT WITH OXYBUTYNIN ABUSE DEVELOPING ON THE BASIS OF UNRECOGNIZED ADHD: A CASE REPORT.

Galdaƒ E, et al.

Anticholinergic agents have been reported to be abused since 1980s. Abuse of those agents among adolescents has received relatively little attention compared to adults. Oxybutynin has relatively weaker anti-cholinergic effects which led to the view that it has lower potential for abuse. The patient was a seventeen year-old adolescent male who was brought to our department with complaints of "weight loss, change in behaviors and mydriasis". Upon questioning it was learned that he had been using at least 50 mg/day of oxybutynin without tolerance or withdrawal symptoms. The abuse had a waxing and waning pattern and coincided with interpersonal stressors. After he had started abusing oxybutynin his sleep and appetite were reduced and he lost 17 kg of weight within the last 10 months. The developmental history was notable for symptoms of hyperactivity, impulsivity and inattention prior to the onset of abuse. Mental status examination revealed reduced grooming, depressed mood with anxious affect. Sleep and appetite were reduced. Psychometric examinations with Beck Depression Inventory and Screen for Childhood Anxiety and Related Disorders revealed scores of 19 (moderate depressive symptoms) and 36 (anxiety symptoms above threshold); respectively. In accordance with the DSM-5 criteria he was diagnosed with other (or unknown) substance use disorder (oxybutynin), ADHD (Inattentive presentation). The depressive and anxious symptoms were judged to be secondary to oxybutynin abuse. He was started on atomoxetine 25 mg/day and quetiapine 25 mg/day and atomoxetine was gradually titrated to 60 mg/day. Oxybutynin abuse remitted within 4 weeks and both the patient and his parents reported improvement in academic and interpersonal domains as well as depressive and anxious symptoms. Clinicians should be aware of the abuse potential of oxybutynin especially by adolescents with unrecognized/untreated ADHD and disruptive behavior disorders. Atomoxetine may be a viable choice for treatment of ADHD in those patients

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Psychiatry and Clinical Psychopharmacology. 2017;27:21.

SERUM UROTENSIN-II LEVELS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Ugur C, Sertcelik M, Uneri O, et al.

Objective: Urotensin-II (U-II) is one of the most vasoconstrictive substrates for the mammals. Lately, this substrate is thought to be responsible for developing of the neuropsychiatric disorders, by causing an abnormal brain bloodstream situation. Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently seen disorders in childhood and their etiologies are remain unclear. This study evaluated the serum urotensin-II levels of children with ASD and ADHD and compared with healthy subjects' urotensin-II levels.

Methods: Total of 179 children, 60 of them diagnosed with ADHD and 60 of children with ASD, according to the DSM-5 criteria and both had no treatment for at least a month and 59 of healthy subjects whom they all presented to the Ankara Pediatric Hematology-Oncology Training and Research Hospital were included. Kiddie-SADS present and lifetime version, a semi-structured interview, was administered to all subjects. Venous samples of the participants were given after a 12-hours starvation. Serum U-II levels were analyzed by the use of ELISA kits. SPSS 16.0 was used for statistical analysis. The alpha level of 0.05 was set to indicate significance.

Results: U-II levels of children with ASD were found significantly higher than those with ADHD. There was also a positive correlation between U-II levels and autism behavior checklist scores.

Conclusions: This study is the first to evaluate U-II levels in children with ASD and ADHD in comparison with a control group. Higher U-II levels and its levels' correlation with symptom severity of disorder are thought to be a responsible factor that could play a role in ASD etiology. There is a necessity to be generalized these results by analyzing U-II levels in larger samples with different aspects of the ASD

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Psychiatry and Clinical Psychopharmacology. 2017;27:101-02.

LONG-ACTING METHYLPHENIDATE TREATMENT IN AN ADOLESCENT GIRL WITH ADHD AND PRIMARY ENURESIS: A CASE REPORT.

Gul MK, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized, by a persistent and impairing pattern of inattention and/or hyperactivity/impulsivity. Enuresis is a pathological state associated with the lack of a developed skill in controlling the urinary bladder, resulting in repeated episodes of involuntary micturition during sleep or waking. Enuresis is a common comorbid disorder in children with ADHD. The rate of enuresis in children with ADHD has been reported as about 30%. In this report, we present an adolescent girl with ADHD and primary enuresis that treated with long acting methylphenidate. A 13-year-old girl was referred to the outpatient clinic by her family with nocturnal bedwetting every night and daytime urinary incontinence. She had same symptoms during 8 years. She also had forgetfulness, difficulty listening and easily distracted. She was experiencing severe problems during making homework and listening classes. Both the clinical interview and the parent and teacher reports were suggestive of an ADHD diagnosis. Until now, there wasn't any improvement with conditioning therapy and imipramine 50 mg/day. We oriented the patient to nephrology and urology departments to detection organic etiology but the results had evaluated normally. Her condition was diagnosed ADHD and primary enuresis. For the treatment long acting methylphenidate drug 10 mg/day was chosen and two weeks later dose was increased to 20 mg/day. She had nocturnal bedwetting only once and no daytime wetting. The ADHD symptoms were decreased during this time. Our case supports the positive scientific findings about the association long acting methylphenidate and the treatment of ADHD with primary enuresis. There are many hypotheses for to explanation of the effects of this medication in the treatment of enuresis and ADHD. But the relationship between the treatment of both these disorders has not been understood clearly yet

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Psychiatry and Clinical Psychopharmacology. 2017;27:254-55.

COMPLICATED PRESCHOOL ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND PHARMACOLOGIC TREATMENT APPROACHES.

Kultur E.

Attention deficit/hyperactivity disorder (ADHD) is a highly comorbid diagnosis and conditions like dysphoric affect, low self-esteem, anxiety, and obsessional traits are often found in patients with a primary ADHD diagnosis, but they can also occur as separate conditions. Comorbidity should be evaluated for all cases with ADHD symptoms. After gathering all the relevant data from clinical interviews, rating scales, and other sources, the clinician must weigh and integrate this information to determine whether the patient meets the diagnostic criteria for ADHD and/or another learning or psychiatric disorder. On the other hand, in many cases it can be impossible to make an official Axis I diagnosis. Some symptoms like irritability can be trans-diagnostic and it can be difficult to make differential diagnosis. Another issue in diagnostic accuracy is the absence of official definitions of symptoms that are developmentally sensitive. Emotional lability is a highly prevalent condition in child psychiatry cases, it can be observed in nearly half of the child psychiatry admissions, and it can be difficult to differentiate an ordinary developmental feature from pathological phenomenology of a spectrum. Clinicians should consider the developmental features during diagnostic evaluations. Official diagnosis is important to plan an evidence based treatment, however symptoms associated to both depression and ADHD can be viewed as occurring along a dimension from sub-syndrome to disorder. Even when these two set of symptoms are viewed as categories, the point at which depression and ADHD criteria reached diagnostic levels hinges on whether enough symptoms are co-occurring to be recognized as a syndrome and whether these symptoms are severe enough and persistent to cause functional impairment. On the other hand, considerable evidence indicates that, subthreshold depressive or ADHD symptoms have found to be associated impaired functioning1,2. The rates of internalizing comorbidity also not change between threshold and subthreshold ADHD1. When planning treatment, highly comorbid symptoms can be viewed as a dimension and "treat what is there" approach can be main strategy to choose pharmacologic agent. In our case of preschool ADHD, chronic irritability and temper outbursts are the main associating symptoms to ADHD symptoms. These symptoms are frequent feature of many disorders like mood disorders, anxiety disorders, disruptive, impulse control disorders and substance use disorders. Irritable children are described as grumpy, annoyed easily and in negative mood in their background. The other feature they have is outbursts with flashes of anger or explosiveness, verbal and/or physical, that are excessive responses to requests or events, and they are usually disruptive to their environment. It can be difficult to differentiate excessively irritable cases from bipolar cases, DSM-5 described a manic episode with A criterion as distinct period of elevated, expansive or irritable mood and increased goal directed activity or energy, lasting at least 1 week and present most of the day nearly every day; B criterion described many associating symptoms to A criteria which should be noticeably different from baseline usual behavior. Other than distinct episodes, family history of bipolar disorder can help to differentiate irritable-ADHD cases from bipolar disorder. Irritable-ADHD cases were described as SMD at first, and in DSM-5 hyperarousal symptoms which may overlap with B criteria of bipolar disorder are excluded from severe mood dysregulation criteria and described as disruptive mood dysregulation disorder. Dimension of angry-irritable mood is highly associated with externalizing disorders and they predict future anxiety and depressive disorders, high comorbidity and functional impairment3,4. So, disruptive mood dysregulation disorder is placed under depressive disorders. Disruptive mood dysregulation disorder is a highly possible diagnosis for our case since irritability is not episodic and stable in between episodes of temper outbursts. Accurate diagnosis can be very difficult, it is very important to make separate family and child evaluations and to follow-up the case in order to observe episodes, change from baseline usual behaviors, presence of symptoms in more than one situation, co-occurrence of symptoms as bundles, routine pattern of outbursts, mood between outbursts, and consider cultural features and developmental level, think about impairment that irritability produces. Treating mood problems in behavioral disorders could be critical to helping these individuals and may be important for their overall outcome. Treatment of these cases is suggested mainly similar to treatment of ADHD with anxiety or depression. So, stimulants and treatments for anxiety depression such as selective serotonin reuptake inhibitors, cognitive behavioral psychotherapies, or a combination of these could be considered. Tourian et al.5 examined empirical evidence supporting the pharmacological treatment for severe angry-irritable mood and found that pharmacotherapeutic treatment for both aggression and chronic irritability includes various options, such as antidepressants, especially selective norepinephrine reuptake

inhibitors, mood stabilizers, psychostimulants, antipsychotics, and alpha-2 agonists. Environmental intervention can also be helpful, and non-pharmacological treatments should also be considered in treatment of severe irritability with ADHD. The available evidence suggests potential efficacy of psychotherapies which have previously been developed for internalizing and externalizing disorders

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Psychiatry and Clinical Psychopharmacology. 2017;27:164.

GENERALIZED ANXIETY DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BASED ON NON-VERBAL LEARNING DISABILITY (NVLD): A CASE REPORT.

Gal G, et al.

Non-verbal Learning Disorder (NVLD) is a clinical syndrome which is not among those in the diagnosis classifications such as DSM-5 and ICD-10. Some of the characteristics of NVLD are the visual-spatial perception disability, the weakness in the handwriting and math skills, and the problems in the perception of social cues. In this report, in an adolescence case, it is aimed to discuss the differential diagnosis of NVLD and to show that the functionality may increase along with the treatment of comorbid disorders. Fourteen year-old patient applied to our clinic with her parents with the complaints of "inability to communicate with people, to express their feelings and to do as expected from her age". During the evaluation, it is found out that she has no friends and low self-esteem. She has low academic success, low arithmetic skills and difficulties in painting class and physical education class that require motor skills. It was reported that verbal and memorizing skills are very well-developed despite those problems and social communication problems. In the light of history, evaluation, test results, it is considered that the patient may meet the DSM-5 criteria for the ADHD-Predominant Inattentive Presentation, Social Communication Disorder (SCD), Specific Learning Disorder, Developmental Coordination Disorder (DCD), and Generalized Anxiety Disorder (GAD) and, she fits in the clinical characteristics of NVLD. After psycho-education was provided to the parents, the treatment was 0.5 mg/kg/day to 1.2 mg/kg/day atomoxetine. Fluoxetine was started at 10 mg/day to 20 mg/day. In the continued weeks, it is observed a decrease in the anxiety, improvement in the attention, a considerable increase in the academic success. In our case, differential diagnosis of the patient included SCD, Asperger syndrome, ADHD, and DCD. The diagnosis of NVLD is a controversial syndrome due to unclear diagnosis criteria and comorbid disorders. The clearer clinical characteristics will provide more correct diagnosis, treatment and guidance

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Psychiatry and Clinical Psychopharmacology. 2017;27:8-9.

ADHD IN EPILEPSY AND PRIMARY ADHD: THE DIFFERENCES ON SYMPTOM DIMENSIONS AND QUALITY OF LIFE.

Ekinci U, et al.

Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is among the most common psychiatric comorbidites in childhood epilepsy. The possible differences of epilepsy-related ADHD and primary ADHD have not been completely clarified. This study aimed to (1) compare quality of life (QOL) among children with epilepsy, epilepsy-ADHD and primary ADHD and (2) compare ADHD symptom dimensions and subtypes between children with epilepsy-ADHD and primary ADHD.

Methods: A total of 140 children; 53 with epilepsy, 35 with epilepsy-ADHD and 52 with primary ADHD were included. KINDL-R, Turgay DSM-IV Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S) and Conners' Parent Rating Scale (CPRS) were administered. ADHD subtypes were diagnosed according to the DSM-IV criteria. Neurology clinic charts were reviewed for epilepsy-related variables.

Results: Children with epilepsy-ADHD had the lowest (poorest) KINDL-R total scores. Epilepsy-ADHD group had more inattentiveness (IA) symptoms, while primary ADHD group had more hyperactivity/impulsivity (HA-IMP) symptoms. The frequencies of ADHD combined and IA subtypes were 60% and 40% in children with epilepsy-ADHD, and 80.7% and 19.3% in children with primary ADHD, respectively (p=0.034). Regarding the epilepsy-related variables, no significant differences were found between children with epilepsy-ADHD and those with epilepsy alone.

Conclusions: ADHD in epilepsy is associated with a significant poor quality of life and predominantly inattentiveness (IA) symptoms

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Psychiatry and Clinical Psychopharmacology. 2017;27:80-81.

DECRESED ANXIETY SYMPTOMS ON EXTENDED RELEASE-METHYLPHENIDATE MEDICATION IN CHILDREN WITH ADHD.

Toz HI, et al.

Objective: Comorbid psychiatric disorders have been commonly seen in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Mean rate of the comorbidity of anxiety disorders in patients with ADHD were reported as 25% in clinical samples. Although psychostimulants are FDA-approved the first rank pharmacological agents in the treatment of ADHD, according to some treatment guidelines, the addition of SSRI to ADHD treatment or only atomoxetine treatment have been preferred in the presence of comorbid anxiety disorders in ADHD. The aim of this study was to evaluate the changes of both severity of ADHD symptoms and comorbid anxiety in children with ADHD after 8 weeks extended-release methylphenidate treatment.

Methods: 33 boys who were diagnosed with ADHD according to DSM IV-TR criteria at the Bakirkoy Mental Health Research and Training Hospital, Child and Adolescent Psychiatry outpatient clinic, were included in the study. All participants were already applied to clinical interview and K-SADS. ADHD symptoms were evaluated by Conners' Teacher and Parent Rating Scale. Symptoms of anxiety were measured using the Conners Parent Rating Scale (CPRS). Symptoms were measured before and after the 8 weeks of methylphenidate treatment.

Results: There was a significant decrease in hyperactivity, attention deficit, and conduct problem subscales of Conners' Teacher Rating Scale (CTRS) and anxiety subscale score of CPRS after 8 weeks of methylphenidate treatment.

Conclusions: It is noteworthy that although potential anxiogenic side effect of psychostimulant, significant decrease in anxiety scores after methylphenidate treatment without any additional pharmacologic therapy or psychotherapy in our patient group with high rates of comorbid anxiety disorders (67% of all). Although it has not been found statistical significant (p=0.058), decreased psychosomatic subscale of the CPRS after the treatment could be related to decreased severity of anxiety symptoms

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Psychiatry and Clinical Psychopharmacology. 2017;27:11-12.

MIGRAINE, TENSION-TYPE HEADACHE, ADHD AND BIPOLAR AFFECTIVE DISORDER IN ADOLESCENCE: A CLINICAL STUDY.

Gal H, et al.

Objective: Headache is a common neurological condition which is frequent in pediatric age group. Numerous studies of children and adults with headache and/or migraine showed that there is a high burden of psychiatric disorders including neuropsychological impairement, ADHD, and bipolar disorder (BD). In this study, we aimed to examine the association between parental and comorbid migraine, ADHD, and BD and assess if there is a relationship between pain degree and psychiatric symptoms in adolesence age group.

Methods: Adolescents who presented with headache to outpatient pediatric neurology clinics of Necip Fazil State Hospital were included in the study. We used The Conners Wells Adolescents form (CASS-L, 87 items) and Mood Disorder Questionnare (MDQ, 13 items).

Results: 119 adolescents were assessed. There were 79 females and 40 males. 30.8% were diagnosed with migraine (17.5% of males and 36.7% of the females, p=0.024) and 69.2% were diagnosed with tension type headache (82.5% of males and 63.3% of the females). 20.8% of them had severe attention problems and 13.3% had severe hyperactivity/impulsivity and 48.8% had severe mood dysregulation problems. According to correlation analyses, pain degree was positively correlated with the number of psychiatric disorder in the family and anger control problems of adolescents. But correlations were generally weak (r=0.18 and r=0.29; p<0.05, respectively). On the other hand, there were strong correlations between MDQ

scores and all CASS-L subscale scores including family, conduct, anger-control, emotional and cognitive problems, hyperactivity-impulsivity scores, and ADHD index ($r>0.50$; $p<0.01$).
Conclusions: Adolescents with headache experience significantly increased levels of attention problems, hyperactivity/impulsivity and mood dysregulation symptoms, and ADHD-BD symptoms were strongly correlated in this age group

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Psychiatry and Clinical Psychopharmacology. 2017;27:143-44.
EFFECT OF METHYLPHENIDATE ON KLEPTOMANIA IN A CHILD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Ifik A.
Kleptomania is an impulse-control disorder defined as the recurrent failure to resist impulses to steal objects that are not needed for personal use or for their monetary value. Kleptomania is a relatively rare condition. A number of case reports found various medications effective in the treatment of the disorder. There are only three different case reports examined the effect of methylphenidate (MPH) in patients with attention-deficit/hyperactivity disorder (ADHD). I describe a child with kleptomania and ADHD, treated with methylphenidate. A 7-year-old boy was brought to our outpatient clinic by his father for his inattention, short attention time, concentration difficulties, hyperactivity, impulsivity, irritability, oppositional defiant behavior, and stealing behavior. He had stolen his friends' school materials, including pencil sharpeners, pen cap, and eraser dust. His parents reported that although he collected the things that he had stolen, he almost never used them. Though his parents were uncertain whether he experienced tension prior to stealing, he typically seemed to be comfortable after the acts. Though the parents had used various punishments to criminate him for his actions, no reduction in his stealing behaviors was observed. In his psychiatric assessment, he met criteria for combined type ADHD, oppositional defiant disorder and kleptomania. An 18 mg OROS-MPH treatment was initiated daily. It resulted in significant improvement in the his ADHD symptoms and the complete resolution of the kleptomania within the first week. In the present case, it seems that the MPH treatment is responsible for the significant improvement in the patient's stealing behavior. Kleptomania is a rare condition and this report observing the complete resolution of kleptomania with a MPH treatment in a school-age child with ADHD. The anti-kleptomaniac effect of the MPH for ADHD patients' needs to be validated through additional studies

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Psychiatry and Clinical Psychopharmacology. 2017;27:216.
UNMET NEEDS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: LONG TERM EFFECTS OF ADHD TREATMENT IN CHILDREN AND ADOLESCENTS.
Tarakiolu MC.
ADHD has been seen widely seen and leads significant functional impairment in childhood1. Although stimulants have been used most frequently in ADHD treatment their long term effects did not investigate well. Methylphenidate which is the most frequently prescribed stimulant's long term side effects on growth-development, cardiovascular, psychiatric and neurological systems are very important2. Stimulant diversion or misuse in long term has growing up in recent years and lead important consequences on community health3. Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) consortium was established in 2012 and experts on ADHD, drug safety, neuropsychopharmacology and cardiology developed a programme which investigates the long term possible side effects of stimulants2. In this presentation, long term side effects of stimulants (methylphenidate) will be reviewed through the perspective of ADDUCE work group study results

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Psychoanal Psychol. 2022 Aug.

BION'S ALPHA-FUNCTION AS A KEY FOR UNDERSTANDING EMOTIONAL PROBLEMS IN ADHD.

Yudilevich P, BenEliahu E.

This article discusses the attention deficit/hyperactivity disorder (ADHD) syndrome in children, from a regulation-based perspective, as a neurodevelopmental deficiency that develops into mental difficulties. Based on research indicating the existence of early markers to ADHD, we propose that the neurodevelopmental difficulty creates certain characteristics in the mother–infant/toddler relationship. We propose the term 'mental sustaining' to describe the capacity to delay response in order to allow stimuli to be perceived and absorbed internally. In children with ADHD, the neurodevelopmental impairment of the regulatory function hinders the capacity for 'mental sustaining,' potentially creating a vicious cycle in the child's relations with its caretakers. We draw on the thinking of Wilfred Bion, proposing that this vicious cycle might affect the quality of the internalization of alpha-function in a manner that results in various functional deficiencies. Three such deficiencies prominent in children diagnosed with ADHD are discussed in light of Bion's theory: the proclivity for idiosyncratic interpretations of reality; difficulty in automation of mental and motoric actions; and a tendency for excessive need for material gratification (the 'bottomless pit' phenomenon). This article wishes to join the contemporary literature that understands children with ADHD from an inclusive theoretical perspective that links neurodevelopmental and psychoanalytic approaches. We propose a psychoanalytic understanding of this neurodevelopmental syndrome relying on Bion's concepts. The contribution of this article to existing psychoanalytic literature lies in its description and discussion of psychic mechanisms that are part of the characteristic psychic landscape of children with ADHD, as well as the presentation of potential etiologies of these mechanisms

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Psychol Med. 2022 Jul;52:1736-45.

SHARED INTRINSIC FUNCTIONAL CONNECTIVITY ALTERATIONS AS A FAMILIAL RISK MARKER FOR ADHD: A RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY WITH SIBLING DESIGN.

Chiang HL, Tseng WYI, Wey HY, et al.

Background: Although aberrant intrinsic functional connectivity has been reported in attention-deficit/hyperactivity disorder (ADHD), we have a limited understanding of whether connectivity alterations are related to the familial risk of ADHD.

Methods: Fifty-three probands with ADHD, their unaffected siblings (n = 53) and typically developing controls (n = 53) underwent resting-state functional magnetic resonance imaging scans. A seed-based approach with the bilateral precuneus/posterior cingulate cortex (PCC) was used to derive a whole-brain functional connectivity map in each subject. The differences in functional connectivity among the three groups were tested with one-way ANOVA using randomized permutation. Comparisons between two groups were also performed to examine the increase or decrease in connectivity. The severity of ADHD symptoms was used to identify brain regions where symptom severity is correlated to the strength of intrinsic functional connectivity.

Results: When compared to controls, both probands and unaffected siblings showed increased functional connectivity in the left insula and left inferior frontal gyrus. The connectivity in these regions was linked to better performance in response inhibition in the control group but absent in other groups. Higher ADHD symptom severity was correlated with increased functional connectivity in bilateral fronto-parietal-temporal regions only noted in probands with ADHD.

Conclusions: Alterations in resting-state functional connectivities with the precuneus/PCC, hubs of default-mode network, account for the underlying familial risks of ADHD. Since the left insula and left inferior frontal gyri are key regions of the salience and frontoparietal network, respectively, future studies focusing on alterations of cross-network functional connectivity as the familial risk of ADHD are suggested

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Psychopharmacology (Berl). 2022 Sep;239:2713-34.

CANNABIDIOL FOR THE TREATMENT OF AUTISM SPECTRUM DISORDER: HOPE OR HYPE?

Pedrazzi JFC, Ferreira FR, Silva-Amaral D, et al.

RATIONALE: Autism spectrum disorder (ASD) is defined as a group of neurodevelopmental disorders whose symptoms include impaired communication and social interaction, restricted and repetitive patterns of behavior, and varying levels of intellectual disability. ASD is observed in early childhood and is one of the most severe chronic childhood disorders in prevalence, morbidity, and impact on society. It is usually accompanied by attention deficit hyperactivity disorder, anxiety, depression, sleep disorders, and epilepsy. The treatment of ASD has low efficacy, possibly because it has a heterogeneous nature, and its neurobiological basis is not clearly understood. Drugs such as risperidone and aripiprazole are the only two drugs available that are recognized by the Food and Drug Administration, primarily for treating the behavioral symptoms of this disorder. These drugs have limited efficacy and a high potential for inducing undesirable effects, compromising treatment adherence. Therefore, there is great interest in exploring the endocannabinoid system, which modulates the activity of other neurotransmitters, has actions in social behavior and seems to be altered in patients with ASD. Thus, cannabidiol (CBD) emerges as a possible strategy for treating ASD symptoms since it has relevant pharmacological actions on the endocannabinoid system and shows promising results in studies related to disorders in the central nervous system.

OBJECTIVES: Review the preclinical and clinical data supporting CBD's potential as a treatment for the symptoms and comorbidities associated with ASD, as well as discuss and provide information with the purpose of not trivializing the use of this drug

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Psychosomatic Medicine. 2022;84:A31-A32.

THE RELATIONSHIP BETWEEN PEDIATRIC AND SYMPTOMS AND ASTMA MANAGEMENT AND OUTCOMES IN MINORITY POPULATIONS.

Silverstein GD, Feldman JM.

Purpose: Children with co-morbid ADHD and asthma are at an increased risk for adverse health outcomes and reduced quality of life. It is unclear what the mechanisms are that contribute to these outcomes. The objective of this study was to examine if ADHD symptoms in children with asthma were associated with asthma medication use patterns, including controller medication adherence and quick-relief medication use.

Methods: We conducted a secondary analysis of data from a behavioral interventional for Black and Hispanic children ages 10-17 with asthma. The current study utilized data that were collected on participants prior to the start of the behavioral intervention. Study participants were recruited from pediatric asthma clinics in the Bronx and completed the Conners-3AI assessment for ADHD symptoms at baseline. Asthma medication use data were collected via electronic devices fitted to participants' asthma medications. Other outcome measures included the Asthma Control Test (ACT), self-reported healthcare utilization questions, and pulmonary function as measured by spirometry testing.

Results: The study sample consisted of 302 participants, with 39.1% identifying as Hispanic, 35.6% as Black, and 14.9% as mixed race. The average age of the pediatric participants was 12.8, with the majority of participants meeting criteria for moderate (45.1%) or severe (31.9%) persistent asthma. Amongst the study sample, increased ADHD symptoms were associated with reduced Inhaled Corticosteroid medication adherence (+¦ =-.19, SE = .13, p=.01) and Leukotriene Receptor Antagonist medication adherence (+¦ =-.21, SE = .18, p=.02). ADHD symptoms were not associated with quick-relief medication use, health care utilization, self-reported asthma control, or pulmonary function.

Conclusions: ADHD symptoms were found to be associated with reduced asthma controller medication adherence. Asthma medication adherence may play a key role in the relationship between ADHD symptoms and asthma outcomes in minority children

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Res Child Adolesc Psychopathol. 2022 Aug;50:1055-66.

LONGITUDINAL TEMPERAMENT PATHWAYS TO ADHD BETWEEN CHILDHOOD AND ADOLESCENCE.

Martel MM, Elkins AR, Eng AG, et al.

The current investigation extended prior cross-sectional mapping of etiological factors, transdiagnostic effortful and affective traits, and ADHD symptoms to longitudinal pathways extending from two etiological domains: polygenic and prenatal risk. Hypotheses were (1) genetic risk for ADHD would be related to inattentive ADHD symptoms in adolescence and mediated by childhood effortful control; (2) prenatal smoking would be related to hyperactive-impulsive ADHD symptoms during childhood and mediated by childhood surgency; and (3) there would be age-related variation, such that mediation of genetic risk would be larger for older than younger ages, whereas mediation of prenatal risk would be larger in earlier childhood than at later ages. Participants were 849 children drawn from the Oregon ADHD-1000 Cohort, which used a case control sample and an accelerated longitudinal design to track development from childhood (at year 1 ages 7-13) through adolescence (at year 6 ages 13-19). Results showed the mediational pathway from prenatal smoking through surgency to hyperactivity-impulsivity at Year 1 was significant (indirect effect estimate=.053, p<.01). The mediational pathway from polygenic risk through effortful control to inattention at Year 6 was also significant (indirect effect estimate=.084, p<.01). Both results were independent of the association between inattention and hyperactivity-impulsivity and control for the alternative etiological input and held across parent- and teacher-report of ADHD symptoms. In line with dual pathway models of ADHD, early prenatal risk for hyperactivity-impulsivity appears to operate through surgency, while polygenic genetic risk for inattention appears mediated by effortful control

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Res Child Adolesc Psychopathol. 2022 Aug;50:1011-25.

MEDIATING FACTORS IN WITHIN-PERSON DEVELOPMENTAL CASCADES OF EXTERNALISING, INTERNALISING AND ADHD SYMPTOMS IN CHILDHOOD.

Speyer LG, Obsuth I, Ribeaud D, et al.

Previous studies have offered evidence for peer problems and academic achievement as mediators in developmental cascades from externalising to internalising problems, and from ADHD symptoms to both internalising and externalising problems. However, these mediators have not been found to fully account for these cascades, indicating that there may be additional mediators involved. This study investigated the role of harsh parenting and parental involvement alongside academic achievement and peer problems in mediating within-person developmental cascades from externalising to internalising problems and from ADHD symptoms to internalising and externalising problems using autoregressive latent trajectory models with structured residuals. Models were fit for parent- and teacher-reports on children's psychosocial development as measured by the Social Behaviour Questionnaire (SBQ) collected over ages 7, 9, and 11 in an ethnically diverse Swiss longitudinal cohort study (z-proso; N=1387, 51% male). Results indicated that, when appropriately disentangling within- from between-person effects, none of the considered factors acted as significant mediators in longitudinal within-person relations between ADHD, internalising and externalising problems; hence, mediating mechanisms in developmental cascades remain to be identified

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Res Child Adolesc Psychopathol. 2022 Aug;50:1027-40.

THE IMPACT OF IRRITABILITY AND CALLOUS UNEMOTIONAL TRAITS ON REWARD POSITIVITY IN YOUTH WITH ADHD AND CONDUCT PROBLEMS.

Waxmonsky J, Fosco W, Waschbusch D, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) and conduct problems exhibit significant variability in functioning and treatment response that cannot be fully accounted for by differences in symptom severity. Reward responsivity (RR) is a potential transdiagnostic means to account for this variability. Irritability and callous-unemotional (CU) traits moderate associations between both ADHD and conduct problems with multiple realms of functioning. Both are theorized to be associated with RR, but associations in clinical samples are unknown. In 48 youth ages 5-12 with ADHD referred for treatment of conduct

problems, we examined RR using a guessing task where participants select a door icon to win and lose money. Analyses focused on the reward positivity (RewP) event-related potential in response to gain and loss feedback, which reliably peaks approximately 300 ms after feedback. Frequentist and Bayesian approaches assessed main effects of ADHD, Conduct Disorder (CD) and non-irritable Oppositional Defiant Disorder (ODD) symptoms with RR, plus interactions between symptoms and affective dimensions (irritability, CU). CD and ODD were hypothesized to be associated with altered RR, with irritability and CU moderating these associations. Across models, a reliable CD x irritability interaction emerged, indicating enhanced RewP when irritability was elevated and CD symptoms were low. CU did not moderate any associations with RR, and little support was found for associations between RR and other symptom domains. As neural response to reward varied with levels of irritability and CD symptoms, RR may hold potential as a clinically-relevant biomarker in youth with ADHD and conduct problems

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Res Dev Disabil. 2022 Sep;128:104286.

SLEEP DISTURBANCES AND BEHAVIOR IN SMITH-MAGENIS SYNDROME.

Garayzabal E, Hidalgo I, Miranda de Souza ALD, et al.

BACKGROUND: The Smith-Magenis syndrome (SMS) shows a collection of neurodevelopmental problems including mild to moderate intellectual disability, change-related anxiety, impulsivity, speech delay, Attention-Deficit/Hyperactivity Disorder (ADH) and sleep disturbances. Sleep disorders, when present, have been treated in several populations with consecutive improvements in cognitive and behavioral aspects. AIMS: To better understand the existing relationships between sleep disturbances and behavioral problems in SMS syndrome this study describes the sleep and behavior problems in the SMS and explores the possible relation between both.

METHODS AND PROCEDURES: 17 individuals with SMS (50% males; 11.2±4.9 years old) and 12 individuals with typical development (50% male; 11.1±4.4 years old) were investigated using the Sleep Disturbance Scale for Children and the Child Behavior Checklist.

RESULTS: A high percentage (60%) of individuals with SMS have an indication of sleep disorders, being the most frequent disorders the sleep-wake transition disorders, and disorders of initiating and maintaining sleep with sleep latency higher than acceptable and total sleep time below acceptable. More than 94% of the SMS group presented clinical or borderline scores on the total behavioral problems scale. The most common behavioral problems were Externalizing Problems, Thought and Attention, ADH and Aggressive problems. There was a positive correlation between disorders of initiating and maintaining sleep, sleep-wake transition disorders, disorders of arousal, disorders of excessive somnolence and behavioral problems.

CONCLUSIONS AND IMPLICATIONS: The worse the sleep disturbances investigated, the more severe the behavioral problems characteristics reinforcing the importance to address the sleep problems in the treatment of SMS individuals

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Res Dev Disabil. 2022;125.

THE FACTOR STRUCTURE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOLCHILDREN.

Arildskov TW, Virring A, Lambek R, et al.

Background: Most studies support a bifactor model of childhood ADHD with two specific factors. However, several studies have not compared this model with a bifactor model with three specific factors, few have tested the actual strength of the factors, and none have examined whether talks excessively should be treated as a hyperactivity versus impulsivity symptom in children with ADHD.

Aims: To examine the factor structure of ADHD symptoms and evaluate the relative strength of potential factors.

Methods: Parent-reports on the ADHD-Rating Scale (ADHD-RS-IV) were collected for 2044 schoolchildren from the general population and 147 children with ADHD from a clinical sample. Single-, two- and three -(correlated and bi) factor models were tested using confirmatory factor analysis.

Results: Most models had a satisfactory fit. However, a correlated three-factor model where talks excessively was included as an indicator of impulsivity, and especially a bifactor model with one strong, well-defined general and two/three (ICD-10 defined) weak specific factors fit the data slightly better than the remaining models.
Conclusions: The factor structure is best characterized by a bifactor model with a strong general factor and two/three weaker specific factors. Therefore, we suggest emphasizing the ADHD-RS-IV total score rather than the subscale scores in clinical practice

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Revista de Psicologia (Peru). 2022;40:1175-211.
GIFTEDNESS AND ADHD: A SYSTEMATIC LITERATURE REVIEW.
Coutinho-Souto WKS, de Souza Fleith D.
The purpose of this study was to examine the scientific production of empirical articles regarding twice exceptionality giftedness/ADHD ΓÇô through a systematic review. The search was carried out in the Portal de Periodicos Capes, SciELO, and PePSIC databases, considering the publications between 2011 and 2021. The terms giftedness, high abilities, ADHD, twice exceptionality, and their counterparts in Portuguese were used as descriptors. We selected 27 articles based on pre-established inclusion criteria. Six categories of studies were identified: socio-emotional factors, interpersonal relationships, identification, inattention and hyperactivity, intelligence quotient, and educational support practices. The conclusion was that by having their individual needs met and school community support, gifted students with ADHD can academically succeed, have a positive self-concept and good interpersonal relationships

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Sci Rep. 2022 Jul;12:12934.
TRAINING A MACHINE LEARNING CLASSIFIER TO IDENTIFY ADHD BASED ON REAL-WORLD CLINICAL DATA FROM MEDICAL RECORDS.
Mikolas P, Vahid A, Bernardoni F, et al.
The diagnostic process of attention deficit hyperactivity disorder (ADHD) is complex and relies on criteria sensitive to subjective biases. This may cause significant delays in appropriate treatment initiation. An automated analysis relying on subjective and objective measures might not only simplify the diagnostic process and reduce the time to diagnosis, but also improve reproducibility. While recent machine learning studies have succeeded at distinguishing ADHD from healthy controls, the clinical process requires differentiating among other or multiple psychiatric conditions. We trained a linear support vector machine (SVM) classifier to detect participants with ADHD in a population showing a broad spectrum of psychiatric conditions using anonymized data from clinical records (N=299 participants). We differentiated children and adolescents with ADHD from those not having the condition with an accuracy of 66.1%. SVM using single features showed slight differences between features and overlapping standard deviations of the achieved accuracies. An automated feature selection achieved the best performance using a combination 19 features. Real-world clinical data from medical records can be used to automatically identify individuals with ADHD among help-seeking individuals using machine learning. The relevant diagnostic information can be reduced using an automated feature selection without loss of performance. A broad combination of symptoms across different domains, rather than specific domains, seems to indicate an ADHD diagnosis

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Sci Rep. 2022 Aug;12:13930.
VISUO-SPATIAL ATTENTION DEFICIT IN CHILDREN WITH READING DIFFICULTIES.
Franceschini S, Bertoni S, Puccio G, et al.
Although developmental reading disorders (developmental dyslexia) have been mainly associated with auditory-phonological deficits, recent longitudinal and training studies have shown a possible causal role of visuo-attentional skills in reading acquisition. Indeed, visuo-attentional mechanisms could be involved in the

orthographic processing of the letter string and the graphemic parsing that precede the grapheme-to-phoneme mapping. Here, we used a simple paper-and-pencil task composed of three labyrinths to measure visuo-spatial attention in a large sample of primary school children (n=398). In comparison to visual search tasks requiring visual working memory, our labyrinth task mainly measures distributed and focused visuo-spatial attention, also controlling for sensorimotor learning. Compared to typical readers (n=340), children with reading difficulties (n=58) showed clear visuo-spatial attention impairments that appear not linked to motor coordination and procedural learning skills implicated in this paper and pencil task. Since visual attention is dysfunctional in about 40% of the children with reading difficulties, an efficient reading remediation program should integrate both auditory-phonological and visuo-attentional interventions

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Sci Rep. 2022 Aug;12:13974.

EYE-TRACKING TRAINING IMPROVES THE LEARNING AND MEMORY OF CHILDREN WITH LEARNING DIFFICULTY.

Chan AS, Lee TL, Sze SL, et al.

Children who experience difficulty in learning at mainstream schools usually are provided with remediation classes after school to facilitate their learning. The present study aims to evaluate an innovative eye-tracking training as possible alternative remediation. Our previous findings showed that children who received eye-tracking training demonstrated improved attention and inhibitory control, and the present randomized controlled study aims to evaluate if eye-tracking training can also enhance the learning and memory of children. Fifty-three primary school students with learning difficulty (including autism spectrum disorder, attention-deficit/hyperactivity disorder, specific learning disorder, specific language impairment and borderline intellectual functioning) were recruited and randomly assigned to either the Eye-tracking Training group or the after-school remediation class. They were assessed on their learning and memory using the Hong Kong List Learning Test before and after 8-month training. Twenty weekly parallel sessions of training, 50Â min per session, were provided to each group. Children who received the eye-tracking training, not those in the control group, showed a significant improvement in memory as measured by the delayed recall. In addition, the Eye-Tracking Training group showed significantly faster learning than the control group. Also, the two groups showed a significant improvement in their reading abilities. In sum, eye-tracking training may be effective training for enhancing the learning and memory of children with learning difficulties

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Top Spinal Cord Inj Rehabil. 2022;28:41-58.

CHILD, PARENT, AND FAMILY ADJUSTMENT FOR PATIENTS FOLLOWED IN A MULTIDISCIPLINARY SPINA BIFIDA CLINIC.

Simpson TS, Grande LA, Kenny JJ, et al.

OBJECTIVES: To characterize child, parent, and family adjustment for patients followed in a multidisciplinary spina bifida (SB) clinic.

METHODS: Participants were drawn from clinical cases seen through a multidisciplinary outpatient SB clinic at a children's hospital between 2017 and 2019. Participants included 209 youth under 19 years old who were diagnosed with SB and their parents. Self-reported internalizing symptoms were measured in youth in grade 3 through 12 using the 25-item Revised Children's Anxiety and Depression Scale-25 (RCADS-25). Self- and parent-reported quality of life and family functioning were obtained using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and Family Impact Modules.

RESULTS: A total of 45.7% of children and adolescents reported at-risk psychosocial functioning on the PedsQL. In contrast, only 5% of patients reported clinically elevated internalizing symptoms on the RCADS. Parents' quality of life and family functioning in the study were higher than in most studies of parents of children with other chronic health conditions, children with attention deficit-hyperactivity disorder, and healthy control samples.

CONCLUSION: Our findings indicate that children and adolescents with SB are at risk for poor health-related quality of life (HRQOL); however, poorer HRQOL may not necessarily be associated with more severe

psychiatric symptoms in this population. Examining resilience factors that may help to buffer against challenges to HRQOL will be important in informing future interventions

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Toxins. 2021;13.

ASSESSMENT OF EXPOSURE TO MYCOTOXINS IN SPANISH CHILDREN THROUGH THE ANALYSIS OF THEIR LEVELS IN PLASMA SAMPLES.

Arcelopez B, Lizarraga E, et al.

In this study, we present, for the first time in Spain, the levels of 19 mycotoxins in plasma samples from healthy and sick children (digestive, autism spectrum (ASD), and attention deficit hyperactivity (ADHD) disorders) (n = 79, aged 2-16). The samples were analyzed by liquid chromatography-mass spectrometry (triple quadrupole) (LC-MS/MS). To detect Phase II metabolites, the samples were reanalyzed after pre-treatment with +¦-glucuronidase/arylsulfatase. The most prevalent mycotoxin was ochratoxin A (OTA) in all groups of children, before and after enzyme treatment. In healthy children, the incidence of OTA was 92.5% in both cases and higher than in sick children before (36.7% in digestive disorders, 50% in ASD, and 14.3% in ADHD) and also after the enzymatic treatment (76.6 % in digestive disorders, 50% in ASD, and 85.7% in ADHD). OTA levels increased in over 40% of healthy children after enzymatic treatment, and this increase in incidence and levels was also observed in all sick children. This suggests the presence of OTA conjugates in plasma. In addition, differences in OTA metabolism may be assumed. OTA levels are higher in healthy children, even after enzymatic treatment (mean OTA value for healthy children 3.29 ng/mL, 1.90 ng/mL for digestive disorders, 1.90 ng/mL for ASD, and 0.82 ng/mL for ADHD). Ochratoxin B appears only in the samples of healthy children with a low incidence (11.4%), always co-occurring with OTA. Sterigmatocystin (STER) was detected after enzymatic hydrolysis with a high incidence in all groups, especially in sick children (98.7% in healthy children and 100% in patients). This supports glucuronidation as a pathway for STER metabolism in children. Although other mycotoxins were studied (aflatoxins B1, B2, G1, G2, and M1; T-2 and HT-2 toxins; deoxynivalenol, deepoxy-deoxynivalenol, 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol; zearalenone; nivalenol; fusarenon-X; neosolaniol; and diacetoxyscirpenol), they were not detected either before or after enzymatic treatment in any of the groups of children. In conclusion, OTA and STER should be highly considered in the risk assessment of mycotoxins. Studies concerning their sources of exposure, toxicokinetics, and the relationship between plasma levels and toxic effects are of utmost importance in children

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Transl Psychiatry. 2016;6.

EXOME CHIP ANALYSES IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zayats T, Jacobsen KK, Kleppe R, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable childhood-onset neuropsychiatric condition, often persisting into adulthood. The genetic architecture of ADHD, particularly in adults, is largely unknown. We performed an exome-wide scan of adult ADHD using the Illumina Human Exome Bead Chip, which interrogates over 250 000 common and rare variants. Participants were recruited by the International Multicenter persistent ADHD CollaboraTion (IMpACT). Statistical analyses were divided into 3 steps: (1) gene-level analysis of rare variants (minor allele frequency (MAF)o1%); (2) single marker association tests of common variants (MAF 1%), with replication of the top signals; and (3) pathway analyses. In total, 9365 individuals (1846 cases and 7519 controls) were examined. Replication of the most associated common variants was attempted in 9847 individuals (2077 cases and 7770 controls) using fixed-effects inverse variance meta-analysis. With a Bonferroni-corrected significance level of 1.82E Γêǽ 06, our analyses of rare coding variants revealed four study-wide significant loci: 6q22.1 locus (P = 4.46E 08), where NT5DC1 and COL10A1 reside; the SEC23IP locus (P = 6.47E 07); the PSD locus (P = 7.58E 08) and ZCCHC4 locus (P = 1.79E 06). No genome-wide significant association was observed among the common variants. The strongest signal was noted at rs9325032 in PPP2R2B (odds ratio = 0.81, P = 1.61E 05). Taken together, our data add to the growing evidence of general signal transduction molecules (NT5DC1, PSD, SEC23IP and

ZCCHC4) having an important role in the etiology of ADHD. Although the biological implications of these findings need to be further explored, they highlight the possible role of cellular communication as a potential core component in the development of both adult and childhood forms of ADHD

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Transl Psychiatry. 2016;6.

ALTERED GRAY MATTER ORGANIZATION IN CHILDREN AND ADOLESCENTS WITH ADHD: A STRUCTURAL COVARIANCE CONNECTOME STUDY.

Griffiths KR, Grieve SM, Kohn MR, et al.

Although multiple studies have reported structural deficits in multiple brain regions in attention-deficit hyperactivity disorder (ADHD), we do not yet know if these deficits reflect a more systematic disruption to the anatomical organization of large-scale brain networks. Here we used a graph theoretical approach to quantify anatomical organization in children and adolescents with ADHD. We generated anatomical networks based on covariance of gray matter volumes from 92 regions across the brain in children and adolescents with ADHD (n = 34) and age-and sex-matched healthy controls (n = 28). Using graph theory, we computed metrics that characterize both the global organization of anatomical networks (interconnectivity (clustering), integration (path length) and balance of global integration and localized segregation (small-worldness)) and their local nodal measures (participation (degree) and interaction (betweenness) within a network). Relative to Controls, ADHD participants exhibited altered global organization reflected in more clustering or network segregation. Locally, nodal degree and betweenness were increased in the subcortical amygdalae in ADHD, but reduced in cortical nodes in the anterior cingulate, posterior cingulate, mid temporal pole and rolandic operculum. In ADHD, anatomical networks were disrupted and reflected an emphasis on subcortical local connections centered around the amygdala, at the expense of cortical organization. Brains of children and adolescents with ADHD may be anatomically configured to respond impulsively to the automatic significance of stimulus input without having the neural organization to regulate and inhibit these responses. These findings provide a novel addition to our current understanding of the ADHD connectome

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Transl Psychiatry. 2017;7.

PROGRESS AND ROADBLOCKS IN THE SEARCH FOR BRAIN-BASED BIOMARKERS OF AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Uddin LQ, Dajani DR, Voorhies W, et al.

Children with neurodevelopmental disorders benefit most from early interventions and treatments. The development and validation of brain-based biomarkers to aid in objective diagnosis can facilitate this important clinical aim. The objective of this review is to provide an overview of current progress in the use of neuroimaging to identify brain-based biomarkers for autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), two prevalent neurodevelopmental disorders. We summarize empirical work that has laid the foundation for using neuroimaging to objectively quantify brain structure and function in ways that are beginning to be used in biomarker development, noting limitations of the data currently available. The most successful machine learning methods that have been developed and applied to date are discussed. Overall, there is increasing evidence that specific features (for example, functional connectivity, gray matter volume) of brain regions comprising the salience and default mode networks can be used to discriminate ASD from typical development. Brain regions contributing to successful discrimination of ADHD from typical development appear to be more widespread, however there is initial evidence that features derived from frontal and cerebellar regions are most informative for classification. The identification of brain-based biomarkers for ASD and ADHD could potentially assist in objective diagnosis, monitoring of treatment response and prediction of outcomes for children with these neurodevelopmental disorders. At present, however, the field has yet to identify reliable and reproducible biomarkers for these disorders, and must

address issues related to clinical heterogeneity, methodological standardization and cross-site validation before further progress can be achieved

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World Journal of Clinical Cases. 2022;10:7749-59.

SERUM FERRITIN LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND TIC DISORDER.

Tang CY, Wen F.

BACKGROUND Iron plays an important role in neurodevelopmental functions in the brain. Serum ferritin levels are different in children with attention deficit hyperactivity disorder and tic disorder than in healthy children.

AIM To explore the current status of iron deficiency in children with neurodevelopmental disorders and its sex and age effects.

METHODS A total of 1565 children with attention deficit hyperactivity disorder (ADHD), 1694 children with tic disorder (TD), 93 children with ASD and 1997 healthy control children were included between January 1, 2020, and December 31, 2021 at Beijing Children's Hospital. We describe the differences in age levels and ferritin levels between different disease groups and their sex differences. The differences between the sexes in each disease were analyzed using the t test. The incidence rate of low serum ferritin was used to describe the differences between different diseases and different age groups. A chi-square test was used to analyze the difference in the incidence of low serum ferritin between the disease group and the control group. Analysis of variance was used for comparisons between subgroups, and regression analysis was used for confounding factor control.

RESULTS A total of 1565 ADHD patients aged 5-12 years were included in this study, and the average serum ferritin levels of male and female children were 36.82 -¦ 20.64 ++g/L and 35.64 -¦ 18.56 ++g/L, respectively. A total of 1694 TD patients aged 5-12 years were included in this study, and the average serum ferritin levels of male and female children were 35.72 -¦ 20.15 ++g/L and 34.54 -¦ 22.12 ++g/L, respectively. As age increased, the incidence of low serum ferritin in ADHD and TD first decreased and then increased, and 10 years old was the turning point of rising levels. The incidence of ADHD with low serum ferritin was 8.37%, the incidence of TD with low serum ferritin was 11.04%, and the incidence of the healthy control group with low serum ferritin was 8.61%, among which male children with TD accounted for 9.25% and female children with TD accounted for 11.62%. There was a significant difference among the three groups ($P < 0.05$). In addition, there were 93 children with ASD with an average serum ferritin level of 30.99 -¦ 18.11 ++g/L and a serum ferritin incidence of 15.05%.

CONCLUSION In conclusion, low serum ferritin is not a risk factor for ADHD or TD. The incidence of low serum ferritin levels in children with ADHD and TD between 5 and 12 years old decreases first and then increases with age

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Zhongguo Dang Dai Er Ke Za Zhi. 2022 Aug;24:869-73.

ASSOCIATION BETWEEN OPPOSITIONAL DEFIANT DISORDER AND PARENTING STYLE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kou C, Wu ZM, Liu J, et al.

OBJECTIVES: To study the association between oppositional defiant disorder (ODD) and parenting style in children with attention deficit hyperactivity disorder (ADHD).

METHODS: A case-control study was performed on 482 children with ADHD, among whom 322 did not have ODD (simple ADHD group) and 160 had ODD (ADHD+ODD group). General demographic data and the Parenting Style Scale assessment scores were collected from the two groups. A multivariate logistic regression analysis was used to identify the association between parenting style and ODD in children with ADHD.

RESULTS: There was no significant difference in parenting style scores (including rejection factor, emotional warmth factor, overprotection factor, and preference factor) and general demographic data between the simple ADHD and ADHD+ODD groups ($P>0.05$). Among the children with the predominantly inattentive type

of ADHD, the older the child or the lower the father's educational level, the higher the risk of ODD ($P<0.05$), while there was no significant association between parenting style and the development of ODD ($P>0.05$).
CONCLUSIONS: Parenting style is not significantly associated with the development of ODD in children with ADHD. In clinical practice, it is necessary to eliminate the stereotype that the parents of children with ADHD and comorbid ODD have a poor parenting style and look for the causes of development of ODD from multiple perspectives, so as to provide reasonable intervention recommendations

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Neuropsychological heterogeneity in ADHD pupils: further evidence from incidental memory testing

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ABSTRACT

This paper reports on a study where the incidental memory of 18 children with ADHD and 18 typically developing (TD) peers was assessed by means of a conventional two-phase recognition memory test. In the study phase participants were required to categorize as a living or non-living a set of 64 stimuli from 8 semantic categories. In the test phase, they were required to recognize "target" (i.e., stimuli from the first set) from "non-target" stimuli. Children with ADHD were overall less accurate and much slower than TD controls in identifying both living and non-living items. Moreover, while most of TD participants made very few, if any, errors, only 7 out of 18 participants with ADHD scored near ceiling, and 2 of them scored below chance level. Following the Signal Detection Theory approach, the participants' performance on the test phase was scored in terms of d prime (d') values. Children with ADHD had lower d' indexes compared to controls both for living and non-living stimuli, although this difference did not reach statistical significance. More interestingly, the variability of the d' values was higher in the ADHD compared to Controls at least for non-living items. Taken together, findings from this study indicate that at least some of the children with ADHD have a genuine impairment in processing visual stimuli. More generally, these results provide further support to the idea that ADHD represents a neuropsychological heterogeneous condition that still requires a deeper characterization to be considered a stable nosographic entity.

Key words

ADHD • Incidental Memory • d prime • Cognitive functioning • Intragroup variability

Introduction

With a prevalence among school-aged children estimated at 7.2% (Thomas et al., 2015) also tending to increase (Rowland et al., 2015), Attention-deficit / hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood. Considering that signs of ADHD often persist into adolescence and adulthood (e.g., Okie, 2006), it can be estimated that ADHD affects approximately 6%-16% of the world population (Barbaresi et al., 2004).

Being characterized by inattention, hyperactivity, and impulsivity – all of which can lead to impairments in school performance, family functioning and peer relationships – ADHD represents a complex challenge for both researchers and clinicians.

However, despite the large corpus of literature on ADHD developed over the last decades, many issues remain to be settled (Furman, 2005; Singh et al., 2015).

Leaving aside any reference to the genetic markers and the neuroimaging patterns, for the purpose of this study it is relevant to note that there is no single cognitive deficit which is pathognomonic for ADHD and the diagnosis merely relies on behavioral descriptors that can be observed in a wide range of other psychopathologies (Roth & Saykin, 2004).

In view of the latter point, a large literature suggests that individuals with ADHD exhibit relatively poor performance on a broad variety of neuropsychological tests of attention, alertness, executive functions, working memory etc. In search for a test that could

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be, albeit not diagnostic, at least highly suggestive for the presence of ADHD, several samples of ADHD participants have been engaged in a series of tasks ranging from Stroop to priming and Go-noGo task (see Nigg, 2005, for a review). The results were far from straightforward: too many measures resulted to have good positive, but also poor negative, predictive power for ADHD (see Marshall et al., 2021 for a review). As a consequence, abnormal scores on several neuropsychological tests can be taken as predictive of the diagnosis; meanwhile, normal scores on the same test cannot rule ADHD out. Namely, not every person with ADHD is impaired on every test while many individuals with ADHD exhibit a normal-range performance on all the cognitive tests usually used to assess ADHD (Doyle, 2006).

In this complex scenario, however, a dysfunction of working memory has been proved that can play a critical role in the occurrence of ADHD in both children and young adults (Alderson et al., 2013). In turn, an extensive meta-analysis (Willcutt et al., 2005) indicated that groups with ADHD exhibited significant impairment on several executive function tasks, especially those involving working memory, vigilance, response inhibition, and planning.

While a large corpus of studies investigated the performance of children and adolescents with ADHD in the Digit Span Backwards test (see Ramos et al., 2020 for a comprehensive meta-analysis on this topic), even when children with ADHD were presented with a comprehensive memory test battery (e.g., Oie, Sunde, & Rund, 1999; Rhodes, Park, Seth & Coghill, 2012), incidental memory (i.e., memories that are acquired without intention, see Baddeley, Eysenck & Anderson, 2009) was not investigated, despite its strict relation with several measures of attention and executive functions (Kontaxopoulou et al., 2017) making incidental memory test a valuable clinical and research tool for use with ADHD. Indeed, to the best of our knowledge, very few, very dated, studies challenged individuals with ADHD with a test of incidental memory. Douglas and Peters (1979) found that children with ADHD were more distracted by irrelevant stimuli than TD children. In the study by Copeland and Wisniewski (1981), children with and without learning disabilities were administered tests of central and incidental learning and selective attention. In the frame of a deterioration of performance on generalized cognitive measures, children with hyperactivity performed more poorly than TD peers on attention and memory tasks. Ceci and Tishman (1984) presented children with ADHD and their typically developing (TD) peers with an experimental paradigm involving a central and a peripheral task and found that while TD children outperformed children with ADHD in the central task, the opposite was true in the peripheral task where children with ADHD were more accurate than TD peers in the recall of extrinsic, irrelevant stimuli. This result was taken as evidence of a more diffuse (i.e., less selective) attention in children with ADHD than TD peers. However, it is worthy to note that children with ADHD showed a superior incidental learning only when the task was easy. As the task demand increased and became more challenging, the performance of children with ADHD declined below that of their TD peers.

Hereafter, we aimed to re-assess the issue of the incidental memory of children with ADHD and TD peers by means of a conventional two-phase recognition memory test.

The experimental paradigm allowed us to explore: a) whether children with ADHD differ from their TD peers in accuracy and/or speed in processing the stimuli presented during the study phase; b) whether the two groups of participants show any difference in the recognition task; c) whether – compared with the group of TD peers – the group of children with ADHD exhibit a heterogeneous rather than a homogeneous pattern of performance.

Methods

Participants

Eighteen (15 males and 3 females) children with ADHD, ranging in age between 8 and 11 years, and 18 chronological age – and gender – matched, TD children participated in the study. All participants had normal or corrected-to-normal visual acuity and were naïve as to the purpose of the study.

The participants with ADHD were referred by the local Neuropsychiatric Unit of the National Health Service. According to the evaluations made by an expert, multidisciplinary team of professionals (i.e., psychologists, child neuropsychiatrists, speech therapists), all of them met DSM-5 diagnosis

for ADHD, and satisfied the following inclusion criteria: IQs in the range of 90-110; no pervasive developmental disorders; no uncorrected sensory or motor deficits; no stimulant medication.

The TD children were recruited from a local school, selected randomly from a pool of those whose parents consented to their participation in the study and teachers did not report any behavioral or learning problems.

The study was approved by the departmental ethics committee and carried out according to Declaration of Helsinki guidelines. Pupils participated with parental consent. However, they were informed that participation was not mandatory and that they had the right to decline at any time. None of them, however, refused to take part in the study, nor dropped out of it.

Stimuli

The experimental stimuli consisted of two sets of 64 colored pictures of living and non-living items in the same proportion. In turn, both living and non-living items could belong to one of four semantic categories so that – in each set of stimuli – there were 8 animals, 8 flowers, 8 fruits, and 8 vegetables (living items), and 8 musical instruments, 8 vehicles, 8 clothes, and 8 manipulable objects (non-living items). Items were paired together across sets with the caveat that the two members of a pair should be similar, but clearly recognizable from each other; so that – for example – there was a light green apple in the set A and a pale-reddish apple in the set B.

Apparatus and procedures

A commercial software program (E-Prime, Psychology Software Tools, Inc.), was used to implement the experimental paradigm. All the experimental sessions were conducted in a sound- and light-attenuated room using an IBM compatible notebook. Stimuli were displayed on the 15-inch notebook monitor while participants were seated in front of it at a distance of about 60 cm. A mouse connected to the notebook via USB port was used to record the participants' responses.

Each participant performed a study and a test session, separated by an interval lasting half an hour during which participants could stretch their legs and have a snack. In both sessions, instructions were given and a few practice trials were performed to ensure that the participant had understood the procedure.

In the study session participants were required to categorize as a living or non-living each of the 64 stimuli from set A or B (the choice of set was counterbalanced across participants). In the test session – for each of the 128 stimuli from both set A and B – participants must indicate whether it was a target (i.e., a stimulus from the first set) or a non-target (i.e., a stimulus not shown earlier).

Each trial began with an acoustic warning signal which prompted the participant to fixate on a cross displayed at the center of the screen. After an interval unpredictably ranging from 200 to 500 ms, the fixation point disappeared and a picture was shown until the participant responded (or until 4 s had elapsed) to the question displayed on the bottom area of the screen (Living / Non-Living? and Old / New? in the study and test phase, respectively) by pressing with the second finger of their preferred hand the mouse button corresponding to his/her choice (i.e., left button for "Living", right button for "Non-Living", in the study session; left button for "Old", right button for "New", in the test session). In each experimental session, each stimulus was presented once in the center of the screen according to a randomized order. Both speed of responding and accuracy were strongly encouraged. Latencies shorter than 300 ms or longer than 4 s were considered to be outliers and discarded.

Data Analysis

In the study (Encoding) phase, two dependent variables were considered: Accuracy and Speed of Response. The number of correct responses was taken as a measure of Accuracy while the median reaction time (RT) of correct responses provided the measure of Speed of Response to the different types of stimuli. Accuracy and RT data were entered in two separate repeated measures ANOVA with Group (ADHD vs. TD) as the between-subjects factor and Semantic Category (living vs. non-living) as the within-subjects factor. In all the analyses, Bonferroni correction for multiple comparisons was applied, and a p-value of $<.05$ was considered to indicate statistical significance.

With regard of the Test phase, on each trial, participants were requested to judge whether a stimulus was a target (i.e., from the first set) or a

non-target. It follows that, qualitatively speaking, participants' responses could belong to any one of these four categories: Hits, Misses, Correct Rejections and False Alarms. Hits occurred when participants recognized a target, while Misses occurred when participants missed it. In turn, Correct Rejections occurred when participants avoided to report as a target an item previously absent (i.e., they responded "New" to an item not shown in the first set), while False Alarms occurred when participants identified as a target an item previously absent (i.e., they responded "Old" to an item not shown in the first set). Following the Signal Detection Theory approach (Banks, 1960; Righi et al., 2015), we estimated the sensitivity index d' (d prime) according to the formula:

$$d' \text{ (d prime)} = (z_{\text{hits}} - z_{\text{false alarms}}).$$

The d' values were entered in a repeated measures ANOVA with Group (ADHD vs. TD) as the between-subjects factor and Semantic Category (living vs. non-living) and Type (Target vs. Non-Target) as the within-subjects factors. Bonferroni correction for multiple comparisons was applied, and a p-value of <.05 was considered to indicate statistical significance.

Results

Study (Encoding) phase

Accuracy and mean values of Speed of Responses across groups and items are reported in Table 1.

Accuracy – Children with ADHD were overall less accurate than TD controls in identifying both living and non-living (see Table 1) items, so that the between-subjects factor Group was significant [$F(1,34) = 7.60$, $p = .009$)], while the within-subjects factor Semantic Category ($F(1,34) = 0.97$, $p = .331$) and its interaction with Group ($F(1,34) = 0.01$, $p = .922$) were not statistically significant. It is worth noting that while most of TD participants made very few, if any, errors with 16 out of 18 scoring >95%, only 7 out of 18 participants with ADHD scored near ceiling, and 2 of them scored below chance level.

Speed of Response – Children with ADHD were overall much slower than TD controls in categorizing both living and non-living items (see Table 1), so that – also in this case – the between-subjects factor Group was significant [$F(1,34) = 11.10$, $p = .002$)], while the within-subjects factor Semantic Category ($F(1,34) = 1.94$, $p = .173$) and its interaction with Group ($F(1,34) = 4.20$, $p = .50$) were not significant.

Test phase

Descriptive statistics about d' values are summarized in Table 2.

Children with ADHD had lower d' values compared to controls both for living and non-living stimuli. However, these differences were not statistically significant ($F(1,34) = 2.46$, $p = .126$). Likewise, d' values associated to non-living stimuli were higher than d' values associated to living stimuli (in both groups) albeit the within-subjects factor Semantic Category was not significant ($F(1,34) = 3.68$, $p = .063$). The minimum and maximum d' values in the ADHD group were min = -1.21, max = 1.38 (4 out of 18 negative values) for living category and min = -0.75, max = 1.73 (4 out of 18 negative values) for non-living category. In turn, the minimum and maximum d' values in the control group were min = -0.34, max = 1.94 (1 out of 18 negative values) for living category and min = 0.00, max = 1.45. Negative values were taken as evidence of the fact that these participants misunderstood the task. Thus, their data were excluded from the analyses.

With regard to the variability of the two groups (Figure 1 and Figure 2), the TD children showed interquartile range values equal to .74 and .55 for living and non-living category respectively.

In reverse, the interquartile range values of d' of children with ADHD was much greater with non-

Tab. 1 - Study phase. Accuracy and Speed of Response across Groups and Items (18 participants for each group).

	ADHD				TD			
	Accuracy (%)		RT (msec)		Accuracy (%)		RT (msec)	
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Living	84.6	16.7	1199	614	96.4	5.9	637	140
Non-living	86.1	21.8	1055	621	98.3	2.2	665	122

Tab. 2 - Test phase. Descriptive statistics about d' across Groups and Items (18 participants for each group).

	ADHD		TD	
	Mean	sd	Mean	sd
Living	0.29	0.63	0.57	0.58
Non-living	0.46	0.71	0.74	0.39

living (.94) than living category of items (.73). Comparing the variances values across groups and category, it was observed that the variability of the d' values was higher in the ADHD with respect to Controls for the non-living items ($F(17,17) = 3.31$, $p = .018$) but not for the living ones.

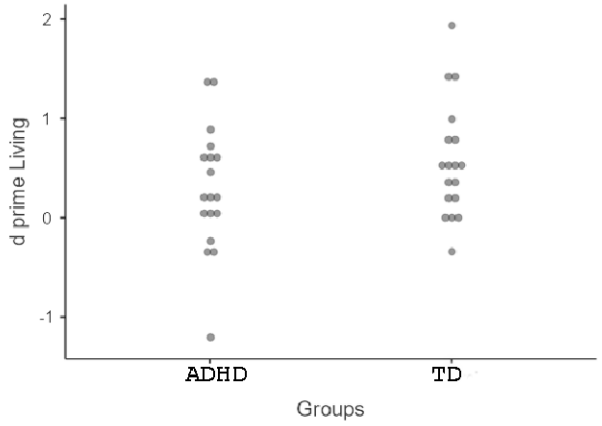

Fig. 1 - Distribution of d' values across Groups for the living category.

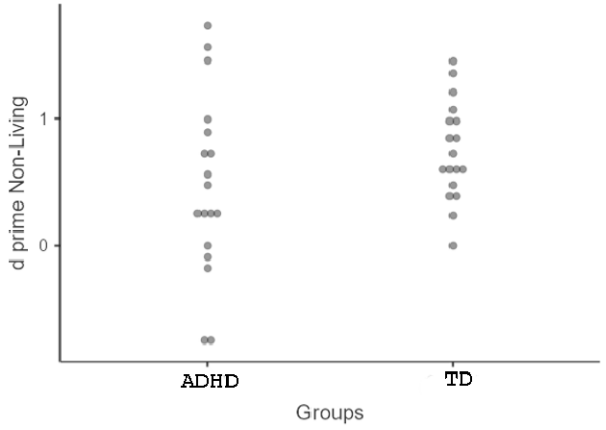

Fig. 2 - Distribution of d' values across Groups for the non-living category.

Discussion

Since the first descriptions (Aman, 1984), decades of research on ADHD have failed to identify a clear and stable pattern of cognitive impairment associated with the syndrome so that a remarkable neuropsychological heterogeneity is perhaps the most distinguished feature of ADHD (Singh et al., 2015) and there is also someone who questions whether the ADHD should be considered as a disease (Furham, 2005).

In particular, there is a lack of consensus on the exact nature of the attention problems typical for ADHD (Johnson et al., 2008) and which other constructs related to attention problems are most affected, although reliable evidence suggests that symptoms of ADHD may arise from a primary deficit of working memory (Ramos et al 2020) and/or executive functions (Willcutt et al., 2005).

In this study we focused on the construct of incidental, non-intentional memory; that is a memory that is acquired without conscious effort or intention to remember. Incidental memory is based on the assumption that any information that was processed meaningfully is remembered, despite the lack of prior effort made to memorize it. In this vein, the typical experimental paradigms used to study incidental memory consist of two phases: the study phase in which participants process stimuli that are not asked to remember, and the test phase in which participants are asked to recall (or recognize) those stimuli. It follows that individual performances on these tests are affected by a series of cognitive abilities such as the ability to focus and sustain attention and the ability to inhibit responses to irrelevant stimuli.

To the best of our knowledge, very few studies addressed the issue of incidental memory in individuals with ADHD. Even more interestingly, the available evidence is far from conclusive. Douglas and Peters (1979) found that children with ADHD are more susceptible than their TD peers to distraction,

not attributable to a deficit of selective attention. Conversely, Copeland and Wisniewski (1981) along with a poorer performance on generalized cognitive measures, found an impairment of selective attention which affected the performance of children with ADHD on incidental memory tasks. Among the others, one paper deserves attention. Ceci and Tishman (1984) investigated the incidental memory of children with ADHD and, quite surprisingly, found that – at least when the encoding demand was very easy – children with ADHD outperformed their TD peers on incidental recognition.

In the present study, we re-addressed this topic by means of a properly devised experimental paradigm. To this purpose, 18 children with ADHD, and 18 chronological age – and gender – matched, TD children were examined with a conventional two-phase recognition memory test. In the study phase participants were required to categorize as a living or non-living a set of 64 stimuli from 8 semantic categories. In the test phase, they were required to recognize "old" (i.e., stimuli from the first set) from "new" (i.e., stimuli not shown earlier) stimuli.

As to the categorization task, the main result was that TD participants were significantly more accurate and faster than participants with ADHD. Actually, while most of TD participants scored at ceiling, children with ADHD were overall less accurate with only 7 of them having a comparable performance to TD peers and 2 of them scoring below chance level. The simplest interpretation would be that the worst performance of children with ADHD depended on their haste and lack of concentration (Rapport, 2009). Such an interpretation, however, is contradicted by the fact that children with ADHD took much more time than TD controls to accomplish this task. Namely, notwithstanding that they spent more time, they made more errors, thus suggesting that at least some of them had a genuine impairment in processing visual stimuli (Kibby, Vadnais & Jagger-Rickels, 2019).

However, the most interesting findings came from the test phase. First, it is worth noting that not all the participants understood correctly the task: four children with ADHD and one TD control recognized as target new rather than old stimuli, as demonstrated by their d' negative values. Thus, their data were excluded from the analysis. That further reduced the relatively small sample of participants and may have contributed to making the differences not statistically significant.

Strictly speaking, the fact that, despite the significant differences in the study phase with reduced accuracy and speed exhibited by ADHD children, no significant differences emerged in the test phase for neither condition, could be interpreted as a proof against the hypothesis of a deficit in incidental memory in children with ADHD in line with Ceci and Tishman (1984).

However, caution should be used before taking this lack of statistical evidence as conclusive proof that no such difference exists. As clearly shown in Table 2, it is evident – from a descriptive point of view – that children with ADHD had lower discriminability capacity between old (i.e., target) and new (i.e., non-target) stimuli compared to controls for both living and non-living stimuli. Furthermore, it is also evident (see Figure 1 and 2) that – consistently with findings from adults (Klein et al., 2006) – interindividual variability was much larger among participants with ADHD than their TD peers, at least for non-living items. There is not a straightforward explanation for this difference: it could be imputable to the lack of statistical power or it may reflect a more meaningful distinction in the processing between different types of items. This issue remains open for future research.

We are aware of some intrinsic limitations of the study, including the relatively small sample size and the absence of definition of the ADHD subtypes, their distribution in the sample and the lack of certainty about the possible presence of psychiatric comorbidities. Notwithstanding that, our findings cast doubt on the notion that ADHD represents a stable nosographic entity (Bayon & Zurita, 2018). Conversely, they further support the idea that ADHD may be best conceptualized as a neuropsychological heterogeneous condition such that neuropsychological testing may only be supportive of the ADHD diagnosis, but it cannot be used in isolation to diagnose ADHD (Nass, 2006).

To sum up, more work is needed to better understand the heterogeneity of ADHD and its clinical and pathophysiologic implications (Doyle, 2006). Meanwhile, ADHD seems to be a syndrome in search of an underlying mechanism and, perhaps, a better name.

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REVIEW

Children with neurodevelopmental disorders: how do they sleep?

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Purpose of review
In this review we summarized the available evidence on sleep disorders in children with neurodevelopmental disorders (NDDs) in particular: intellectual disability (including some genetic conditions such as Prader–Willi Syndrome, Smith-Magenis Syndrome), Autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), Developmental Coordination Disorder, language disorders, and specific learning disorders.

Recent findings
Children with NDDs frequently suffer from sleep disturbances, with a higher prevalence than that of the general pediatric population.

Summary
These problems tend to be chronic and may cause additional cognitive and behavioral difficulties, often affecting the whole family's well-being. Sleep behaviors are also related to other important developmental skills, such as attention and listening. Investigating sleep disorders in children with NDDs is therefore crucial in clinical practice. For a systematic approach in clinical practice, we propose the use of a short and easy to remember sleep screening tool.

Keywords
attention-deficit/hyperactivity disorder, autism, intellectual disability, neurodevelopmental disorders, sleep disorders

INTRODUCTION

Neurodevelopmental disorders (NDDs) include a wide range of neuro-psychiatric conditions presented during infancy or childhood. According to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), they include intellectual disability (ID), autism spectrum disorders (ASD), communication disorders, attention-deficit/hyperactivity disorder (ADHD), learning disorders, and motor disorders [1].

Children with NDDs frequently suffer from sleep disturbances, with a higher prevalence than the general population [2], representing at least 35% of children that refer to a neuropsychiatric unit for sleep troubles [3]; for this reason during the last years sleep disorders in NDDs have become a field of greater interest and understanding distinctive features of sleep patterns is crucial to set up target treatments [4].

Sleep disturbances in NDDs children are determined by multifactorial etiology, also considering several neurologic, medical, and psychiatric comorbidities. Moreover, their sleep problems tend to be chronic and affect the whole family's well-being, often exacerbating learning and behavior difficulties [2].

Pathophysiology of sleep disorders may depend on the dynamic interaction of biological (e.g. hormone or neurotransmitter release alterations), psychological and/or social factors (e.g. dysfunctional perception of the Zeitgebers such as light-dark cycle or food schedule) [2,5]. Furthermore, problematic sleep may represent a phenotypic characteristic of specific neuropsychiatric disorders or genetic syndromes, suggesting a relationship between altered

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KEY POINTS

- The prevalence of sleep disturbances in children with NDDs is higher than in the general pediatric population.
- Sleep problems in children with NDDs can be of clinical relevance, with significant impact on daily life activities, learning processes and the patient's family well-being.
- Investigating sleep disorders in children with NDDs is crucial in clinical practice, and the use of sleep screening tools should be encouraged.
- Several neurodevelopmental problems can cause, coexist with, or proceed from poor sleep.
- Characterization of sleep disturbances in children with NDDs might be helpful in guiding therapeutic management.

brain networks and neurodevelopmental phenotypes [6].

Children with NDDs might exhibit mainly difficulties in falling asleep or awakenings during the night but also daytime sleepiness, irregular sleep schedule, circadian rhythm disorders, parasomnias, and respiratory difficulties (e.g. sleep apnea) [2,7].

AUTISM SPECTRUM DISORDER

In children with autism spectrum disorder sleep problems represent a common comorbidity and seem to have a higher prevalence (64–93%) and greater severity than in typically developing children (3.7%) or in children with other NDDs [8]. In some genetic syndromes associated with or predisposing to ASD - such as Rett syndrome, Fragile X syndrome, and Prader-Willi Syndrome (PWS) -impaired sleep pattern is a frequent symptom or a supportive criterion for diagnosis [9]. The most reported sleep problem and a frequent reason for medical consultation in ASD children are insomnia, presenting as delayed sleep-onset, high bedtime resistance, frequent and prolonged nocturnal awakenings, early morning waking, and/or reduced sleep duration [8,10,11]. Other sleep problems frequently observed in ASD children are sleep anxiety, sleep-disordered breathing, parasomnias, and excessive daytime sleepiness [8,10,12,13]. Poor sleep tends to persist also in adults with ASD [14].

Previous publications have suggested how these disorders may not only worsen daytime behaviors and core symptoms of ASD as self-injury, anxiety, hyperactivity, stereotypes, repetitive behaviors, and impairment in social reciprocity [4,9,15▪▪,16,17], but also contribute to parental stress levels, affecting daily routines and parent's own sleep [18,19].

Hypothesis on neurobiological abnormalities causing sleep disturbance in ASD comprehend alterations in genes controlling the circadian rhythm and in genes involved in the melatonin synthesis pathway [20,21]. Nocturnal melatonin secretion is diminished or delayed in ASD and levels of melatonin and/ or its urinary metabolic derivatives inversely correlate with sleep problems and autistic behaviors [22].

Several neurobehavioral deficits of children with ASD may contribute to the increased difficulty in initiating and maintaining sleep: the limited ability in emotional regulation and self-soothing, the difficulty in switching from daytime activities to sleep, the anxiety about falling asleep, the hyper-arousal to sensory stimuli, and the inability to understand social cues related to sleep [3,4]. In addition to these, sleep in ASD children can be disturbed by drugs (e.g., selective serotonin reuptake inhibitors) and common medical comorbidities, such as gastrointestinal problems and neurologic problems (e.g., epilepsy) [23]. Finally, changes in daily routine can exacerbate sleep problems in ASD children [24▪,25].

Given the high prevalence in ASD children and the significant impact on the quality of life of patients and their families, screening for sleep problems should be performed in all patients with a diagnosis of ASD and treating these conditions should be a primary therapeutic goal. Due to the above-mentioned neurobiological abnormalities, treatment with melatonin in ASD children often proves effective and, recently, several studies have reported the efficacy and safety of prolonged-release melatonin [26▪].

INTELLECTUAL DISABILITY

Sleep disturbances appear to be prominent in children with ID, with prevalence rates ranging from 25.5% to 36.2% [27]. Moreover, sleep disturbances in children with ID are more prevalent and severe and, if untreated, more persistent than in typically developing children [28]. Sleep problems may share common pathophysiological mechanisms with ID or be its consequence: alterations of the brain systems involved in the control of sleep and wakefulness are indeed likely to be associated with ID [29], and an intellectually disabled child may struggle to learn good sleep habits, not registering or understanding the environmental cues about when it is time to sleep.

Overall, the more frequent sleep disorders in children with ID are insomnia, obstructive sleep apnea syndrome, and periodic limb movement disorder [2]. However, it should be noticed that some syndromes in which ID is a prominent feature are frequently associated with specific sleep disturbances

or peculiar sleep patterns. As for alterations of circadian sleep-wake rhythm, it has been found that peak melatonin level occurs later in boys with X-Fragile Syndrome (FXS) compared to controls, suggesting a possible delay of melatonin secretion [30]. Sleep problems in Smith-Magenis Syndrome (SMS) are thought to be caused by an inverted melatonin rhythm, related to genetic variations in melatonin regulation [31]. Children with William Syndrome (WS) show a longer sleep latency, more time awake at night and an increased sleep fragmentation probably due to the lack of a normal melatonin increase during the day before going to sleep [32].

Insomnia is also a common complaint in a variety of genetic syndromes with ID. Children with Angelman syndrome often have difficulties both in initiating and maintaining sleep [33]. Fragmented and shortened sleep cycles with frequent nighttime awakenings are a common complaint in children with Rett Syndrome (RTT) [34] and SMS [35] as well. Also, children with FXS and Down Syndrome (DS) are frequently reported to have insomnia, with sleep onset delay, daytime sleepiness, and problems maintaining sleep [36]. Children with WS have been found to have later bedtimes, more night awakening and longer nighttime wakefulness and a shorter nighttime sleep duration compared to neurotypical children [37].

Sleep-disordered breathing has a prevalence of 89% in children with PWS [38] and of 80–94% of individuals with RTT [34,39]. In PWS syndrome-specific sleep abnormalities have been identified in the form of reduced arousal responses and central apneas. Sleep-disordered breathing and/or sleep apnea is indeed one of the minor diagnostic criteria for PWS [40]. In children with DS, the estimated prevalence of OSAS ranges from 50 to 80% [41]. Individuals with SMS have more sleep-disordered breathing than typically developing children, as well, probably due to their facial anatomy or to obesity-related ventilatory problems [42].

Limb movement disorder has been found to be common in patients with RTT [43] and WS [44]. Adolescents with WS have a higher percentage of non-rapid eye movement sleep, increased slow-wave sleep, a lower percentage of rapid eye movement sleep and an increased number of leg movements and irregular sleep cycles [45].

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD is one of the most diagnosed disorders of childhood, affecting approximately3–5% of children and often enduring throughout adolescence and adulthood [46]. In clinical practice, sleep disturbances are very common in children with ADHD (around 25–75% of individuals) [47–49], so in the past classification of sleep disorders (DSM-III-R) sleep problems were considered part of the diagnostic criteria of ADHD [50]. It has been shown that ADHD and sleep problems are probably in a reciprocal relationship, in which children with more severe ADHD have more severe sleep disorders as a consequence of ADHD, whereas inadequate sleep may worsen the ADHD symptoms [51–53]. In fact, some of the symptoms of insomnia (including difficulties with executive functions and emotional regulation) are closely related to symptoms of ADHD [54]. Several studies have also pointed out common etiological pathways between ADHD and specific sleep problems [53,55]. For instance, it has been shown that certain regions of the thalamus (responsible for sleep spindles and synchronization) have a smaller volume the higher the scores of inattention were in ADHD patients [56]. Furthermore, there are also shared neurotransmitters pathways between ADHD and sleep: dopamine and serotonin are both factors in waking, whereas also being respectively implicated in reward seeking and exploration of the environment; similarly, gamma-aminobutyric acid is responsible for arousal reduction and emotional regulation, having therefore a role both in sleep and ADHD [55,57,58]. With regard to specific sleep disorders, studies have shown that insomnia in particular is more common in children with ADHD than in typically developing ones [47,59]. ADHD patients, indeed, tend to suffer from lower sleep efficiency, prolonged sleep-onset latency, more nighttime awakenings, and daytime sleepiness [60,61]. Moreover, these sleep difficulties are often exacerbated by comorbid psychiatric disorders, such as anxiety (very common in association with ADHD), medical conditions (i.e. asthma), medications, and poor sleep practices [53,62,63]. Children with ADHD are also more likely to have restless legs syndrome (RLS) [64,65], which consists of an urge to move their legs when they are at rest in order to counter unpleasant sensations, often resulting in difficulty initiating and maintaining sleep. Despite the prevalence of RLS in typically developing children being around 2%, some studies have shown that almost half of children with ADHD have at least some symptoms of RLS [66,67▪▪]. This common comorbidity might be explained by several factors, such as shared neurobiological anomalies (e.g. dopaminergic dysfunction in the midbrain, frontal, and prefrontal areas) and genetic factors between ADHD and RLS [66,67▪▪, 68,69]; it has also been proposed that lower serum ferritin levels (frequently reported in ADHD children) may be associated with comorbid RLS (probably due to the role of iron as an essential cofactor for dopamine synthesis) [64,70▪]. Obstructive sleep apneas

and delayed sleep phase syndrome are also frequently reported among children with ADHD [71–73]. Finally, another aspect that should be carefully considered is the concomitant use of stimulant medications, often prescribed for ADHD symptoms. It is indeed well-documented that children on stimulants have more sleep problems and are more likely to be taking sleep medications [74–77]. Despite that, some studies show opposite results, underlining that change in sleep during treatment with stimulants may be either positive or negative [78,79], and therefore must be carefully monitored, balancing the daytime benefits with the possible sleep difficulties.

OTHER NEURODEVELOPMENTAL DISORDERS

Although sleep is sometimes neglected in the management of minor NDDs, sleep troubles can be of clinical relevance, having a significant impact on daily life activities and learning processes at all ages of life [80,81].

Children with communication disorders have poorer sleep than controls, with difficulties falling asleep and early morning awakenings. The severity of sleep problems is directly related to language skills. Moreover, sleep behaviors may predict difficulties in expressive, receptive language, and social communication [82].

The relationship between developmental dyslexia (DD) and sleep disorders is scarcely investigated, but sleep disturbances are more common in children with DD than in typically developing ones, especially considering difficulties in initiating and maintaining sleep, sleep breathing disorders and disorders of arousal [83].

Considering the role of non rapid eye movement (NREM) sleep in neurocognitive processes, an altered sleep spindles activity or sigma power may influence declarative memory consolidation, language learning, and dyslexic impairment severity [81,84].

Sleep disturbances in children with Developmental Coordination Disorder (DCD) are considered a relevant comorbidity. DCD school-children, with respect to controls, have indeed a higher prevalence of bedtime resistance, parasomnias, and sleepiness during the day [85], but also presleep arousal and daytime fatigue [86]. At a neurophysiological level, the reported REM percentage reduction in DCD children may be considered a sign of altered cortico-cerebellar network activity [87] and NREM sleep instability organization may be linked to motor coordination disorders, suggesting a significant role of Cyclic Alternating Pattern phases (subtypes A2 and A3) on motor coordination development [88].

Sleep disorders are described in up to 64% of patients with tics and Tourette syndrome (TS) [89]. During all stages of sleep both motor and vocal tics can be present [90] and, moreover, sleep troubles can exacerbate daily tic symptoms [91]. In detail, TS patients have an increased risk of difficulties in initiation and maintenance of sleep, parasomnias, excessive arousals, and daytime sleepiness [92], that is even higher when comorbidity with ADHD or Obsessive Compulsive Disorder co-occurs [91]. Treating sleep problems in TS patients may be helpful in improving sleep disorders themselves, but also in reducing the severity of tics [93].

ASSESSMENT AND PRINCIPLES OF TREATMENT

Due to the heavy impact of sleep problems in children with NDDs on affected individuals and their caregivers [23,94], it is essential that clinicians screen such children for sleep problems at regular intervals and with a systematic approach.

Some authors propose the 'BEARS' acronym as a useful mnemonic tool for clinicians aiming to investigate thoroughly a child's sleep [95]. B – Bedtime issues, including difficulty falling asleep and bedtime resistance [6]. E – Excessive daytime sleepiness (difficulties in waking up in the morning, naps during the day, and involuntary daytime sleep). The quality and the amount of night sleep should be carefully estimated, as daytime sleepiness in children is more often secondary to an inappropriate night sleep duration, than primary [96]. A – Night awakenings. Characterization of the pattern of awakenings during the night might be helpful in guiding therapeutic management [97]. Parental interventions used to put the child back to sleep should be investigated as well, in order to discourage counterproductive practices (e.g. interventions promoting sleep-onset association disorder) [98]. R –Regularity (and routines). This includes inquiring as to bedtimes and risetimes, their night-to-night variability, and the child's bedtime routine. Recommendations about consistency in children's bedtime schedules and routines for better sleep are supported by a strong level of evidence [99]. S – Snoring (and screens). This includes asking about the presence of abnormal nocturnal behaviors, such as snoring and sleep apneas, parasomnias, enuresis, bruxism, and seizures [95]. Questions about the child's screentime, both during the day and before bedtime, should be included, due to the well-known association between the use of electronic devices and sleep problems in childhood [100,101].

For a more accurate and reproducible assessment of sleep disorders in children with NDDs, a

validated screening questionnaire should be used. Several standardized scales are available for identifying sleep disturbances in the pediatric age, but only a few of them have been reported to fulfill all the methodological steps needed to adequately develop a psychometrically sound sleep assessment tool [102]. Among the questionnaires that meet these requirements, the Sleep Disturbance Scale for Children (SDSC) [103,104] has been widely used in pediatric populations with NDDs, such as ADHD, ASD, and ID in a genetic syndrome [105–108].

A comprehensive dissertation on the treatment of sleep disorders in children with neurodevelopmental disabilities is outside the scope of this article. However, some useful principles of treatment can be outlined here. Clinicians should always approach sleep problems in children in a stepwise fashion, with the first-line intervention being sleep education and the implementation of healthy sleep practices [109]. The second level of intervention includes the use of specific behavioral strategies, i.e., procedures based on the principles of learning and behavior aimed at developing positive sleep-related habits, as well as relaxation and self-soothing skills [26▪]. The use of sleep medications in children should be considered the third-level intervention. However, due to the severity of sleep disturbances and the presence of relevant comorbidities, in children with neurodevelopmental disabilities pharmacological treatment is sometimes convenient as a first-line strategy; nevertheless, if a decision is made to start a pharmacologic treatment, behavioral interventions and good sleep hygiene practices should always be associated [97,110].

Due to the scarcity of controlled studies in children, sleep-promoting agents are widely prescribed off-label, the most commonly used being sedating antihistamines (e.g., diphenhydramine or hydroxyzine), melatonin, alpha-2-receptor agonists (e.g., clonidine), benzodiazepines, pyrimidine derivatives (e.g., zaleplon and Zolpidem), antipsychotics (e.g., risperidone and quetiapine), and sedating antidepressants (e.g., trazodone and mirtazapine) [111]. As for nonprescription medications - including over-the-counter (OTC) drugs and nutritional supplements - they are widely used to treat sleep disturbances in children, as they are generally easily accessible, well accepted by caregivers, and considered a 'safe choice' by clinicians, due to their less significant side effects in comparison to some prescription hypnotic drugs [112,113].

Both prescription hypnotic drugs and OTC sleep-promoting agents may be useful in clinical practice and the choice should be guided by the patient's needs and characteristics [26▪].

CONCLUSION

This review offers a general picture of sleep problems in children with NNDs, underlining their high prevalence and unique features in this population, as well as their connection with daytime symptoms. Poor sleep compromises the quality of life of children and their families and is associated with worse developmental outcomes. Recognizing and treating sleep disorders is fundamental for the correct management of children with NDDs and may positively impact on their daytime behavior. Future research on this topic could provide an increasing understanding of the relationship between atypical brain networks and phenotypes of neurodevelopmental disability, helping to clarify how several neurodevelopmental problems can cause, coexist with, or proceed from poor sleep [114]. Understanding this sleep-wake interplay is fundamental to amplify the knowledge about the role of sleep across neurodevelopment [115] and may be important not only for sleep researchers, but for all clinicians dealing with children and NNDs.

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Methylphenidate Use for Emotional Dysregulation in Children and Adolescents with ADHD and ADHD and ASD: A Naturalistic Study

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Abstract: Emotional dysregulation (ED) is common in attention-deficit/hyperactivity disorder (ADHD). Nonetheless, research on ADHD in children with autism spectrum disorder (ASD) and ADHD is still ongoing. Several studies suggest that methylphenidate (MPH) may be effective for ED in ADHD, while there is not enough evidence about its use in ASD with comorbid ADHD. This naturalistic study aims to investigate the effectiveness of immediate- and extended-release MPH in the treatment of ED in 70 children and adolescents (6–18 years), with a diagnosis of ADHD (n = 41) and of ASD with comorbid ADHD (n = 29), using the Child Behavior Checklist—Attention/Aggressive/Anxious (CBCL-AAA). Their parents completed the CBCL twice—first during the summer medication-free period, that is, at least one month after drug interruption; and again after three months of treatment restart. Results demonstrate that MPH is associated with a statistically significant reduction in ED in ADHD and ASD, without substantial adverse events, supporting the use of psychostimulants for the treatment of ED in these neurodevelopmental disorders.

Keywords: methylphenidate; MPH; emotional dysregulation; ED; autism spectrum disorder; ASD; attention-deficit/hyperactivity disorder; ADHD

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1. Introduction

Emotional dysregulation (ED) is characterized by an inability to modulate emotional responses, resulting in extreme reactions of an internalizing or externalizing nature, inappropriate for developmental age [1]. It has long been recognized that ED is common in individuals with neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [2–5]. ADHD is defined by age-inappropriate inattention, hyperactivity, and impulsivity and has a prevalence of 5% (2–9.4% [6–8]; 12.9% in boys, 5.6% in girls [8]). Individuals with ADHD often present excessive and rapidly shifting emotions, associated with irritable and aggressive behavior [9], susceptibility to anger and low tolerance for distress [10–18]. These symptoms are more prevalent in the ADHD combined subtype, especially when comorbid with oppositional defiant disorder [19], and their severity increases with the severity of other ADHD symptoms [4]. Individuals with ADHD combined with ED were more impaired in global functioning [20]. ASD is defined by persistent deficits in social interaction and communication, as well as restricted, stereotyped and repetitive behaviors, and has an overall prevalence between 1 and 2.93% [21–23]. Even if ED is not a formal criterion for the diagnosis of ASD, emotional and behavioral problems, including irritability, temper outbursts, anxiety, aggression, and self-injury are frequently observed in ASD [5,24]. Research

shows that, when compared to typically developing individuals, people with ASD are generally less effective or maladaptive at using emotional regulation strategies [2,25–27].

As for therapy, to date, no data are available regarding a specific pharmacological treatment for ED. To date, in most cases, treatment choice was guided by the main psychiatric condition behind ED. In ADHD individuals, preliminary evidence suggests that psychostimulants improve emotional recognition and reduce emotional lability and irritability [28]. Nevertheless, most studies demonstrated the effect of MPH treatment on ED in patients with uncomplicated ADHD [28–35]. There have been far few studies investigating the efficacy and safety of MPH in those with ADHD and co-existing disorders: some studies concluded that MPH remains effective at reducing ADHD symptoms in the presence of affective comorbidities, without an effect on comorbid conditions (anxiety, depression [36]); other studies suggested that MPH treatment can also reduce other emotional and behavioral problems (such as aggression and antisocial behavior [37]), mood lability [30] and obsessive and compulsive symptoms [32]. Indeed, there is a lack of studies about the effect of psychostimulants on ED in ADHD individuals with coexisting ASD.

The aim of this study was to evaluate the effectiveness and tolerability of immediate- and extended-release MPH treatment on ED in children and adolescents with ADHD, with or without ASD.

2. Materials and Methods

2.1. Participants and Procedures

This was a naturalistic study based on a clinical database of Caucasian young people, aged between 6 and 18 years, consecutively referred to the Child Neuropsychiatric Unit of the University of Bari during a two-year period (September 2019–September 2021). The inclusion criteria were a diagnosis of moderate to severe ADHD, according to DSM-5 [38], pharmacological treatment with immediate-release MPH (IR-MPH) or extended-release MPH (ER-MPH) and therapy lasting at least three months. Given the naturalistic design of this study, patients who already took other pharmacological treatments were not excluded. All the subjects were diagnosed according to clinical judgement from the expert team, composed of child and adolescent neuropsychiatrists and psychologists, specialists in neurodevelopmental disorders. Diagnosis was also supported by standardized diagnostic tools, specific for ADHD and ASD: the Revised Conners' Parent Rating Scale (CPRS-R) [39], the Autism Diagnostic Observational Schedule, Second Edition (ADOS-2) [40,41], the Autism Diagnostic Interview-Revised (ADI-R) [42] and the Autism Spectrum Diagnostic Interview (ASDI) [43]. Moreover, the intellectual quotient of all subjects was assessed with Wechsler scales: the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) [44] and the Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) [45], or the Leiter International Performance Scale-Revised (Leiter-R) [46] in patients with communication impairment. Subjects were also screened for other psychiatric disorders using medical history, clinical observation and the Child Behavior Checklist (CBCL) [47]. All the therapeutic procedures, as well as the follow-up and data collection, were part of our standard routine. All subjects and parents received detailed information on different treatment options and gave their written informed consent to the treatment with MPH. Medication was prescribed as clinically indicated, in addition to routine community care (including psychoeducational interventions), as part of a management protocol.

The starting dose of MPH was 0.3–0.5 mg/kg/day. The dosage could be increased up to 1 mg/kg/day depending upon the subject's clinical response and tolerability, up to a maximum of 60 mg/day. The total dose could be administered in two or three doses/day. After one month of titration, the IR-MPH was generally replaced with ER-MPH. The therapeutic management of ADHD children in our unit comprises short breaks in summer, in agreement with parents and patients about the best pattern of use, with the aim of investigating the ongoing benefit of medication, helping to verify need and the possibility of a reduction in side effects relating to sleep and appetite, albeit considering

its reintroduction whenever needed. The median MPH dose and therapy duration are described in Table 1.

Table 1. MPH treatment.

	ADHD		ADHD and ASD		*p* Value
	Median	IQR	Median	IQR	
MPH dose (mg/kg/day)	0.78	0.64–0.93	0.8	0.57–1	0.79
Therapy duration (months)	24	3–48	36	3–48	0.32

ADHD—attention-deficit/hyperactivity disorder; ASD—autism spectrum disorder; MPH—methylphenidate; IQR—interquartile Range.

For the specific purpose of this study, ED was studied through the evaluation of CBCL scores.

The CBCL is a self-reported scale developed by Achenbach and Edelbrock to evaluate existing competencies and behavioral, emotional, and social problems in children and adolescents aged between 6 and 18 years, through information derived from parents. The behavioral problems scales include 118 items, divided in internalizing and externalizing subscales. The internalizing subscale contains items concerning withdrawn behavior, somatic complaints, and anxious/depressed behavior. The externalizing subscale includes items concerning delinquent and aggressive behavior. Furthermore, there are subscales that contain social, thought, and attention problems. The higher score represents a higher level of problems. A computer program calculates the t scores (mean 50, standard deviation 10) for each scale. Raw scores are converted to gender- and age-standardized scores.

According to Biederman [13,48–51], ED was defined as positive if the sum of the CBCL "attention problems", "aggressive behavior", and "anxious-depressed" (CBCL-AAA) t scores was equal or higher than 180. Moreover, it is possible to distinguish two different profiles: (1) CBCL-DESR (Deficient Emotional Self-Regulation) when t scores are between 180 and 210; (2) CBCL-SED (Severe Emotional Dysregulation) when t scores are higher than 210. When scores are lower than 180, no profile is developed (no-ED). In order to evaluate the effects of MPH therapy on ED, the research team analyzed the CBCL scores obtained during the summer medication-free period, at least one month after drug interruption (T0), and after three months of treatment restart (T1).

Data obtained from the ADHD group and the ADHD and ASD group were compared to each other, henceforth analyzed.

2.2. Ethic Considerations and Sampling

The Ethic Committee of the Azienda Ospedaliera-Universitaria Consorziale Policlinico di Bari approved the study. Informed consent from parents and assent from children and adolescents were obtained prior to enrollment. Among 75 patients who were prescribed MPH, 5 were excluded because their caregiver did not sign the informed consent. The enrolled sample consisted of 70 patients of which 41 had a diagnosis of ADHD (henceforth named the ADHD group) and 29 had a diagnosis of ASD with comorbid ADHD (henceforth named the ADHD and ASD group).

2.3. Statistical Analysis

Comparisons between the two groups were analyzed by t-test or Wilcoxon test for independent samples, appropriately selected according to the evaluation of normality of quantitative variables. Comparisons of proportions between independent groups have been performed by the chi-square test or the Fisher exact test, according to appropriateness. Comparisons between proportions in paired samples were compared by the McNemar test. A general linear model was also applied to evaluate the difference between the two groups at the two timepoints. The main aim was to evaluate whether there was a

difference between the two groups (ADHD vs. ADHD and ASD) in terms of effectiveness and tolerability of MPH on ED; therefore, a test of equivalence was performed: the Two One Side Test (TOST) was applied comparing the limits of the 90% confidence interval of the difference between the two means with the of equivalence (D). They were determined as the product between the effect size (ES) (fixed at 0.5 according Cohen's medium *es*) and the pooled standard deviation: $D = es \times S_p$.

All the analyses were performed using SAS 9.4 for personal computer. The significance level was set at $p < 0.05$. The test of equivalence was performed by the *t*-Test Procedure applying the TOST option with the option Alpha 0.05 (i.e., the TOST will be performed comparing limits of 90% CI of the difference between two means).

3. Results

3.1. Sociodemographic Characteristics

Demographic and clinical characteristics of the two groups, comorbidities and pharmacological treatments in addition to MPH are described in Table 2.

Table 2. Demographic and clinical characteristics of the sample, comorbidities, and other psychotropic medications in addition to MPH.

	ADHD Group (*N* = 41)		ADHD and ASD Group (*N*= 29)		*p* Value
	N	%	*N*	%	
Sex					
M	29	70.7	23	79.3	
F	12	29.3	6	20.7	0.42
	Median	**IQR**	**Median**	**IQR**	
Age (years)	13.4	10–17	13.3	11–16	0.95
ADHD specifiers					
Inattentive	4	9.8	3	10.3	
Combined	37	90.2	26	89.7	0.48
	Median	**IQR**	**Median**	**IQR**	
Intelligence quotient (IQ)	97.2	86–112	96.3	82–112	0.85
Comorbidities	*N*	%	*N*	%	
ID and limited intellectual functioning	3		3		
LD	31	7.3	19	10.3	0.69
MCD	2	75.6	1	65.5	0.36
Tic disorder	1	4.9	0	3.5	0.77
Mood/Anxiety disorder	3	2.4	1	0	0.64
DMDD	2	7.3	0	3.5	0.51
ODD	8	4.9	1	0	0.04
		18.5		3.5	
Other psychotropic medications					
Antipsychotics (FGA and SGA)	4	9.8	2	6.9	1.00
Mood stabilizer	1	2.4	0	0	1.00

ADHD—attention-deficit/hyperactivity disorder; ASD—autism spectrum disorder; ID—intellectual disability; LD—learning disorder; MCD—motor coordination disorder; DMDD—disruptive mood dysregulation disorder; ODD—oppositional defiant disorder; FGA—first-generation antipsychotics; SGA—second-generation antipsychotics.

3.2. Effectiveness

3.2.1. CBCL-AAA Profiles

Comparing the ADHD group with the ADHD and ASD group, the difference between CBCL-AAA profiles (DESR, SED and no-ED) at T0 and at T1 was not statistically significant ($p = 0.08$ and $p = 0.18$, respectively). Conversely, comparing CBCL-AAA profiles in T0 and T1 in each group and in the total sample, the difference was statistically significant ($p < 0.01$) (Table 3).

Table 3. Changes in CBCL-AAA profiles over 3 months of MPH treatment in the two groups.

CBCL-AAA Profile	ADHD Group *N* (%)	ADHD and ASD Group *N* (%)	*p* Value	Total Sample
T0				
SED	13 (31.7)	7 (24.13)	0.08	20 (28.57)
DESR	24 (58.52)	13 (44.82)		37 (52.86)
Non-ED	4 (9.75)	9 (31.03)		13 (18.57)
T1				
SED	4 (9.76)	3 (10.34)	0.18	7 (10)
DESR	17 (41.46)	6 (20.69)		23 (32.86)
Non-ED	20 (48.78)	20 (68.97)		40 (57.14)
***p*-value**	<0.01	<0.01		<0.01

ADHD—attention-deficit/hyperactivity disorder; ASD—autism spectrum disorder; CBCL-AAA—Childhood Behavior Checklist—Attention/Aggressive/Anxious; CBCL-SED—severe emotional dysregulated profile; CBCL-DESR—deficient emotional dysregulation profile; CBCL-non-ED—not emotional dysregulated profile.

3.2.2. CBCL-AAA Scores

Comparing the ADHD group with the ADHD and ASD group, the difference between each subscale of CBCL-AAA both at T0 and at T1 was not statistically significant (T0 anxious: $p = 0.32$, attention: $p = 0.42$, aggressive: $p = 0.27$; T1 anxious: $p = 0.31$, attention: $p = 0.04$, aggressive: $p = 0.29$). Conversely, comparing the scores of CBCL-AAA subscales in T0 and T1 in each group and in the total sample, the difference was statistically significant ($p < 0.01$).

Comparing the two groups, the difference in CBCL-AAA total scores at T0 and T1 was not statistically significant ($p = 0.24$ and $p = 0.12$, respectively). Conversely, comparing the CBCL-AAA total score in T0 and T1 in each group and in the total sample, the difference was statistically significant ($p = 0.01$) (Table 4).

Table 4. Change in CBCL-AAA subscale scores and total scores over 3 months MPH treatment in the two groups.

CBCL Scores	ADHD Group Mean (SD)	ADHD and ASD Group Mean (SD)	*p* Value	Total Sample
Subscales				
T0				
Anxious	65.4 (7.6)	63.2 (10.9)	0.32	64.5 (9.1)
Attention	69.8 (7.8)	68.1 (10.3)	0.42	69.09 (8.9)
Aggressive	67 (11)	63.8 (13.1)	0.27	65.69 (11.9)
T1				
Anxious	60.8 (87.9)	58.8 (8.4)	0.31	60.01 (8.18)
Attention	61.3 (7.4)	57.9 (5.6)	0.04	59.89 (6.85)
Aggressive	58.9 (9.7)	57.3 (10.7)	0.29	58.79 (10.1)
***p*-value**	<0.01	0.01		<0.01
	<0.01	<0.01		<0.01
	<0.01	0.01		<0.01
Total score				
T0	202.2 (20.7)	195 (30.5)	0.24	199.27 (25.3)
T1	181.9 (20.2)	174 (21.4)	0.12	178.69 (20.9)
DIFF T0–T1	20.3	21	0.87	<0.01

CBCL—Childhood Behavior Checklist; ADHD—attention-deficit/hyperactivity disorder; ASD—autism spectrum disorder; SD—standard deviation.

Evaluating the equivalence between the difference T0–T1 of the CBCL-AAA total scores, the two groups were equivalent to each other.

Conversely, evaluating the equivalence between the CBCL-AAA scores in the two group at T0 and at T1, the two groups were not equivalent to each other.

3.3. Tolerability

No severe adverse events were reported; indeed, among these, no cardiovascular events neither suicidal ideation or behaviors were seen (Table 5).

Table 5. Side effects.

	ADHD Group *N* (%)	ADHD and ASD Group *N* (%)	*p*-Value
Loss of appetite	19 (46.34)	13 (44.83)	0.90
Abdominal discomfort	10 (24.39)	10 (34.48)	0.49
Headache	7 (17.07)	5 (17.24)	1.00
Palpitation	4 (9.76)	3 (10.34)	1.00
Irritability	1 (2.44)	4 (13.79)	0.15
Anxiety	3 (7.42)	2 (6.89)	1.00
Insomnia	2 (4.88)	0	0.51
Hyperfocusing	0	2 (6.89)	0.16

ADHD—attention-deficit/hyperactivity disorder; ASD—autism spectrum disorder.

The most frequent side effects in the ADHD group were loss of appetite, abdominal discomfort, and headache (46.34%, 24.39% and 17.07%, respectively), each only temporary, in the first days or weeks of treatment; the same side effects were seen in the ADHD and ASD group (44.83%, 34.48% and 17.24%, respectively). The difference between each side effect in the two groups was not statistically significant. Two ASD patients with comorbid ADHD, both with intellectual disability, of which one was affected by level 3 ASD and the other by level 2 ASD, presented worsening of behavior, with restlessness and increased stereotypes that caused the interruption of treatment and completely resolved after treatment discontinuation.

4. Discussion

This study analyzes MPH effectiveness and tolerability on emotional dysregulation (ED) in a naturalistic setting of 70 ADHD patients, of which 29 also had ASD. To the best of our knowledge, this is the first study focusing on the effect of MPH on ED in ASD children and adolescents.

Several studies analyzed the prevalence of ED both in ADHD, finding percentages between 24 and 55% in children and adolescents and 34 to 70% in adults [3,13], and in ASD, finding a percentage between 50% and 82% [5,24,25]. In this study, the prevalence of ED within ADHD subjects is 90.25% (DESR in 58.52%, SED in 31.7%), higher with respect to previous findings, probably because our patients are affected by moderate to severe ADHD; the prevalence of ED within ASD with comorbid ADHD is 68.95% (DESR in 44.82%, SED in 24.13%), lower with respect to previous findings, probably because of a low rate (3.45%) of intellectual disability.

ED is a challenging pharmacological target, and the scientific literature to date does not provide tailored guidelines for its management, probably because most of the available pharmacological trials did not focus on ED per se. Given the transnosographic quality of ED, pharmacological approaches aimed at it are largely guided by the presence of comorbid illnesses: risperidone and aripiprazole in the context of ASD and/or intellectual disability, serotonin reuptake inhibitors in the context of depression or generalized anxiety

disorders, and mood stabilizers (lithium and divalproex) in the context of bipolar spectrum disorders [3,52–55].

Previous research and clinical experience clearly demonstrated that MPH has a beneficial effect on ADHD core symptoms [56–58]. Recent studies extend these results also on ED in young patients with ADHD, although most of the evidence concerns uncomplicated ADHD [3,28–31,33,34,37]. To date, not many studies have investigated the efficacy and safety of MPH in ADHD patients with comorbid disorders, albeit preliminary data demonstrated MPH efficacy on oppositional, aggressive and antisocial behaviors, on mood lability, and on obsessive and compulsive symptoms [28,53,54].

Concerning the use of MPH in ASD patients, efficacy and safety data are controversial: some early studies reported that stimulant medication resulted in increased stereotypical movements in children with ASD or in additional adverse events that may impact negatively on social interaction. However, these results are based on small samples of patients (frequently case report), often comorbid with intellectual disability [59–61]. Thus, most recent literature on MPH treatment in children with ASD with comorbid ADHD suggests more positive outcomes [12,62–66], with an ES between 0.54 [67] and 0.67 [68] particularly in the case of average intellectual functioning [69]. Indeed, in our previous study, involving 80 ADHD children and adolescents of whom 40 had high-functioning ASD, long-term MPH treatment resulted in amelioration of global functioning [69]. Although promising results on the efficacy of MPH in ASD individuals have been described, no studies have been conducted on its effect on ED to date.

The present study suggests that MPH is associated with a significant improvement in ED in ADHD children and adolescents with or without ASD. Actually, after MPH use, a statistically significant ($p \leq 0.0001$) reduction in CBCL-AAA score was found both in the ADHD group and in the ADHD and ASD group. Within these findings, it is remarkable to note that the median of intellectual quotient was 97.2 in the ADHD group and 96.3 in the ADHD and ASD group. As for tolerability, treatment with MPH was well tolerated; there were no serious adverse events, with the main adverse events being temporary loss of appetite, abdominal discomfort, and headache, without significant differences in the two groups.

Only two ASD patients with comorbid ADHD, both with intellectual disability, presented worsening of behavior, with restlessness and increased stereotypes that caused the interruption of treatment and completely resolved after treatment discontinuation.

Previous review studies comparing MPH to placebo in children with ASD [62,68] globally show that it was mildly superior for inattention, irritability and stereotypes, and did not worsen the core symptoms of ASD.

Even though the low number of individuals with intellectual disabilities in our sample did not allow us to draw conclusions about the role of intellectual disability on the effects of MPH, our findings are in accordance with previous studies [64] in which high-functioning ASD was more likely to have a favorable response to MPH treatment in terms of efficacy and tolerability than low-functioning ASD and suggest greater caution in monitoring the effects of MPH in ASD with intellectual disability.

The present study has different strengths: it describes the effectiveness and tolerability of MPH on moderate to severe ADHD and ADHD and ASD patients from a well phenotypically characterized sample (intellectual profile, severity specifiers, diagnostic subtypes, and comorbidities), with a specific focus on ED, assessed through a standardized measure. Being a naturalistic study, medication titration and dose adjustment were possible as necessary, almost like in a real-life setting.

Study limitations include the lack of randomization or blinding and control of other pharmacological/behavioral treatments and the small sample size. The suitability of our study design used to measure ED administering the CBCL during the summer medication-free period and after three months of treatment restart (employing each patient as his/her own control) could be discussed. Future research in this field should involve proper administration of the CBCL before the beginning of treatment and the extension of ED

assessment through other measures, as objective as possible and preferably not only parent mediated.

In conclusion, our study shows that MPH treatment is well tolerated and effective in reducing ED in children and adolescents with ADHD who may also have high-functioning ASD. Thus, the routine use of MPH in this group of children and adolescents is recommended.

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Informed Consent Statement: Informed consent from parents and assent from children and adolescents were obtained prior to enrollment.

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Review article

Psychological disorders, adverse childhood experiences and parental psychiatric disorders in children affected by headache: A systematic review

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ABSTRACT

Background: Pediatric headaches have been linked to adverse life events or psychological factors in children and their families, with a complex and bidirectional association. Moreover, it is well-known that psychological stress can trigger headaches.
Methods: We searched three databases for studies focusing on headaches and adverse events or psychological factors in children up to 12 years old or in their caregivers.
Results: We included 28 studies. Child psychological factors, including internal and external symptoms, were commonly associated with all types of headaches. Sleep disturbances showed a positive association with headaches in 3 out of 5 studies. Family conflict and unhappiness were frequently found in children suffering with headaches, while single-parent families and divorce were not associated. Stressful environments and adverse life events, particularly bullying, were also found to be linked with headaches.
Conclusions: Childhood headaches represent an alarm bell for clinicians to investigate and treat psychological or psychiatric disorders in children and their family. Further studies are needed to elucidate the role of early-life adverse events in children and their families.

1. Introduction

Headaches are one of the most frequent complaints in the general population, as well as in the pediatric one. Epidemiologic studies on childhood headaches from across the world report widely variable prevalence rates (Nieswand et al., 2020). However, it has been estimated a median frequency of headaches in children and adolescents of 58.4% (1-month to lifetime prevalence) (Abu-Arafeh et al., 2010), while 31.5% of children in primary and secondary school suffered from headaches twice or more per month during the previous 3 months (Nieswand et al., 2019). Despite being more frequent in adolescence (Nieswand et al., 2020; Philipp et al., 2019), headaches are a very common concern in pre-school and school age as well. The onset of a headache is between 7.5 and 8.5 years of age (Jeong et al., 2018; Straube et al., 2013), although 28% of children have experienced recurrent headaches at the age of 7 (Sillanpää and Saarinen, 2017). Moreover, a study reported that 85% of children and adolescents consulting the emergency department for headaches were children up to 12 years, including pre-schoolers (Conicella et al., 2008). It has been reported that 29% of children younger than 5 years have had a headache during the previous year (Lateef et al., 2009; Scheller, 1995). Headaches may actually be an issue for even a larger proportion of pre-school children: it has indeed been shown that parental reports, often used in studies with preschoolers, underestimate headache frequency if compared to when children self-report. (Colombo et al., 2011; Lundqvist et al., 2006).

Headache disorders have a relevant burden of disease, being ranked as the second cause of years of life spent with disability all over the world (GBD 2016 Disease and Injury Incidence and Prevalence

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Collaborators, 2017; Saylor and Steiner, 2018). In the European Union the annual economic losses due to headaches amongst adults are well over €100 billion (Linde et al., 2012). A nationwide study found that 42% of children with headache symptoms experienced restrictions in their daily activities (Philipp et al., 2019). Additionally, more than 20% of pupils suffering from headaches had lost ≥ 1 day of school during the previous 4 weeks, and 7% of their parents had lost at least 1 day of work the preceding month (Wöber-Bingöl et al., 2014). It should be noted that childhood-onset headaches tend to persist into adolescence and adulthood (Kienbacher et al., 2006), even if some clinical features differ between children and adults (Straube and Andreou, 2019). Recurrent headaches at the age of school entry are associated with a higher likelihood of headaches in young adulthood, with a risk increased by 3.36-fold for childhood migraines and by 1.72-fold for other headaches, in comparison with subjects with no childhood headache reported. (Sillanpää and Saarinen, 2017). Thus, the costs concerning headaches in adulthood might be prevented or reduced through an early intervention, at the age of onset, particularly during childhood.

Quality of life is overall poorer in children with headaches than in those without (Philipp et al., 2019; Wöber-Bingöl et al., 2014), with a headache being the most frequent cause of pain affecting quality of life and social activities in developmental age (Philipp et al., 2019).

As for the aetiology of childhood headaches, secondary headaches - i.e., caused by an underlying disease, such as viral infections - are uncommon in children with recurrent symptoms. The majority of headaches in school children are primary, most often migraine and tension-type headache (TTH) ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition, ", 2018). Primary headaches have been linked to several psychological and psychiatric conditions, such as mood disorders, anxiety disorders and obsessive-compulsive disorders (Galli and Gambini, 2019; Minen et al., 2016; Hamelsky and Lipton, 2006; Guidetti et al., 1998; Balottin et al., 2018). This relationship is complex and often considered bidirectional, both in adults (Hamelsky and Lipton, 2006; Minen et al., 2016), and in children (Powers et al., 2006). However, it has been observed that, in a clinical setting, in a mixed-aged population of children and adolescents (up to 18 years) suffering from migraines, drawn behaviour, thought problems, social problems, delinquent or aggressive behaviour were no more likely to be associated with migraines than in a healthy population. On the other hand, migraine population presented more internalising symptoms and somatic complaints than controls (Balottin et al., 2013; Bruijn et al., 2010).

The association with psychological risk factors in both children and families has also been identified in childhood periodic syndromes such as benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome (Tarbell et al., 2017; Devanarayana et al., 2014; Lee et al., 2014; Reale et al., 2011; Tarbell and Li, 2008; Forbes et al., 1999). Some researchers have hypothesised that childhood periodic syndromes may be the early life phenotypic expressions of a common genotype that later in life is expressed as migraine headache (Gelfand, 2018).

Even if biological factors play a crucial role in headache pathophysiology, it is now recognised that these disorders should be studied according to bio-psycho-social models, in which psychological factors could indeed contribute, maintain or be a consequence of headache (Nicholson et al., 2007). There are well-known factors, such as school-related problems or parents' divorce which are related to the onset of headache, both in childhood and adolescence (Larsson, 1988; Passchier and Orlebeke, 1985). These factors, like others, can likely give rise to acute or long-term stress, but it is not clear whether children with headaches have a more stressful daily life, or whether they are more sensitive to stress, so that they develop headaches. On the other hand, it is well established that psychological stress triggers pain episodes in headache sufferers (Marmura, 2018; Martin, 2016; Kelman, 2007; Meng and Cao, 2007). More recent research suggests that psychological stress, caused by Adverse Childhood Experiences (ACEs), can contribute to headache onset as well as in the absence of psychological disorders (Marmura, 2018). The term ACEs generally includes several negative life events in developmental age, such as parental divorce, death, or incarceration, exposure to a close adult with psychiatric illness or addiction, physical or emotional abuse, and neglect (Karatekin and Hill, 2019; Mansuri et al., 2020). Several studies have found an association between ACEs and headaches in adults (Tietjen et al., 2017; Brennenstuhl and Fuller-Thomson, 2015; Juang and Yang, 2014; Anda et al., 2010; Felitti et al., 1998), with the most accepted mediating factors being chronic stress (Sachs-Ericsson et al., 2017) and anxiety and/or depression (Tietjen and Peterlin, 2011).

However, not enough attention has been paid to childhood: few studies have investigated the relationship between psychopathology or ACEs and the onset of headache in paediatric age, also with the objective of guiding the therapeutic approach (Mansuri et al., 2020; The Lancet, 2019; Zafar et al., 2012; Haavet et al., 2004). Furthermore, the studies investigating these relationships usually included subjects in a wide age range (i.e. from preschool age to young adulthood) (Mansuri et al., 2020; Kröner-Herwig and Gassmann, 2012; Seshia, 2004). Such mixed-aged populations undermine the strength of the evidence found on pre-pubertal children, given the relevant bio-psychosocial changes occurring during adolescence.

This systematic review aims to clarify the association between childhood-onset headaches and psychological factors or ACEs, including psychiatric illnesses or psychological issues in caregivers. In particular, given the lack of specific evidence on childhood, our work will focus on children up to 12 years of age.

2. Materials and methods

Aiming to achieve a high standard of reporting, we followed the procedures indicated by the 2009 update of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) (Moher et al., 2009).

2.1. Eligibility criteria, information sources and search strategy

A systematic database search was performed on MEDLINE/PubMed, Web of Science, and Scopus. Our search included records published from the inception of databases up to April 3rd, 2021. The following combination of keywords has been used: (Migraine*[ti] OR Headache*[ti]) AND (Child*[ti] OR Pediatr*[ti] OR Paediatr*[ti]) AND ("Life event" OR "Adverse event" OR ((historical OR psychological OR physical OR sexual) AND (stress* OR trauma* OR abuse*)) OR Grief OR Mourning OR ((parent* OR famil*) AND (death OR loss OR suicid* OR Divorce* OR separat* OR Conflict*)) OR "Psychiatric disease* " OR "Psychiatric disorder* " OR "Mental Disorder* " OR "Psychiatric Illness* " OR Psychopatholog*). Pharmacological trials and studies on animal models have been excluded. Both cross-sectional studies and perspective studies were retained. We did not include reviews and case reports, but searched their reference lists to identify other eligible studies. Articles in English, French, and Italian were included. The obtained records were assessed for eligibility through a Delphi process, based on successive rounds, in which the principal investigators participated, until unanimous consensus was achieved on included articles.

2.2. Study selection

Inclusion criteria were: (a) studies including children up to 12 years of age affected by any kind of headache, and (b) one or more of the followings: (1) studies investigating psychological symptoms, attachment styles or psychiatric disorders in participants; (2) studies investigating parental psychiatric disorders; (3) studies investigating family conflict; (4) studies investigating ACEs in participants.

Studies with mixed-aged populations were included if data on children up to 12 years of age were presented separately.

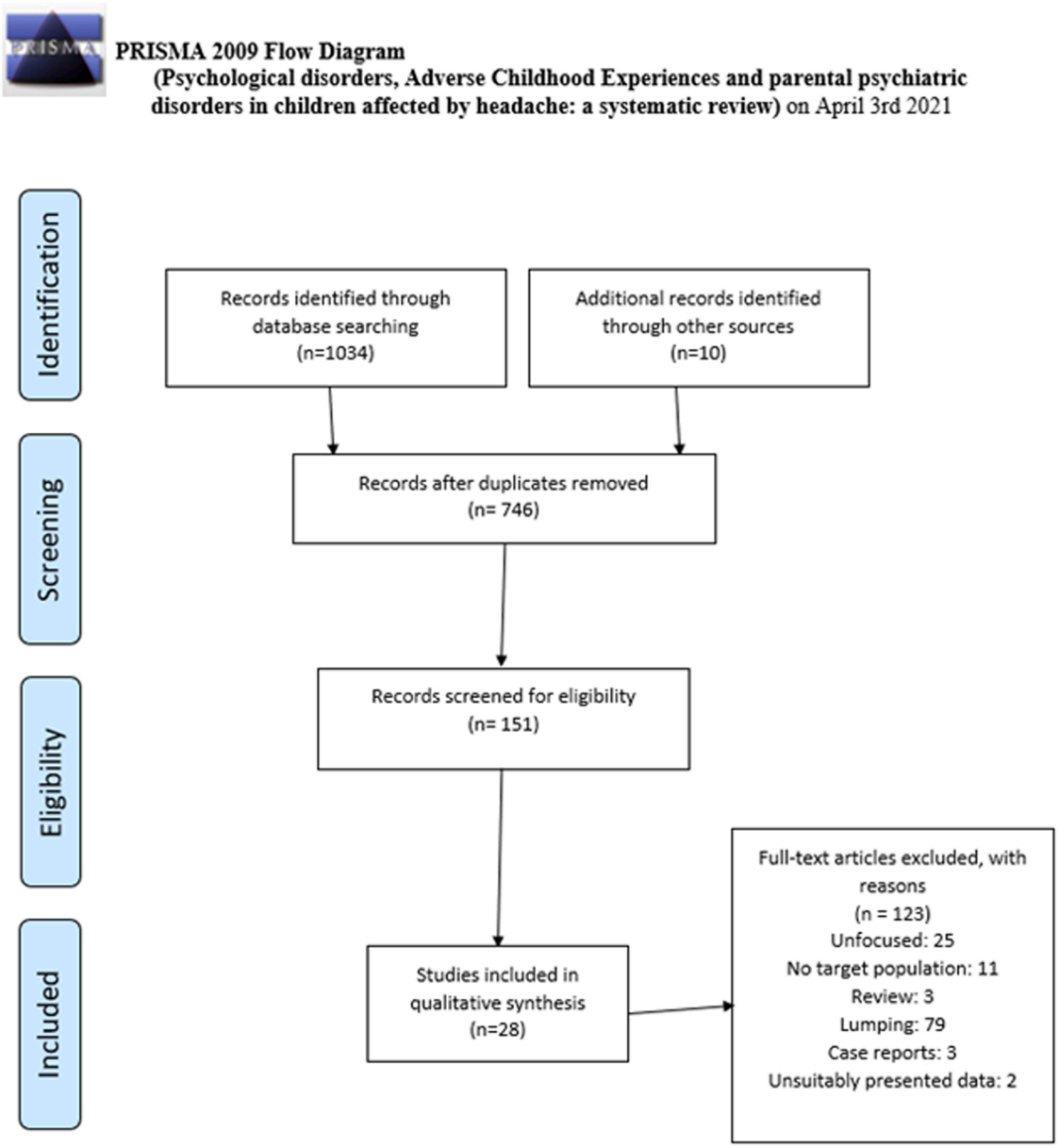

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

Exclusion criteria were: (a) studies on children affected by epilepsy; (b) studies on children with Autism Spectrum Disorders or intellectual disability; (c) studies on headaches secondary to organic illnesses; (d) studies explicitly focusing on psychological symptoms as consequences of headache; (e) studies focusing on socio-economic variables only; (f) studies not reporting clinical outcomes.

2.3. Data collection process

Three authors conducted a two-step literature search examining all titles and abstracts, and assessing the full texts of potentially relevant papers. Two more authors examined the full texts of included articles and approved the final decision. Any discrepancy was solved by consultation with the senior authors. Data was sought for the following characteristics: Participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) (Miller and Forrest, 2001). Specifically, the recorded variables for each article included in the review were: author (s), year of publication, study design, sample size, follow-up or control group - if present -, outcome measures, conclusions, limitations, quality score and quality differentiation. For further quality evaluation, we completed the A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2) worksheet (see Supplements) (Shea et al., 2017).

2.4. Scoring and ranking of the studies

The present systematic review purposely encompassed a broad range of records and different types of study designs. Any potential bias affecting cumulative evidence (e.g., publication bias, selective reporting within studies) was assessed through the study evaluation process. Risk of bias was assessed through the Newcastle-Ottawa Scale (NOS), a tool for observational studies recommended by the Cochrane Collaboration (see supplemental material) (Higgins et al., 2019; Wells et al., 2013).

3. Results

3.1. General data

The records yielded by our search were 197 on Pubmed, 144 on Web

of Science and 693 on Scopus. Thus, our database revealed a total of 1034 records. After removing duplicates, 746 records were screened and 151 were considered eligible, finally leaving 28 articles included (Table 1). The process of article selection is shown in Fig. 1. For this review, we completed the PICO (Population, Intervention, Comparison, and Outcome) Worksheet and Search Strategy (Miller and Forrest, 2001), and the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) worksheet (Shea et al., 2017), which provided a Moderate Quality Review verdict. We include these documents along with the PRISMA checklist (see Supplements) (Moher et al., 2009).

Eleven studies did not specify the type of headache (HD-NOS in Table 2). Other 6 papers did not distinguish data concerning patients with migraine and non-migrainous headache HD-mix in Table 2). Three papers described in detail the type of headache: one reported a comparison between headache not otherwise specified (HD-NOS) and migraine (Anttila et al., 2000), while the others compared migraine and TTH (Arruda et al., 2020; Fielding et al., 2016; Waldie et al., 2014). Three studies studied TTH only (Anekar et al., 2015; Anttila et al., 2002; Odegaard et al., 2003). Four studies focused on migraine only (Esposito et al., 2013a, 2013b; Karlson et al., 2013; Salvadori et al., 2007).

In order to reduce the heterogeneity of investigated factors, we categorised the factors potentially associated with headache in three broad domains: child factors, parental factors, and other stressing events.

All studies investigating child factors found a positive association between at least one of them and headache. The presence of at least another factor - such as a parental factor or an ACE - associated with headache, was observed in 10 studies, while it was not found by 5 studies, and 4 studies showed controversial results. The remaining 8 studies did not consider other factors than child-related ones. However, in the 17 studies which investigated parental factors, an association between headache and at least one parental factor was found in 13 studies, while only 4 showed no association.

3.2. Child factors

Concerning the child factors in our study we distinguished four main categories, which were:

1) psychological symptoms, including psychosomatic, internalising and externalising symptoms and personality traits;
2) attachment style;
3) attention;
4) sleep.

Out of the 28 selected studies, 23 showed a positive association of headache with psychological symptoms, mainly internalising ones, such as anxiety, and/or externalising ones, such as behavioural problems (Anekar et al., 2015; Anttila et al., 2002, 2000; Aromaa et al., 1998; Arruda et al., 2020, 2010; Arruda and Bigal, 2012; Balottin et al., 2005; Barone et al., 2016; Borge and Nordhagen, 1995; Correia and Linhares, 2013; Fielding et al., 2016; Karlson et al., 2013; Kowal and Pritchard, 1990; Lanzi et al., 2001; Odegaard et al., 2003; Pitrou et al., 2010; Salvadori et al., 2007; Sillanpää et al., 1991; Stevenson et al., 1988; von Gontard et al., 2019; Waldie et al., 2014; Zuckerman et al., 1987). The remaining 5 studies did not investigate psychological symptoms (Esposito et al., 2013a, 2013b; Metsähonkala et al., 1998; Swedean et al., 2013).

Of these 23 papers, 8 articles investigated internalising symptoms only and 4 articles externalising symptoms only, while 11 papers enquired both types of psychological disorders (Aromaa et al., 1998; Arruda et al., 2010; Arruda and Bigal, 2012; Balottin et al., 2005; Correia and Linhares, 2013; Kowal and Pritchard, 1990; Pitrou et al., 2010; Salvadori et al., 2007; Sillanpää et al., 1991; Stevenson et al., 1988; von Gontard et al., 2019; Waldie et al., 2014). Only one study showed no association between headache and behavioural symptoms in preschool age (Borge and Nordhagen, 1995). One study reported an association with personality traits, such as shyness and sensitivity (Kowal and Pritchard, 1990). Ten studies showed somatic complaints or psychosomatic symptoms (Aromaa et al., 1998; Arruda and Bigal, 2012; Balottin et al., 2005; Correia and Linhares, 2013; Kowal and Pritchard, 1990; Lanzi et al., 2001; Pitrou et al., 2010; Salvadori et al., 2007; von Gontard et al., 2019), while only one study observed no association between headache and somatic problems (Sillanpää et al., 1991). Insecure attachment style was investigated by two studies (Barone et al., 2016; Esposito et al., 2013a): one paper (Barone et al., 2016) showed that attachment security reduces parental stress related to children's behavioural problem, while the other one (Esposito et al., 2013a) found a positive association between avoidant attachment style and childhood headache and a negative association between both secure and insecure/ambivalent attachment style and the frequency and intensity of headache episodes. Moreover, two studies showed an association between headache and dependency (Stevenson et al., 1988; Zuckerman et al., 1987). Five studies evaluated problems of attention in children affected from headache: 4 studies out of five reported a association (Aromaa et al., 1998; Arruda and Bigal, 2012; Salvadori et al., 2007; Waldie et al., 2014). Three studies out of 28 investigated the association between headache and ADHD (Arruda et al., 2020, 2010; Pitrou et al., 2010), with mixed findings: one of them reported no significant association (Arruda et al., 2010), another one found ADHD to be associated to migraine but not to TTH (Arruda et al., 2020), while another one reported an association of ADHD with HD-NOS (Pitrou et al., 2010). Remarkably, several studies reported inattention alone (Arruda and Bigal, 2012; Salvadori et al., 2007; Waldie et al., 2014) or concentration difficulty (Aromaa et al., 1998) and not hyperactivity or impulsivity in children suffering from headache. Among the 28 included articles, 5 articles investigated sleep disturbances: 3 out of 5 studies reported a positive association (Anttila et al., 2000; Aromaa et al., 1998; Waldie et al., 2014), while the other 2 reported no association (Correia and Linhares, 2013; Kowal and Pritchard, 1990).

3.3. Parental factors

We analysed the association between children's headaches and the following parental factors:

1) parental psychiatric symptoms or personality trait;
2) separation from parents and divorce;
3) high parental stress or family conflict;
4) parental expectation in the relationship with the children.

Six out of 28 studies investigated parental psychiatric symptoms. One study found that mothers of children with migraines showed higher levels of paranoia, social introversion, anxiety, obsessiveness, depression, health concerns, bizarre mentation, cynicism, avoidant attachment (type A), and low self-esteem (Esposito et al., 2013b). Other authors reported that more than 1/3 of parents of children with chronic TTH showed a strict parenting style (Anekar et al., 2015). Another study reported an association between headache and mother's perception of poor health in her child at 9 months old, together with feeding problems and sleep difficulties at 3 years old (Aromaa et al., 1998). In addition, maternal depression was found to be associated with headaches by one study (Zuckerman et al., 1987), while another study found no association with it (Stevenson et al., 1988).

High parental stress and family conflict seem to be involved in higher incidences of headaches. Four studies described an association between headache and parental style, overprotective parents with low punitive behaviour, family conflict, unhappiness in family (Odegaard et al., 2003; Pitrou et al., 2010; Waldie et al., 2014; Zuckerman et al., 1987). Three studies found childrens headaches to be associated with the mother's depression (Zuckerman et al., 1987), mother's personality traits (Esposito et al., 2013b), parental style or family phobia (Anekar et al., 2015). Whilst a study reported no association with maternal

Table 1
Synthesis of studies included in the review.

Study	Population	Design/type of headache	Results	Conclusions
Anekar et al. (2015)	85 children with chronic TTH divided in 3 age groups: 32 children with 6–10 yoa	Cross-sectional study + single group interventional study (psychotherapy). Descriptive questionnaire for psychosocial factors. Chronic TTH (ICHD 2 criteria).	Emotional stressors and school phobia or fear of family members were identified in more than 65% of primary school children. Both parental over- (46.9%) and under-expectations (53.1%) have been reported in this population. All children achieved complete remission from TTH over 3–6 mos. of psychological counselling.	Psychosocial stressors as well as internalising symptoms are very common in children with chronic TTH. It is not clear the role of achievement orientation of parents in the genesis of chronic headache. Psychotherapy seems particularly useful in children with chronic TTH.
Anttila et al. (1999)	Among 1433 children aged 6 and 7 years, the final sample size was 725 children with headache	Prospective study (follow up from school start to the 18th month of school). Questionnaires on the occurrence and risk factors of headache (sociodemographic and school-related factors). Unspecified diagnostic criteria for headache.	2.3% of children had a headache at least once a week by the end of the second school year. A significant increase in the frequency of headache in children was found during the first 12 school months. Parents of children who began suffering from headache after school entry had a higher socioeconomic status than those of children who already had a headache before school started.	The parents with higher socioeconomic status may expect good school results from their children, thus possibly causing stress and provoking the occurrence of headache in them. School start appears to significantly increase the incidence of headache. It is therefore important to develop preventive intervention methods and to prepare children to cope with the life changes caused by school start.
Anttila et al. (2000)	513 children aged 10 years with episodes of headache during the 6 months before the study were initially selected	Prospective, follow up study Structured questionnaire about factors that can provoke headache. Two groups were compared: Migraine and non-migraine headache (IHS criteria)	10% of the sample suffered from migraine, while 90% suffered from non-migraine headache. Children with migraine reported unhappiness in the family, low economic status, fear of failure, fear of teachers, more than those of children with non-migraine headache. No differences in bullying, loneliness, behaviour problems and learning difficulties were found between the two groups. Having an unemployed family member was associated with both types of headache.	Familial paroxysmal headache and unhappiness in the family were independently predictive of migraine in children. Unsatisfactory living conditions were found to be an adjunctive risk factor. Socio-economic status conditions the co-occurrence of headache, with no significant differences between the two types of headache.
Anttila et al. (2002)	138 children aged 12 years reporting episodic TTH (selected from a cohort of 1135 children)	Cross-sectional. Structured questionnaire on headache and its predisposing factors. Tension-type headache (IHS criteria)	Episodic TTH is associated with depressive symptoms, but not with major depression. Sleep disturbances were one of the most distinctive depressive symptoms of children with headaches. The father's occupation as a lower-level white-collar worker increases the child's risk for episodic tension-type headache. Episodic tension-type headache in children was not associated with a one-parent family, unemployment of parents or economic problems.	The connection of depressive symptoms with tension-type headache may be bidirectional. Depressive mood can provoke headache in a person susceptible to headache or vice versa. The impact of socioeconomic status on headache is problematic. Since data on unemployment, divorce and social level are not accurate measures for acute or chronic stress, the results of different studies may be inconsistent.
Aromaa et al. (1998)	1443 families expecting their first child, of which: 144 cases (children that at the age of 6 had headaches in the previous 6 months) and 764 controls.	Longitudinal (from the onset of pregnancy to 6 years of life), case-control study. Questionnaires during pregnancy and childhood. Presence of headache at 6 years as outcome variable. HD-NOS in the previous 6 months	Concentration difficulties, behavioural problems, unusual tiredness, and high sociability at 5 years strongly predicted headache at 6 years. Mother's perception of poor health in her child at 9 months old was a signal of family problems and was associated both with headache at 3 years old. Depression and sleep problems at 3 years were strong predictors of later headache as well. The presence of family members suffering from headache, especially the mother, was a risk factor for preschool headache in the child. Conversely, divorce, one-parent family, or number of siblings were not.	Some factors of a child's early life, among which psychological factors, are predictive of preschool headaches. Parents often recognise the child's psychological problems long before the onset of headache. Concentration difficulties may be a useful predictor of preschool headache in clinical settings. Excessive maternal worrying about the child's health is a factor to take into account for the prevention of childhood headache.
Arruda et al. (2010)	1856 children (5–12 yoa)	Cross-sectional population study. Interviews with parents and teachers using standardised questionnaires about HD and ADHD. Episodic and chronic Migraine and TTH. ICHD-2 criteria.	Children with migraine have higher prevalence rates of ADHD. Both migraine and TTH were comorbid to childhood hyperactivity-impulsivity, whereas there was no evidence of comorbidity between any subtype of HD and lack of attention. There is no specific association	Migraine and TTH were specifically associated with symptoms of behavioural hyperactivity-impulsivity, but not with ADHD or lack of attention. Data point to a shared biological predisposition or environmental risk factors to justify the comorbidity,

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Table 1 (*continued*)

Study	Population	Design/type of headache	Results	Conclusions
			between HD frequency and ADHD or subtypes.	rather than suggesting that pain contributed to externalising symptoms.
Arruda and Bigal (2012)	1856 children (5–12 yoa)	Cross-sectional populational study. CBCL, Questionnaires for HD. Episodic and chronic Migraine and TTH. ICHD-2 criteria.	Children with migraine were significantly more likely to have abnormalities in the following CBCL scales: somatic complaints, anxious-depressed, social isolation, attention, internalising and total score. Children with TTH were significantly different from controls in the same domains but at a lower rate than migraine.	Migraine and TTH were significantly associated with several behavioural symptoms (migraine > TTH), and headache frequency affects the association. Internalising symptoms were more frequent in children with HD rather than in controls, while there was no significant difference with regard to externalising symptoms.
Arruda et al. (2020)	5671 children (5–12 yoa)	Cross-sectional, population-based study. Questionnaires were administered to teachers and parents. DSM-5 criteria were used for ADHD. ICHD-2 criteria were used for headache. Headache was subdivided in episodic migraine, chronic migraine, episodic TTH and chronic TTH.	Prevalence of ADHD was significantly higher in children with migraine than healthy controls, while it was not in children with TTH compared to controls. The prevalence of ADHD increased with increasing frequency of headache episodes and achieved statistical significance in children with chronic migraine compared to those with episodic migraine. The strongest predictors of the migraine/ADHD association were frequency of migraine attacks and poor school performances.	ADHD, as well as hyperactivity-impulsivity alone and inattention alone, was found to be in comorbidity with migraine but not with TTH. The chronicity of migraine increases the risk of comorbidity with ADHD. Male gender, prenatal tobacco exposure, headache frequency, and poor school performances were identified as risk factors for this association. When attending children with headaches, clinicians should investigate school performances and the presence of symptoms of inattention, hyperactivity, and impulsivity, especially in male children with frequent headache attacks.
Balottin et al. (2005)	Patients with headache referred before the age of 6 years. 25 children (12 males; 13 females) (2.8–6.6 years: 4,2 years on average)	Longitudinal study SDQ. MWoA and TTH (IHS criteria, ICHD-II Criteria)	Early Somatic disorders were significantly more frequent in children with headache persistence compared to children with headache remission. No significant differences between the two groups with regard to psychiatric diagnosis and life events.At follow-up children with psychiatric disorders were significantly more affected by headache. Psychosocial and environmental stressors were present in 10/25 children. Behavioural disorders in 16/25 at the beginning and in 12/25 at follow-up, mainly anxiety disorders.	A significant association was found between persistence of headache and early somatic disorders and the presence of psychiatric disorders at the end of follow-up. Life events, even if not statistically significant associated with the evolution of the headache, may influence the course of the headache. Favoured events were associated with the resolution of headache. Environmental and psychological factors play a fundamental role in idiopathic headache with onset in preschool age.
Barone et al. (2016)	71 children (mean 9.8 yoa) seen in HD centre + 71 controls	Case-control study. Measures of attachment style (SS), CBCL, PSI/SF Migraine, TTH and HD-mix. ICHD-2 criteria.	Higher level of behavioural problems in children with HD, but no higher parental stress. In children with HD, perception of attachment security decreased the strength of the association between maternal stress and behavioural problems.	The mother–child interactions could be considered as a protective factor against the association between maternal stress and externalising symptoms, in children with headache.
Borge and Nordhagen (1995)	136 children (follow up from 4 to 10 years of age)	Longitudinal, case-control study. Questionnaires at 4 and 10 years of age + questions on maternal and family characteristics and school-related stress. 4 groups (stomach-ache only; headache only; stomach-ache + headache; control) HD-NOS	'Headache only' group showed higher scores than the control group for: - emotional problems at 4 and 10 years - behaviour problems at school - strenuous homework - child ambitions. The aim of this study was characterising the 'stomachache + headache group'. Statistical significance of score differences between the 'headache only group' and the other groups are therefore not reported by the authors.	Children with headache only didn't show behavioural problems as preschoolers, appeared to be strongly motivated towards high achievement at school and their mothers were more frequently employed outside the home. The present study gives no indication of headache being a warning sign of vulnerability to stress. Children with both headache and stomach-ache seemed to be a separate group with different psychosocial risk factors.
Esposito et al. (2013a)	219 children (6–11 yoa, mean 8.9) with MWoA + 381 controls	Cross-sectional study. Questionnaires for attachment style (SAT), HD. MWoA. ICHD-3 criteria.	Significantly higher prevalence of avoidant (type A) attachment and a significantly lower prevalence of secure (B) attachment in children with MWoA. Avoidant attachment style was positively associated with frequency, intensity, and duration of migraine	In comparison to normal controls, children with MWoA have higher prevalence of avoidant attachment style (type A) and significantly lower prevalence of secure attachment styles (type B). There was a positive correlation between avoidant attachment style

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Table 1 (*continued*)

Study	Population	Design/type of headache	Results	Conclusions
			episodes, while insecure/ambivalent (type C) attachment was negatively related with the frequency and intensity of migraine attacks.	and the frequency, intensity, and duration of migraine episodes.
Esposito et al. (2013b)	269 mothers of children with MWoA (6–12 yoa, mean 8.9) + controls	Cross-sectional study. MMPI-2, Questionnaires for HD. MWoA. ICHD-3 criteria.	Mothers of children with MWoA showed significantly higher scores in the clinical subscales for paranoia, social introversion, anxiety, obsessiveness, depression, health concerns, bizarre mentation, cynicism, avoidant attachment, low self-esteem, work interference. Children's MWoA duration is positively related with hypochondriasis, hysteria, psychasthenia, schizophrenia, anxiety and health concerns scores of their mothers. The frequency of MWoA episodes is positively related with anxiety and low self-esteem.	Some maternal personality traits may alter self-perception and coping strategies of children. Therefore, instead of developing active strategies to cope with headache pain, children could use passive coping strategies (extrinsically determined behaviours), that are associated with higher headache intensity.
Fielding et al. (2016)	Parents of 27 children with anxiety disorders and 36 controls. Average ages of respectively 8,59 years and 7,92 years.	Cross-sectional; Questionnaire on headache based on ICHD-II criteria. (ICHD-II Criteria)	Children with anxiety disorders had a higher incidence of headache compared to controls. Children with separation anxiety disorder had a higher incidence of headaches compared to girls without anxiety disorders and children with other anxiety disorders. Children with both anxiety disorders and headaches had more severe self-reported anxiety symptoms compared to children with anxiety disorders without headaches.	Anxiety symptoms are associated with headache and are more in children with both anxiety disorders and headaches than in children with anxiety disorders only.
Karlson et al. (2013)	69 children aged 7–12 yoa	Cross-sectional for CBCL and questionnaires about quality of life. Longitudinal (2 weeks) for headache diaries and rating of daily mood. Migraine at least once a week. ICHD-II criteria.	Quality of life score consistent with pediatric chronic illness. Normal behavioural functioning on the CBCL. Children reported a significantly greater number of stressful events on headache days than on non-headache days. Worse mood was associated with same-day occurrence, duration and severity of headache, but not with next-day headache. HD was not associated with the next-day mood.	HD seems to be associated with same-day bad mood but not with worse mood the previous or next day. Quality of life is consistently worse in children with HD.
Kowal and Pritchard (1990)	23 children (9–12 yoa) with HD for > /= 1 y and > /= 2 HD episodes/mo; no comorbidities.	Case-control study. Questionnaires about emotional problems, parenting, children's life events, family environment, HD symptoms + HD diary. HD-NOS (as defined in Population section)	Children with HD have higher shyness-sensitivity, psychosomatic problems and behavioural disturbances and lower parental expectations than children in the control group. Higher anxiety and perfectionistic-compulsive scores and lower stress derived from life events in the previous year ('life change units') were predictive of greater severity of HD.	No support for the hypotheses that children with HD were more disturbed in mood, nor that they have experienced greater life stresses in the previous year, nor that their parents will have a greater degree of achievement orientation. Major life events may not contribute to the persistence of HD once it is established, nevertheless they could be responsible for the initial development of the HD.
Lanzi et al. (2001)	57 patients with HD (age 8–18 years, mean age 12.4, separate data for different age groups)	Cross-sectional. Personality tests; 53 patients (8–17 years) completed the CDI; 42 patients (aged 11–18) completed the TAI. Mixed headache: MwA, MwoA, TTH (IHS classification).	Personality traits: 6–8 years showed submissiveness and lack of emotional independence; lack of imagination; spontaneity and sincerity; low self-esteem and a tendency to feel guilty. CDI: all patients had significantly higher scores. TAI: Only subjects aged 15–18 years old showed significantly higher scores.	In the age group of our interest (up to 12 years), subjects with HD showed common personality traits. Anxiety symptoms were not correlated to headache. Depressive symptoms were associated with headache and tended to be more common in migraine than in TTH sufferers. The personality traits detected were not correlated with social variables and with HD duration, suggesting them to be peculiar features of children with HD.
Correia and Linhares (2013)	75 children (3–5 yoa, mean 54 mos) divided in 2 groups: with (n = 22) and without (n = 53) HD episodes	Cross-sectional study. Questionnaires for child temperament, psychological symptoms, HD in children and mothers. (CBCL, CBQ, HST, SSI, SRRS) HD-NOS.	Mothers of children with HD had significantly higher probability to have HD symptoms than mothers of children in the control group. Children with HD have higher scores for discomfort /negative affect temperament, emotional and behavioural problems than children without HD. No association between HD and sleep complaints was found.	Preschool children with HD symptoms may develop emotional and behavioural problems and they indeed present more externalising and internalising problems than the control group. HD tends to aggregate in families, probably because genetics, psychosocial factors, parental pain modelling or a

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Table 1 (*continued*)

Study	Population	Design/type of headache	Results	Conclusions
				combination of them may influence the outcome of HD.
Metsiihonkala et al. (1998)	3580 children, followed since birth up to 8–9 yoa	Prospective Cohort study. Screening questionnaire once a year from 1 to 6 yoa + additional questionnaire if HD reported. HD mix (migraine and non-migrainous headache) ICHD-I criteria (1988)	Migraine: 2.7%; Non-migrainous HD: 27.3% already at 5 yoa Lower employment status and level of education of fathers were reported in children with HD vs children without HD. Children with HD reported more often being bullied in school (♀>♂), stress in school, learning difficulties and problems in getting along with other children than children without HD.	Children with both migrainous and non-migrainous HD reported being bullied at school, problems in dealing with other children, general school stress and slight school difficulties more often than children without HD. It could be that children with HD tend to be more negatively affected by school stress than other children who also experience the same situations.
Ödegaard et al. (2003)	14 children 10–12 yoa with HD during the previous 2 months, selected in school nurseries.	Interview study through structured interview and qualitative analysis in order to identify themes involved in the headache attacks. TTH	Main themes resulted to be: noise and disorder in the school environment; "insecure relationships" with the schoolmates; difficulties with school subjects; conflict relationship with family or conflict within the family. All the children had parents with full-time jobs outside the family. All children suffering from headache had poor socio-economic conditions.	The children tend to associate HD with external events more than psychological issues. Many children were bullied. Even if the family matters represented the main part of what they reported about their life, they did not consider a correlation with the headache. However, the children considered certain patterns of how they tended to react, such as their feeling unable to master some task, to contribute to the onset of a headache.
Pitrou et al. (2010)	Among 2324 children the final sample size was 1308 children, aged 6–11 years old, from a large French region.	Cross-sectional study; Survey conducted in primary schools, using two different structured interviews for parents and children (SDQ and the child-reported Dominic Interactive). HD-NOS.	11% of the children already experienced frequent headaches in their lifetime, with no difference by age or gender. Headaches were associated with parent-reported emotional problems and self-reported general anxiety disorder. Comorbid physical conditions appeared as an independent factor significantly associated with headaches. Inversely, low parental punitive behaviours were less frequently associated with headaches.	Headaches, emotional disorders, and comorbid physical conditions are associated in children aged 6–11 years old.
Salvadori et al. (2007)	30 children with migraine and 30 healthy subjects, 7–16 years old.	Longitudinal case-control study (Migraine Group, MG vs Control Group, CG). CBCL was administered to the mothers and ratings were obtained for the past two age periods (0–3 and 4–6 years) and for the present state (7–16). Migraine with early juvenile onset (ICHD-II).	In the longitudinal perspective, internalising traits were present in the premorbid period in MG. During the premorbid period 0–3 years old the MG showed significantly higher mean scores on total problems, internalising, somatic and anxious-depressive symptoms. During the premorbid period 4–6 years old children from MG showed statistically significant higher total problems, internalising, somatic, anxious-depressive, attention, social problems and withdrawal. In the 7–16 years group have also been observed to have higher somatic problems, thought and attention problems.	Migraine could be considered as the expression of a previous vulnerability. Both internalising and externalising problems during the preschool period are stable and are correlated to the development of migraine. When migraine appears, children affected from it have a higher rate of behavioural problems compared to healthy children.
Sillanpää et al. (1991)	5356 children of which 4402 patients (82,2%) have been observed also at the follow-up.	Longitudinal prospective study from birth to 5 years old. Questionnaires were administered to public nurses of well-baby clinics and to parents. HD-NOS.	Low economic status and poor living conditions, day-care nursery, leisure activities have been correlated with increased frequency of headache. The following associated symptoms have been found: diurnal and nocturnal enuresis; problems of interaction with other children (1.5 times more frequent); temper tantrums (twice more frequent); stomach aches.	HD was usually functional and a result of social stress, distress and other environmental factors. Socio-economic factors, difficult housing, the daycare nursery and leisure activities predicted the occurrence of headache. Apparently, children at preschool age can also be stressed by having too many activities. Psychological factors connected to HD (diurnal enuresis, problems of interaction with other children and temper tantrums), while the main physical symptom found was the stomach ache.
Stevenson et al. (1988)	189 children aged from 2 years and 6 months to 3 years and 6 months	Cross-sectional. Interview of the mother and BSQ. Recurrent stomach ache and HD-NOS (at least one episode of stomach ache or HD during the previous 4 weeks and one episode before).	No trend was found for recurrent headaches to be associated with the family characteristics investigated. Conversely, recurrent headaches were significantly associated with	Compared to recurrent stomach aches, recurrent headaches are less strongly associated with adverse family factors. In particular, unlike previously reported, recurrent headaches in the child are not

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Table 1 (*continued*)

Study	Population	Design/type of headache	Results	Conclusions
			externalising and internalising (fears, dependency) problems of the child.	associated with depression of the mother. Recurrent headaches and recurrent stomach aches in preschool children should be considered as separate symptoms, with possibly different psychosocial concomitant factors.
Swedean et al. (2013)	Military-dependent 548 children divided in 3 groups: 5–9, 10–13 and 14–17 yoa. 132 with parental deployment and 416 without it	Cross-sectional study. Questionnaires for HD. Recurrent HD defined as recurrent episodes in the past 12 months. HD-NOS.	Overall prevalence of recurrent HD in sample: 23.6%. Younger children (5–9 yoa) with recurrent HD and recent parental deployment had the highest rates of headache worsening during parental deployment in comparison with older children.	Military-dependent children (and adolescents) commonly showed recurrent HD and its worsening, independently of whether a parent was deployed or not. However, during military parental deployments, younger children (5–9 yoa) report a higher incidence of worsening headaches. Although not statistically significant ($p < 0.072$), this trend might show a more relevant effect of parental deployments on younger children.
von Gontard et al. (2019)	585 children (4.5–7.3 yoa, mean age 5.8) before school entry	Cross-sectional study. SDQ; Questionnaires about HD, incontinence and constipation HD-mix: migraine, TTH and other non-primary HD ICHD-III criteria	Headache episodes in 27.2% of children. 1.5% (10) children only fulfilled ICHD criteria for frequent HD, mostly unclassifiable. Only constipation, but not incontinence, was associated with HD. Primary HD were associated with total, externalising and internalising symptoms; while secondary HD only with emotional problems. However, constipation and faecal incontinence predicted both internalising and externalising problems.	HD are frequent conditions also in preschool children, not just in school-aged children and adolescents. Probably the diagnostic criteria of the ICHD are not sensitive enough for this age group. Primary headache and functional gastrointestinal disorders such as constipation are closely related. Children with HD have more frequently internalising problems, while externalising symptoms predominate in those with incontinence.
Waldie et al. (2014)	871 New Zealand European children	Longitudinal study. Data were collected at birth, 1, 3.5, 7, and 11 years of age. SDQ; Questionnaires about perinatal risk factors, sleep duration, percent body fat, television watching, parent and self-reported total problem behaviour, being bullied, and depression. ICHD-II criteria.	Migraine and TTH were both significantly associated with self-reported borderline/abnormal scores even after controlling for other risk factors. Physical violence, verbal teasing, sexual harassment or racist comments have been associated with TTH.	Though an association between headache and depression has not been found, this study indicates that many other areas of psychological functioning are significantly associated with childhood headache. Despite some inconsistencies, findings suggest that primary headache in childhood is complicated by, or occurs due to, a combination of a predisposition and psychosocial and behavioural difficulties.
Zuckerman et al. (1987)	308 preschool children	Longitudinal, case-control study (follow up from 0 to 3 years). Semi-structured interview with questions on demographics, maternal and child health, child behaviour and psychosocial factors. Recurrent headache (HD-NOS).	Recurrent headache in the child is associated with maternal depression. Children with recurrent headaches showed more behavioural problems than those without. Other psychosocial stresses (like marital problems, poor support to the mother, single-parent family or overcrowding in the house) were not associated with recurrent headache.	Mother's psychological condition may influence the development of somatic complaints in the child. It is possible that preschool children express their distress through somatic complaints, especially if they have learnt that such complaints are effective in engaging the attention of depressed mothers.

Abbreviations: ADHD, attention deficit and hyperactivity disorders; BSQ, Behaviour Screening Questionnaire; CBCL, child behaviour checklist; CBQ, child behaviour questionnaire; CDI, Children's Depression Inventory; HD, headache disorder; HD-NOS, headache-not otherwise specified; ICHD, International Classification of Headache Disorders; mo(s), month(s); MMPI-2, Minnesota Multiphasic Personality Inventory – second edition; M-NOS, migraine-not otherwise specified; MWoA: migraine without aura; MWA: migraine with aura; TTH, tension-type headache; HD-mix, mixed patterns of headache; HD-NOS, headache not otherwise specified; HST, headache screening test; PSI/SF, parenting stress index, short-form; SAT, separation anxiety test; SDQ, Strengths and Difficulties Questionnaire; SRRS, social readjustment rating scale; SS, security scale; yoa, years of age; SSI, stress symptom inventory; ♀, female sex; ♂, male sex.

depression, nor with marital problems (Stevenson et al., 1988), two studies did not show any association with parental variables (Aromaa et al., 1998; Barone et al., 2016).

As for the presence of high or low parental expectations, two studies (Anekar et al., 2015; Kowal and Pritchard, 1990) investigated it and one of them found a positive association between headaches and low degree of achievement orientation (Kowal and Pritchard, 1990).

Divorce, parental status and single parent families deemed not to be associated with headaches in children in 6 studies (Anttila et al., 2002; Aromaa et al., 1998; Borge and Nordhagen, 1995; Correia and Linhares, 2013; Stevenson et al., 1988; Zuckerman et al., 1987), while an association was found in only one study (Odegaard et al., 2003). Only one work analysed parental military employment and showed an association with it (Swedean et al., 2013). We analysed socio-economic factors when associated with psychological disorders in children suffering with headaches. Low socio-economic status and low cultural level resulted in an association with headaches (Anttila et al., 2002, 2000; Metsähonkala et al., 1998; Sillanpää et al., 1991, p. 1991). In particular, poor housing conditions were associated with presence and frequency of headaches (Sillanpää et al., 1991).79 One of these studies highlighted a link

Table 2
Associations between headache in children and environmental and psychological factors.

	Child Factors				Parental Factors					Other Stressing or Adverse Events
Articles (type of HD)	Psychological symptoms (internalising and externalising symptoms, somatic complaints) and personality traits	Attachment style	ADHD and lack of attention	Sleep disturbances	Parents psychological symptoms and personality traits	Separation from parents and divorce	High parental stress or family conflict	Parental expectations	Parental socio-economic and cultural status	Child life stress, bullying, school stress and other adverse events
Anekar et al., 2015 (chronic TTH)	+ internalising symptoms				34.4% strict parenting style			46.9% over-expectations; 53.1% under-expectations	62.5 % social milieu stress	56.2% environmental stress; 68.7% education phobia; 65.6% emotional stressors; 63.5% school phobia and fear of family members
Anttila et al., 1999 (HD-NOS)									+ high parental socioeconomic status	+ school start 0 school phobias, fear of teachers, fear of failure, bullying, loneliness at school, other school problems
Anttila et al., 2000 (M-NOS and HD-NOS)	+ internalising symptoms (fear of failure) + externalising symptoms (behaviour problems);						+ unhappiness in the family		+ low economic variables (M-NOS > HD-NOS); + unemployed family member	+ school start
Anttila et al., 2002 (TTH)	+ internalising symptoms (depressive symptoms)			+ sleep problems		0 one-parent family			+ lower level work of the father 0 economic problems; 0 parental unemployment	
Aromaa et al., 1998 (HD-NOS)	+ internalising symptoms (depression); + externalising symptoms (behavioural problems); + high sociability (personality trait) +somatic problems (unusual tiredness, feeding problems at 9 months)		+ concentration difficulty	+ difficulties in falling asleep at 3 years old	+ mother perceives that her child is in poor health at 9 months old	0 divorce; 0 one-parent family	0 parenthood problems			0 several relocations
Arruda et al., 2010 (HD-mix)	+ externalising symptoms (behavioural hyperactivity and impulsivity, but not ADHD);		0 ADHD and inattention: no difference in headache group versus controls							
Arruda and Bigal, 2012 (HD-mix)	+ somatic complaints; + internalising symptoms (anxiety-depression, social isolation, M > TTH) + externalising symptoms (M>TTH; in TTH males >controls)		+ lack of attention in episodic M							
Arruda et al., 2020 (M-NOS and TTH)			+ ADHD and migraine (chronic > episodic)							

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Table 2 (*continued*)

			0 ADHD and TTH							
Balottin et al., 2005 (HD-mix)	+ internalising (anxiety, depression); + externalising (behavioural disorders); + early somatic disorders; + psychiatric disorders at follow-up									0 life events
Barone et al., 2016 (HD-mix)	+ internalising symptoms	0					0			
Borge and Nordhagen, 1995 (HD-NOS)	0 externalising symptoms (behavioural problems) in preschool age + child ambitions at school (personality trait)					0 stability of family characteri-stics (marital status, residence, employment and family size)			+ mother working outside the home	
Esposito et al., 2013 a (MWoA)		+ type A (avoidant) - type B (secure) - type C (insecure/ ambivalent)								
Esposito et al., 2013 b (MWoA)					+ maternal personality traits*					
Fielding et al., 2016 (MWA, MWoA, TTH)	+ internalising symptoms (GAD, social phobia, specific phobia, SAD, panic disorder, depression)									
Karlson et al., 2013 (M-NOS)	+ internalising symptoms (worse mood with same-day HD)									+ stressful events in HD-days compared with non-HD-days
	0 internalising symptoms (worse mood with next-day and previous-day HD)									
Kowal and Pritchard, 1990 (HD-NOS)	+ somatic complaints + externalising symptoms (behaviour disturbances) + personality trait (shyness-sensitivity)* 0 internalising symptoms (anxiety and depression)*			0 no sleep disturbances in two groups (case, control)				+ low parental expectations		0 life stress in previous year
Lanzi et al., 2001 (HD-mix)	+ internalising symptoms (depressive symptoms 8-11y); + personality traits (submissiveness, pragmatism and lack of imagination, spontaneity and sincerity, low self-esteem and tendency to feel guilty 6-8y) 0 internalising symptoms (anxiety symptoms 11-12y)	+ emotional dependency								
Leonetti Correia and Linhares, 2013 (HD-NOS)	+ somatic complaints + internalising symptoms (withdrawal, discomfort/negative affect dimension) + externalising symptoms (aggressive behaviour, emotionally reactive)			0 no sleep complain In the two groups (case, control)		0 marital status			0	0 life adverse events
Metsiihonkala et al., 1998 (HD-mix)									+ education level; + employment (only for males)	+ school stress (♀>♂) + poor relationship with other

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Table 2 (*continued*)

										children (♂>♀) + difficulty in school subjects (slightly) + being bullied at school (♂>♀)
Ödegaard et al., 2003 (TTH)	+ somatic complaints; + internalising symptoms (sense of mistrust and loneliness, angriness, inability to cope)					+ divorce; + single parent family; + parents with full-time jobs outside the family	+ family conflict; + insecurity within the family			+ school stress (noise and disorder in the environment; difficulty in school subjects); + being bullied or picked up on by other children
Pitrou et al., 2010 (HD-NOS)	+ internalising symptoms (GAD, SAD, emotional problems); + externalising symptoms (CD, altered prosocial behaviours); + somatic complaints (comorbidity with physical conditions)*		+ ADHD				+ high parental over-protective behaviour; - parental low punitive behaviour 0 other parental behaviours			
Salvadori et al., 2007 (M-NOS)	+ internalising (anxiety, depression, thought problems, withdrawal); + externalising disorders (aggressivity, social problems); + somatic complaints		+ lack of attention							
Sillanpää et al., 1991 (HD-NOS)	+ internalising symptoms; + externalising symptoms (behavioural problems); 0 externalising symptoms (temper tantrum); 0 somatic complaints (stomachache, diurnal and nocturnal enuresis)								+ economic status; + housing standards/living conditions	+ number of relocations; + high number of leisure activities; 0 problems of interaction
Stevenson et al., 1988 (Recurrent HD-NOS)	+ internalising symptoms (fears); + externalising symptoms (temper tantrums)	+ dependency (trend)			0 maternal depression; 0 irritability of the mother	0 one-parent family	0 marital problems; 0 inadequate social support for mother		0 social class; 0 mother education	
Swedean et al., 2013 (HD-NOS)						+ military parental deployment				
von Gontard et al., 2019 (HD-NOS)	+ internalising symptoms; + somatic complaints (constipation)									
Waldie et al., 2014 (TTH and M-NOS)	internalising symptoms: + overall symptoms; + externalising symptoms (hyperactivity/ Impulsivity, conduct problems) 0 internalising symptoms (depression)		+ lack of attention	+ shorter sleep duration at 7y (only M-NOS); 0 sleep duration at 11y			+ maternal perceived stress;		+ maternal school leaving age	+ problems with peers; + being bullied
Zuckerman et al., 1987 (recurrent HD-NOS)	+ externalising symptoms (behavioural problems)	+ dependency			+ maternal depression	0 single-parental family	0 marital problems; 0 poor support to the mother		0 overcrowding in the house	
	Psychological symptoms (internalising and externalising symptoms, somatic complaints) and personality traits	Attachment style	ADHD and lack of attention	Sleep disturbances	Parents psychiatric symptoms and personality traits	Separation from parents and divorce	High parental stress or family conflict	Parental expectations	Parental socio economic and cultural status	Child life stress, Bullying, school stress and other adverse events

Abbreviations: + , positive correlation; -, negative correlation; 0 in grey cells, no correlation found; White cells indicate that the specific factors were not studied. ADHD, attention deficit and hyperactivity disorders; CD, conduct disorder; GAD, generalised anxiety disorder; HD, headache; HD-NOS, headache-not otherwise specified; HD-mix, mixed patterns of headache; ICHD, International Classification of Headache Disorders; M-NOS, migraine-not otherwise specified; MWoA: migraine without aura; MWA: migraine with aura; SAD, separation anxiety disorder; TTH, tension-type headache; y, years of age; ♀, female sex; ♂, male sex.
* , *See* Table 1 *for further details.*

between headache and unhappiness in the family (Anttila et al., 2000). However, four studies reported no association between headache and low socio-economic status (Anttila et al., 2002; Correia and Linhares, 2013; Stevenson et al., 1988; Zuckerman et al., 1987). Surprisingly, one study reported that higher socioeconomic status was associated in children suffering from headaches after school entry. The authors explained this data proposing that the parents with higher socioeconomic status may have higher expectations from their children, thus possibly causing stress (Anttila et al., 1999). See Table 2.

3.4. Other stressing or adverse events

Seven works showed a direct association between headache and school-related stress, such as school start, fear of school, loneliness at school or problems with peers, difficulty with school subjects, noisy or messy environment at school (Anekar et al., 2015; Anttila et al., 2000, 1999; Karlson et al., 2013; Metsähonkala et al., 1998; Odegaard et al., 2003; Waldie et al., 2014). One paper reported no association between headaches and problems with peers (Sillanpää et al., 1991). Four studies highlighted an association between being bullied and headaches (Anttila et al., 2000; Metsähonkala et al., 1998; Odegaard et al., 2003; Waldie et al., 2014). The remaining studies did not investigate school-related problems. Others reported stressful events like a number of relocations, high number of leisure activities, or general environmental stress: four papers did not report an association between them and headaches (Aromaa et al., 1998; Balottin et al., 2005; Correia and Linhares, 2013; Kowal and Pritchard, 1990), while three found it (Anekar et al., 2015; Karlson et al., 2013; Sillanpää et al., 1991). Only one study reported a specific association between learning difficulties and headaches (Anttila et al., 2000).

4. Discussion

In this review, an association between headaches and several determinants of psychological suffering in children (up to 12 years of age) was found. Even if a clear causative association can hardly be identified, positive associations between headaches and several psychological factors in children were found, in particular internalising symptoms. This is in line with previous data on children and adolescents (Dyb et al., 2015; Jeyagurunathan et al., 2020), and with the higher frequency of headaches in adolescents suffering from depression if compared to not depressed adolescents (Hamelsky and Lipton, 2006; Pine et al., 1996). In support of this evidence, it has been reported that psychiatric comorbidity (i.e. depression) is an important risk factor for chronicization of headaches in adulthood (Just et al., 2003; Rossi et al., 2018).

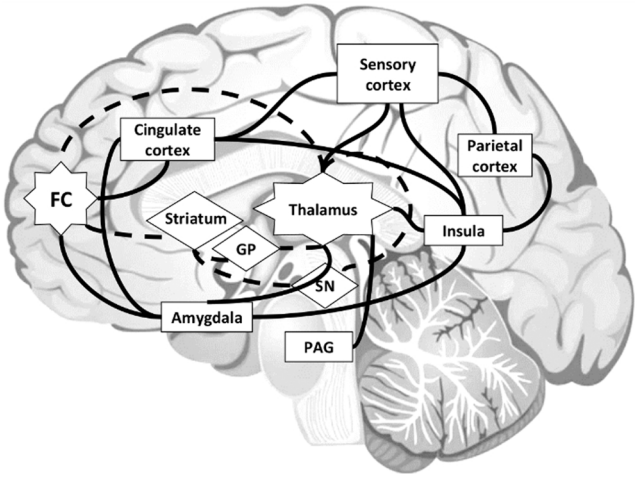

Fig. 2. Schematic representation of the main areas involved in the pain matrix and in frontostriatal circuits (FSCs). The areas inscribed in rectangles and connected by solid lines represent elements of the pain matrix. The areas enclosed in rhombuses and connected by dashed lines represent the FSCs. The areas involved in both networks are represented within 8-pointed stars. FC: frontal cortex, GP: globus pallidus, PAG: periaqueductal grey, SN: substantia nigra.

Primary headaches in children are generally thought to be the result of a complex interaction of bio-psycho-social factors (Nicholson et al., 2007) and can determine a variety of behavioural problems (Kernick and Campbell, 2009). The association of headaches with psychological disorders may be explained through the existence of common neurobiological mechanisms - such as the serotonergic system hypofunction and/or imbalance in dopamine levels (Zarcone and Corbetta, 2017) - between mood and anxiety disorders, and headaches (Fig. 2).

From a neurobiological standpoint, both headache and many psychiatric conditions share anatomical and functional networks, such as frontostriatal circuits (FSC) which play a role in the comorbidity between headache and psychological disturbances (Ozge et al., 2021). FSC are frontosubcortical networks which mediate motor activity and behaviour, connecting specific areas of the frontal cortex to the striatum and thalamus with afferent and efferent pathways (Tekin and Cummings, 2002). For instance, the orbitofrontal circuit has been implicated in mood disorders, as well as in disinhibition and emotional lability. Moreover, the medial frontal circuit has been associated with apathy and attention deficit and hyperactivity (Ozge et al., 2021).

A number of these circuits have been described as part of another clinically significant network, often referred to as the 'pain matrix'. This is a group of connected cortical areas (including somatosensory, insular, cingulate, frontal and parietal areas) processing nociceptive stimuli and generating the experience of pain. The pain matrix has consequently been implicated in chronic pain syndromes and, specifically, in headache and migraine (Legrain et al., 2011; Dresler et al., 2019). Fig. 2 summarises the main central areas involved in the pain matrix and the FSCs.

The association found in this review also includes psychological symptoms, which might involve parental or other environmental factors. For instance, a causative role of psychological aspects, secondary to environmental factors, in the onset and maintenance of headaches may also be considered. In favour of the hypothesis of a psychological origin of a headache is also the effectiveness of psychotherapy in improving headache symptoms in children and also in adults (Anekar et al., 2015; Faedda et al., 2019; Probyn et al., 2017; Sieberg et al., 2012).

In specific conditions of stress, because of their developmental characteristics, children may not be able to express directly psychological difficulties or emotional distress, showing instead concrete somatic complaints, such as headaches (Guidetti et al., 2016; Rossi et al., 2018; Zuckerman et al., 1987). The data shown in the present systematic review suggests that psychological symptoms may precede the development of the headache, representing an important risk factor. A headache might be a consequence of psychological problems in children with previous subjective vulnerability and family problems. Environmental stress, such as school-related stress, and ACEs, specifically being bullied or peer problems, can be associated with childhood headache, so they

should also be investigated in this condition. A recent study showed an improvement in primary headaches both in children and adolescents during the COVID-19 pandemic, with lower levels of school-related stress during the lockdown being the main factor explaining symptom improvement (Papetti et al., 2020).

Moreover, as confirmed by the present review, several authors have demonstrated an association between somatic symptoms, including headache, and ACEs (like bullying and being bullied) (Fekkes et al., 2006; Gini and Pozzoli, 2009).

The main mediating factors in both ACEs and headaches are thought to be altered stress responses (Nelson et al., 2017). According to the central sensitisation theory, stress induces an abnormal activation of the trigeminal nucleus caudalis, which has been hypothesised to be involved in pain processing (Grassini and Nordin, 2017). Moreover, prolonged stress and the consequent chronic activation of the hypothalamic-pituitary-adrenal axis have been found to enhance pain signals transmitted by the trigeminovascular pathway, thus playing a major role in headache (Burstein and Jakubowski, 2009). Data suggest that, after an emotional stressor, children with migraine (vs. healthy peers) have a prolonged physiological recovery period accompanied by changes in the autonomic nervous system and by sympathovagal imbalance that may explain the occurrence of headache associated with ACEs (Huss et al., 2009).

Decreased levels of resilience or lack of vitality, secondary to the family and the social context, and to adverse events, should also be considered and investigated through neuropsychological assessments (Borsook et al., 2012; Maccari et al., 2017). Indeed, these aspects may be underestimated in clinical practice, leading to unsatisfactory results of the pharmacological therapy only. Migraine medications may act on pain, but the underlying psychological and social problem may remain untreated, possibly reappearing later in adolescence or in adulthood, even in a worsened form. Psychological interventions - including those on parents - may be appropriate in these disorders in childhood, in order to prevent more severe psychiatric disorders in adolescence (Maccari et al., 2017; Winding and Andersen, 2019).

Familial depression and anxiety are frequently observed and might be implicated in pathogenesis of the headache. Family conflict, unhappiness in the family, low socioeconomic conditions and high level of stress and psychiatric symptoms in caregivers should be considered in the evaluation of children affected by headaches. For instance, parental psychological disorders may often make the children's evaluation more difficult, as parental reports could present missing information about the circumstances of headache onset and recurrence. On the other hand, it is remarkable that single parent family and divorce were not associated with headaches.

Primary headache can therefore be considered a red flag for clinicians to investigate psychological symptoms and family conditions. It is interesting to note that psychological disorders have also been observed as a comorbidity in children affected by 'migraine equivalents' or periodic syndromes, such as benign paroxysmal torticollis, cyclical vomiting syndrome, abdominal migraine and paroxysmal vertigo (Devanarayana et al., 2014; Forbes et al., 1999; Lee et al., 2014; Reale et al., 2011; Tarbell and Li, 2008; Tarbell et al., 2017). Patients with such syndromes have an increased likelihood to develop migraine (Guidetti et al., 1998). Psychological issues could therefore predict both episodic periodic syndromes and migraine in children.

In addition, three out of five studies investigated and found the presence of sleep disturbances in children affected by headache. In particular, total sleep time has been found to be reduced in children with headaches. No difference has been found in sleep disturbances between episodic and chronic headache sufferers. Notably, sleep disturbances can represent a comorbidity with both headache and mood/anxiety disorders (Hamelsky and Lipton, 2006), involving the serotoninergic system in all of these disorders.

Finally, in the present study the different types of headaches (e.g. migraine or TTH) did not show significant differences in the association with psychiatric conditions or psychological issues, as observed in previous research (Ashina et al., 2017). This may be explained considering that childhood headache is presently considered a vision of continuity from TTH to migraine, including intermediate unspecified phenotypes (Margari et al., 2013). On the other hand, it should be noted that most studies did not specify the type of headache, except for a few papers (Esposito et al., 2013a, 2013b; Fielding et al., 2016; Karlson et al., 2013; Salvadori et al., 2007; Waldie et al., 2014). Given the high heterogeneity and the overlap of the above-mentioned headache types, it is difficult to define distinct trends of factors associated with migraine rather than TTH or vice versa. Further studies are needed to clarify this specific association, especially in this younger age group (up to 12 years old), accurately differentiating between childhood and adolescence.

Moreover, a self-reported symptoms evaluation from the children, together with the parental reports, as well as a psychological assessment of both children and their parents should be obtained whenever possible, in order to identify a global and more effective treatment strategy for headache.

The main limitation of the present review consists in the high heterogeneity of samples, methods and assessment tools of the included studies (see Supplements for Cochrane Risk of Bias Tool). For example, only a few studies used comparable standardised assessment tools. Moreover, a clear difference between the types of headache has not been specified by the majority of the studies.

It should also be noted that it was impossible to assess ethnic and transcultural factors that may have influenced the investigated subject because of lack of data. These aspects should be conceived as focus for future research.

5. Conclusions

In this review, in 22 studies out of the 28 selected articles, an association has been found between headaches in children and psychological disorders, including both internalising and externalising symptoms. The influence of parental factors on childhood headaches has also been observed. Parental depression may be associated with headaches, in particular for the mother, while single parental family and divorce appeared not to be associated with it. Family conflict and unhappiness showed an association with headaches. The main adverse events found to be associated with headache were school problems and problems with peers, most of all bullying, which should be investigated and faced. Finally, a child's headache can be an alarm bell for clinicians to investigate and treat psychological or psychiatric disorders in children and their family, in order to prevent psychiatric disorders in adolescence and in adulthood.

Future directions may be additional psychological investigations on children and their family, in order to identify both risk and protective factors. Further studies on the directionality of the relationship between headaches and psychological symptoms are needed. The impact of different ACEs on headache should be more specifically investigated.

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Declarations of interest

None

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104798.

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Visuo-spatial attention deficit in children with reading difficulties

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Although developmental reading disorders (developmental dyslexia) have been mainly associated with auditory-phonological deficits, recent longitudinal and training studies have shown a possible causal role of visuo-attentional skills in reading acquisition. Indeed, visuo-attentional mechanisms could be involved in the orthographic processing of the letter string and the graphemic parsing that precede the grapheme-to-phoneme mapping. Here, we used a simple paper-and-pencil task composed of three labyrinths to measure visuo-spatial attention in a large sample of primary school children (n = 398). In comparison to visual search tasks requiring visual working memory, our labyrinth task mainly measures distributed and focused visuo-spatial attention, also controlling for sensorimotor learning. Compared to typical readers (n = 340), children with reading difficulties (n = 58) showed clear visuo-spatial attention impairments that appear not linked to motor coordination and procedural learning skills implicated in this paper and pencil task. Since visual attention is dysfunctional in about 40% of the children with reading difficulties, an efficient reading remediation program should integrate both auditory-phonological and visuo-attentional interventions.

Developmental dyslexia is a specific reading disorder despite normal intelligence, teaching experience and absence of any manifest sensory deficit. The diagnostic and statistical manual for mental disorders (DSM-5) classifies developmental dyslexia as a possible outcome of a specific learning disorder. The diagnosis of a specific learning disorder is often accompanied or preceded by other diagnoses within the group of neurodevelopmental disorders, such as language disorder, attentional deficit and hyperactivity disorder, developmental coordination disorder and autism spectrum disorder[1].

The phonological core deficit theory argues that reading difficulties (RD) in children with developmental dyslexia stems from deficits in the ability to identify and explicitly act upon sounds of spoken words, leading to difficulties in learning appropriate grapheme to phoneme mapping[2,3]. Thus, the left temporoparietal junction, involved in auditory-phonological processing and memory of the speech sounds[4], could play a crucial role in the first phases of reading acquisition in which grapheme-to-phoneme mapping plays a pivotal role in the sub-lexical and lexical route development[5].

The time required for a prereading child to quickly and accurately name an array of well-known visual stimuli, known as rapid automatized naming (RAN), is one of the best predictors of future reading skills[6,7]. Exactly as reading, RAN tasks require: (i) attention to the stimuli; (ii) visual processes that are responsible for initial feature detection, discrimination, and stimuli identification; (iii) integration of visual information with stored orthographic and phonological representations; (iv) lexical processes, including access and retrieval of phonological codes; and (v) organization of articulatory output[8]. Longitudinal studies have shown that phonological awareness and visuo-spatial working memory, as well as RAN, appear to be good predictors of future reading development[2,7,9,10].

The fronto-parietal network, involved in visuo-attentional processing, could play a crucial role in the first phases of letters identification and orthographic development[11,12]. Efficient abilities in extraction and selection of the visual information through visuo-spatial attention allow to create stronger visual word form representations[13] (see[14–17] for reviews; see[18] for a meta-analysis). As reported by Grainger et al. (p. 171)[17]: "processing of orthographic information begins with scale-invariant gaze-centered letter detectors that conjunctively encode letter identity and letter location. Visual acuity, crowding, and spatial attention conjointly determine activity in these gaze-centered letter detectors".

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Combining signal-enhancing and noise-exclusion mechanisms, the right fronto-parietal network is involved in attentional shifting (i.e., disengagement of attentional focus) and scaling (zoom-in and zoom-out of attentional focus)[19].

The presence of sluggish attentional shifting[20–24], as well as an altered perceptual noise-exclusion mechanism[25,26], could be at the basis of difficulties in rapid stimulus-sequence processing often observed in children with developmental dyslexia[14]. Several longitudinal studies have confirmed that visuo-spatial attention abilities are good predictors of future reading skills[26–29] (see[18] for a meta-analysis in pre-reading children), suggesting that graphemic parsing and letter-string processing demand: (i) rapid and accurate deployment of visual attention along the letter strings[17,30,31]; (ii) good abilities in global extraction and spatio-temporal integration of visual information[32–34]; (iii) a large visual-attention span and; (iv) a reduced visual crowding effect[26,30] (see[35] for a review). Crucially, visuo-attentional training appears to improve reading skills in children with and without developmental dyslexia[26,33,34,36–42] (see[43] for a review), confirming the causal role of the fronto-parietal attentional network in reading acquisition[44].

The fronto-parietal network is involved not only in attentional deployment crucial for reading acquisition but also in multiple interactions with the environment, particularly in action recognition and action planning[45]. It is intriguing to note that children with developmental dyslexia show a rate of comorbidity from 16 to 70% with a developmental coordination disorder[46,47] and that this neurodevelopmental disorder is characterized by visuo-attentional deficits[48]. However, despite the evidence about the correlation between visuo-motor and reading and spelling skills achievement[49,50], some longitudinal studies on the possible links between fine and gross motor skills and reading development have not shown consistent results[2,29]. Specifically, some studies linked manual dexterity to future reading skills when evaluated with writing tasks[51]. However, this correlation is sometimes better explained by attentional and working memory functions[49,52], and sometimes manual dexterity does not appear to be related to future reading skills[53]. A possible explanation for these inconsistent results could be the different levels of engagement of visuo-attentional mechanisms involved in the specific experimental tasks[54].

In children with developmental dyslexia, a sequential procedural learning (the ability to acquire a general task procedure) deficit has also been observed mainly in serial reaction time tasks[55]. Interestingly, in their meta-analysis, Lum and colleagues[56] showed that the observed deficit appears to be mainly linked to a possible dysfunction in medial-temporal areas, involved in the attentional spatiotemporal sequence processing. Also, in tasks that strongly involve visuo-hand coordination, such as mirror drawing, children with developmental dyslexia show slower execution times[55,57]. Although visuo-motor coordination deficits and procedural learning disorders have been shown in developmental dyslexia, a basic visuo-attentional deficit could indirectly explain these motor and learning disorders[14].

We supposed that a specific visuo-spatial attention deficit characterizes children with RD. The typical tasks used to index the pure visuo-spatial attention functioning in children with RD require complex behavioral[21] and psychophysics procedures[20] that are difficult to apply in a clinical setting. Thus, here we used a simple paper-and-pencil task composed of three Cs labyrinths (see Fig. 1, panel A). Efficient execution of the Cs labyrinths task requires multiple attentional mechanisms. Children must be able to rapidly zoom-in and zoom-out[19] onto the different parts of the path, as well as disengage, move and engage their attentional focus[16,21–23]; see[58] for a review. A large attentional focus could allow the child to analyze multiple items (Cs) of the labyrinth simultaneously. However, this efficient attentional procedure could be used only if noise[25] or crowding of the peripheral stimuli[26] is not excessive and if the visual attention span is adequate[31,59]. At the same time, a fast attentional zoom-in will allow children to rapidly disentangle the direction that must be serially selected item by item. Later, a rapid orientation of visual attention[21,36] will allow quick analysis of subsequent path steps.

We hypothesized that the execution of this task allows the detection of differences between children with and without RD. We assumed that children with RD would have shown difficulty performing the attentional task, regardless of the different length of the first and second labyrinths.

To better understand the other cognitive mechanisms involved in this task, we tried to separate the role of visuo-attentional abilities from the possible effects of procedural learning and visuo-motor skills using three sheets in which the first and the third labyrinths path are equal. The visuo-spatial attention difficulties would have become less relevant if the path of the labyrinth had been the same as a labyrinth already solved. In this case, procedural learning would have played a more important role, than the visual-attentional abilities that would have been less engaged. Reducing the load on visuo-attentional skills by administering the first of the two labyrinths for a second time, we can control the effects linked not only to the procedural learning but also the visuo-motor coordination skills.

We tested this hypothesis in a large sample of primary school children (from the second to the fifth grade), administering word and pseudoword reading tasks and the three labyrinths composed by a series of Cs. We built the first and second labyrinths with different paths, whereas the first and third labyrinths were identical. Then, we measured the specific visuo-spatial attentional effect using the two labyrinths with different paths. Finally, our labyrinths task does not require a load of working memory processes, in contrast to the typical visual search tasks in which working memory of the target is highly involved.

Material and methods

The entire investigation process was conducted according to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent, and the Ethics Committee of the Department of General Psychology of the University of Padua approved all procedures.

Participants. Three hundred ninety-eight children (188 males and 210 females; 8% left-handed) took part in our study. The children, partially evaluated in schools in different regions of Italy, attended from the second to

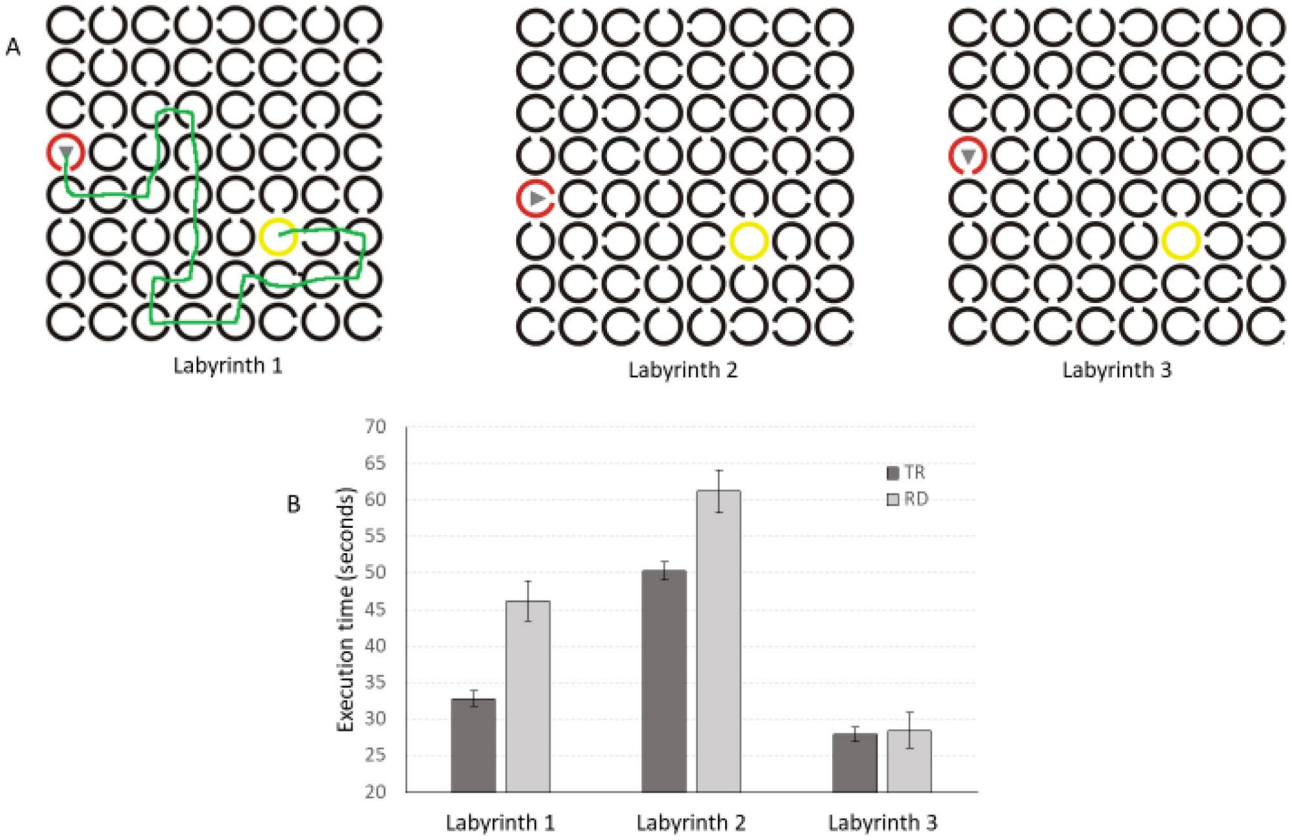

Figure 1. Panel (**A**) Representation of the three labyrinths that compose the visuo-spatial attention task. In the first labyrinth, an example of correct execution is represented; panel (**B**): Execution times (mean in seconds) in typical readers (TRs) and children with reading difficulties (RDs) in the three labyrinths. Error bars represent standard errors of the mean.

	Typical readers (TRs)			Children with reading difficulties (RDs)			
School grades	Sample size	Age in years	Males/females	Sample size	Age in years	Males/females	t test
2	82	7.72 (0.31)	49/33	6	7.85 (0.40)	3/3	$t_{(86)} = -1.009$ $p = 0.316$
3	85	8.75 (0.36)	39/46	21	8.75 (0.46)	10/11	$t_{(104)} = 0.123$ $p = 0.903$
4	87	9.56 (0.52)	39/48	18	9.7 (0.37)	7/11	$t_{(103)} = 1.453$ $p = 0.149$
5	86	10.65 (0.40)	35/51	13	10.75 (0.25)	6/7	$t_{(97)} = -1.015$ $p = 0.313$
Total	340	9.34 (1.00)	162/178	58	9.23 (1.14)	26/32	$t_{(396)} = -0.851$ $p = 0.395$

Table 1. Sample size, chronological age (mean and standard deviation) and gender (number of males and females) characteristics of typical readers (TRs) and children with reading difficulties (RDs) in the different school grades.

the fifth grade of primary school (see Table 1). Children had normal or corrected to normal vision. No hearing difficulties or neurological deficits were reported. Clinicians evaluated children's reading abilities using standardized word and pseudoword reading tasks (see the "Word and pseudoword reading tasks"). Based on their performance in standardized word and pseudoword reading tasks, they were classified as typical readers (TRs) or children with RD. A child was classified in the RDs group if they showed at least two performance measures (speed and/or accuracy) in word and/or pseudoword reading tasks -2 standard deviations (SDs) below the average scores calculated for a normative sample[60]. A subgroup of these children (n = 19) with RDs was recruited from clinical centers using the same reading disorders criteria. These children have already received a clinical diagnosis of developmental dyslexia based on the specific criteria established by the Italian Institution of health. These children may present other specific learning disabilities, but they did not receive other diagnoses of neurodevelopmental disorders. The other children were classified in the TRs group. A sample of 340 TRs (52% female) and 58 children with RDs (55% female) were tested (see Table 1).

	Sample size	Word reading speed (Z score)	Word reading accuracy (Z score)	Pseudoword reading speed (Z score)	Pseudoword reading accuracy (Z score)
Typical readers (TRs)	340	0.018 (0.92)	0.06 (0.92)	−0.10 (1)	0.02 (1.1)
Children with reading difficulties (RDs)	58	−4.18 (3.42)	−3.70 (3.54)	−3.61 (4)	−2.44 (1.75)
		$t_{(396)} = 19.067$ $p < 0.001$	$t_{(396)} = 16.671$ $p < 0.001$	$t_{(396)} = 13.903$ $p < 0.001$	$t_{(396)} = 14.388$ $p < 0.001$

Table 2. Reading performance (means and standard deviations in Z score) in typical readers (TRs), children with reading difficulties (RDs) and reading performance differences between the two groups.

Word and pseudoword reading tasks. Reading skills and phonological decoding abilities were measured using lists of standardized word and pseudoword reading tasks, respectively[60]. See Table 2 for the descriptive statistics of the reading tasks.

Cs labyrinth task. The task consists of three sheets of labyrinths. On each sheet, there is a square grid (8 × 8) of Cs (2.2 cm in diameter; the opening part of the C is about 0.5 cm), oriented in four cardinal directions. A red C with a triangle inside indicates the starting point, whereas a yellow circle indicates the endpoint. The participant was asked to draw a solid line from the triangle to the final circle using the opening of the black C to reach the adjacent C (see Fig. 1, panel A). In detail, the instructions given to the child were "In this test you must be able to drive this car (triangle) out of the labyrinths. The car can move from circle to circle, but it can only pass by the part where the circle is open, and then arrive in the consecutive circle, up to the yellow circle: you have to be fast and accurate". Before the test, the child was shown an example sheet, where the administrator showed how to carry out the test, and a second sheet, where the participant carried out a training trial him-/herself. The three labyrinths were always administered in the same order to allow us to investigate the procedural learning skills. In particular, it is expected that the double administration of the same labyrinth path should cause an improvement in the second administration–an implicit facilitatory visuo-motor effect at the basis of procedural learning mechanism[50].

Despite the path of the first labyrinth was composed of 21 passages and the path of the second labyrinth was composed of 36 passages, the attentional shifting index (measured as the ratio of total passages to the direction changes) was similar between them (first labyrinth: 12 direction changes with attentional shifting difficulty index = 1.75; second labyrinth: 21 direction changes with attentional shifting difficulty index = 1.71).

For each of the three labyrinths, the execution time in seconds and the number of errors were measured. It was not necessary for the pencil line to pass precisely inside the opening of the C. Each time the participant made a mistake entering in the wrong adjacent C, she/he restarted from the last correct circle.

Trained psychologists individually administered the reading and visuo-spatial attention tasks.

Results

Visuo-spatial attentional differences between TRs and children with RDs: analysis of (co)variance. Data analysis was performed using a 3 × 2 mixed analysis of variance (ANOVA) (3 labyrinths*2 groups: TRs and RDs children), where the three labyrinths are the repeated measures and the group is the between-subject factor. The dependent variable was the labyrinth execution times and errors (raw score). Considering that the participants were recruited from second to fifth grade of primary school, we decided to perform the same analysis, adding the school grade factor as a covariate.

Execution times. The first ANOVA on labyrinth execution times showed that the main effect of the labyrinth was significant: $F_{(2792)} = 143.619$, $p < 0.001$, partial $\eta^2 = 0.266$. Post hoc (Bonferroni correction) revealed that the execution times of the three labyrinths were significantly different from each other (all ps < 0.001; execution time of labyrinth 1 mean = 34.77 s, SD = 21.02; labyrinth 2 mean = 51.88 SD = 22.91; labyrinth 3 mean = 29.99, SD = 18.92). Also, the group's main effect was significant: $F_{(1396)} = 13.402$, $p < 0.001$, partial $\eta^2 = 0.033$. The mean execution time of TRs (37 s, SD = 15.65) was shorter than that of children with RDs (45.29 s, SD = 17.41). In children with RD the execution time was 22% slower in comparison to TRs. The labyrinths x group interaction was also significant: $F_{(2792)} = 8.684$, $p < 0.001$, partial $\eta^2 = 0.021$. To better understand this interaction, we run an ANOVA for each labyrinth. The main effects of group showed that the TRs group (first labyrinth mean = 32,82, SD = 19.98; second labyrinth mean 50.29, SD = 22.09; third labyrinth mean = 27.92, SD = 19.87) performed both first ($F_{(1395)} = 21.056$, $p < 0.001$, partial $\eta^2 = 0.05$) and second ($F_{(1395)} = 11.593$, $p = 0.001$, partial $\eta^2 = 0.028$) labyrinths significantly faster, compared to the RD group (first labyrinth mean = 46.19, SD = 23.36; second labyrinth mean = 61.23, SD = 25.5; third labyrinth mean = 28.45, SD = 12.06). Performance was not statistically different in the third labyrinth ($F_{(1395)} = 0.039$, $p = 0.843$, partial $\eta^2 < 0.001$). Both TR ($t_{(339)} = 3.318$, $p = 0.001$ Cohen's d = 0.180) and RD ($t_{(57)} = 5.965$, $p < 0.001$, Cohen's d = 0.649) groups showed a significant improvement between the first and third labyrinth execution. Thus, children with RD were significantly slower only in the first and second labyrinth compared to TRs.

In the ANCOVA, with the same 3 × 2 (3 labyrinths*2 groups) analysis, in which we use the school grade as covariate, the main effect of school grade was significant: $F_{(1395)} = 14.383$, $p < 0.001$, partial $\eta^2 = 0.035$. Also, the main effect of labyrinths was significant: $F_{(2790)} = 34.301$, $p < 0.001$ partial $\eta^2 = 0.080$. The differences between the three labyrinths were still significant (all ps < 0.001). Labyrinth x school grade interaction was not significant:

	Labyrinth 1 errors	Labyrinth 2 errors	Labyrinth 3 errors
TR group	0.57 (0.96)	0.59 (1.01)	0.23 (0.69)
RD group	0.72 (1.37)	0.60 (0.94)	0.16 (0.41)

Table 3. Number of errors (mean and standard deviation) in the three labyrinths of children without (TR) and with reading difficulties (RD).

$F_{(2790)} = 1.877$, p = 0.154, partial $\eta^2 = 0.005$. The main effect of groups was significant: $F_{(1395)} = 15.085$, $p < 0.001$, partial $\eta^2 = 0.037$. Also, the labyrinths x group interaction was still significant: $F_{(2790)} = 8.770$, $p < 0.001$, partial $\eta^2 = 0.022$. To better understand this interaction, we run an ANCOVA for each labyrinth. The main effects of group showed that the TRs group performed both first ($F_{(1395)} = 22.084$, $p < 0.001$, partial $\eta^2 = 0.053$) and second ($F_{(1395)} = 13.147$, $p = 0.001$, partial $\eta^2 = 0.032$) labyrinths faster compared to the RDs group, whereas the execution times in the third labyrinth did not differ ($F_{(1395)} = 0.098$, $p = 0.754$, partial $\eta^2 < 0.001$; see Fig. 1). Thus, children with RD were significantly slower only in the first and second labyrinth compared to TRs independently of school grade.

Errors. A second (3 labyrinths*2 groups) mixed ANOVA, which considered the labyrinth error numbers as a dependent measure, was executed. The main effect of the labyrinth was significant: $F_{(2792)} = 21.642$, $p < 0.001$, partial $\eta^2 = 0.052$. The number of errors was not different between the first (mean = 0.6, SD = 1.03) and second labyrinth (mean = 0.59, SD = 1, $F_{(1396)} = 0.677$, p = 0.411, partial $\eta^2 = 0.002$), whereas the error numbers in both the first ($F_{(1396)} = 31.4$, $p < 0.001$, partial $\eta^2 = 0.073$) and second labyrinth ($F_{(1,396)} = 41.965$, $p < 0.001$, partial $\eta^2 = 0.096$) were significantly different from the third labyrinth (mean = 0.22, SD = 0.65). The main effect of the group was not significant: $F_{(1396)} = 0.103$, $p = 0.748$, partial $\eta^2 < 0.001$. The group x labyrinth interaction was not significant: $F_{(2792)=}1.112$, $p = 0.329$, partial $\eta^2 = 0.003$.

The ANCOVA with the same design (3 labyrinths*2 groups), in which school grade was the covariate, showed that the main effect of school grade was not significant ($F_{(1.395)} = 1.625$, $p = 0.203$, partial $\eta^2 = 0.004$). The school grade x labyrinth interaction was not significant ($F_{(2.790)} = 0.197$, $p = 0.822$, partial $\eta^2 < 0.001$). The main effect of the labyrinth was significant ($F_{(2.790)} = 4.692$, $p = 0.009$, partial $\eta^2 = 0.012$), whereas the main effect of the group ($F_{(1395)} = 0.142$, $p = 0.707$, partial $\eta^2 < 0.001$), as well as the group x labyrinth interaction, were not significant ($F_{(2.790)} = 1.122$, $p = 0.326$, partial $\eta^2 = 0.003$). Thus, children with RD were not significantly different to TRs when the errors in the labyrinth task were considered (see Table 3).

Finally, these findings were not different when these analyses were performed considering only RDs selected in the schools excluding children with DD, showing that these results are not uniquely driven by the clinically diagnosed children with DD.

Relationship between visuo-spatial attention and reading: partial correlation analysis. Besides investigating differences in visuo-spatial processing between children with and without RDs, we further investigated the correlation between individual visuo-spatial attentional abilities and reading skills, across our entire sample of children (n = 398).

We carried out partial correlations between the execution time in the Cs labyrinths and reading speed (syllables for second) and errors, controlling for school grade. Significant correlations were found between the mean execution time in the first and second labyrinths and the mean of word and pseudoword reading speeds (r = − 0.28, $p < 0.001$; See Fig. 2 Panel A) and errors (r = 0.26, $p < 0.001$; See Fig. 2 Panel B). In contrast, no significant correlation was found between the execution time of the third labyrinth and the mean of word and pseudoword reading speeds (r = − 0.08, $p = 0.113$) and errors (r = − 0.03, $p = 0.621$).

A significant correlation was also found between the mean of errors in the first and second labyrinths with the mean of word and pseudoword reading errors (r = 0.19, $p < 0.001$), but not with speed (r = − 0.08, $p = 0.113$). No significant correlation was found between the number of errors in the third labyrinth and the mean of word and pseudoword reading speeds ($r < 0.001$, $p = 0.994$) and errors (r = − 0.016, $p = 0.746$).

In addition, to investigate the different cognitive mechanisms involved in the execution of the same visuo-motor paths, the correlation between the performance (errors and execution time) of the first and the third labyrinths was carried-out controlling for the school grade. Although the correlation between the mean of errors in the first and in the third labyrinth was significant (r = 0.12, $p = 0.014$), the same correlation was not significant (r = 0.08, $p = 0.119$) when the more sensitive execution times were analysed. These findings suggest that the same visuo-motor path executed the second time is able to measure a different cognitive mechanism, that is, procedural learning.

Moreover, the correlation between the pure visuo-spatial attention deficit controlling for procedural learning skills (measured through the delta of the execution time between 1st and 2nd administration of the same labyrinth) and reading speed (mean of syll/sec of word and pseudoword) was significant: (r = − 0.15, $p = 0.003$) also controlling for school grade. This result indicates that a more severe visuo-spatial attention deficit was linked with slower reading speed. Accordingly, this pure visuo-spatial attention deficit was also significantly correlated with the reading errors mean (r = 0.22, $p < 0.001$), indicating that a more severe attentional deficit was linked with more reading errors. The same visuo-spatial attention deficit calculated using the delta in errors between the 1st and 2nd administration was not significantly correlated with the reading speed (r = − 0.07, $p = 0.14$), whereas it was significantly correlated with the reading errors mean (r = 0.18, $p < 0.001$).

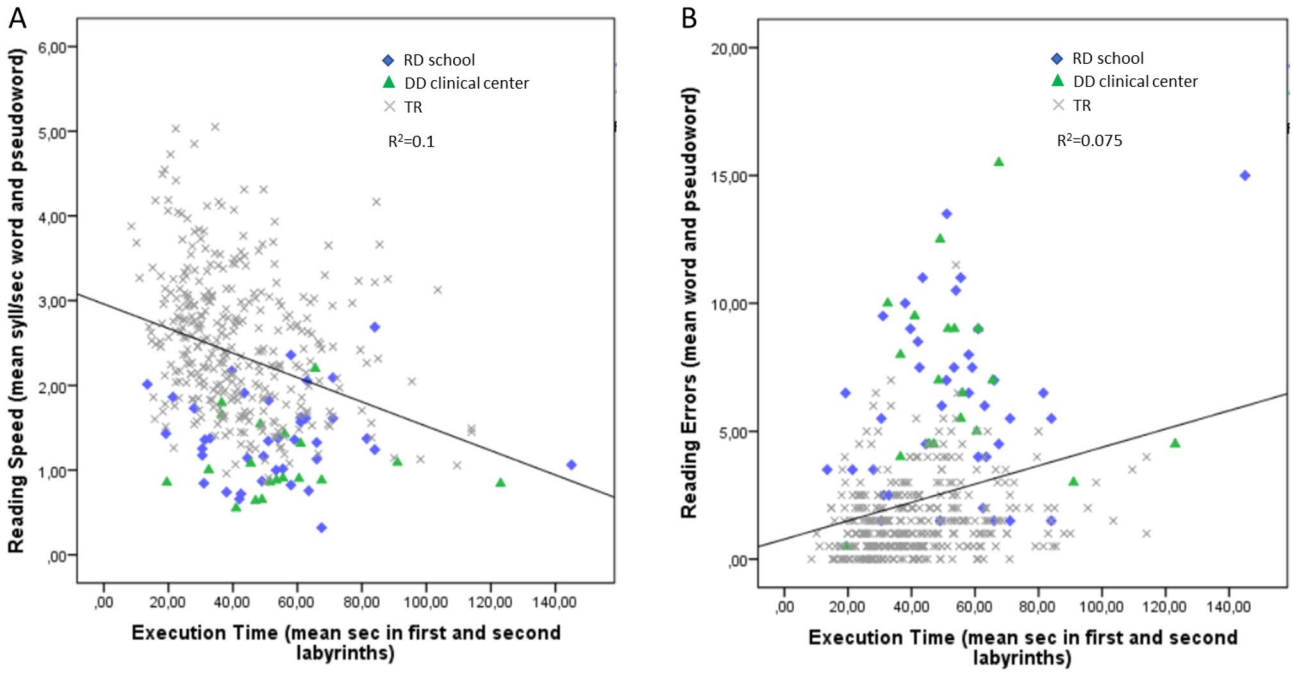

Figure 2. Panel (**A**) Representation of the bivariate correlation between the mean execution time in the first and second labyrinths and the mean of word and pseudoword reading speeds; Panel (**B**) Representation of the bivariate correlation between the mean execution time in the first and second labyrinths and the mean of word and pseudoword reading errors.

	2° grade (n = 82)	3° grade (n = 85)	4° grade (n = 87)	5° grade (n = 86)
Time (seconds)	44.11 (18.77)	44.64 (20.19)	37.42 (16.17)	38.3 (17.64)
Errors (number)	0.62 (0.76)	0.69 (0.87)	0.51 (0.82)	0.51 (0.80)

Table 4. Mean execution time (in seconds) and errors (mean and standard deviation) in labyrint one and two of the typical reader sample divided by school grade.

Visuo-spatial attention deficit in children with RDs: individual data and odds ratio analysis. In the labyrinths 1 and 2, 34.5% (20/58) of children with RDs showed a visuo-spatial attention performance below one SD in comparison to the mean execution time of TRs (see Table 4 for normative date in TRs).

The odds ratio was 3.13 (95% confidence interval between 1.68 and 5.81), indicating a moderate connection between the presence of RDs and a pure visuo-spatial attention deficit.

Discussion

A visuo-spatial attention dysfunction plays a pivotal role in the development of reading abilities hampering orthographic processing[16,17,26,28,29]; see[18] for a meta-analysis). We found a significant difference between children with and without RDs in visuo-attentional skills using a simple paper-and-pencil task in which no auditory-phonological abilities were involved.

Computational models of reading assume a form of graphemic parsing to achieve the level of representation on which the grapheme-to-phoneme conversion mechanism operates. Visual input is segmented into single letters that are serially and individually processed[61]. Other models assume segmentation into sublexical units that are assigned to specific slots according to their position in the syllable[62–64].

Regardless of how graphemic parsing is conceived, it requires primarily an efficient distributed visuo-spatial attention on entire letter-string, and then a focusing of visuo-spatial attention on each sublexical unit (single letter or letter cluster), inhibiting the flanking units[61]; see[18] for a meta-analysis).

Distributed and focused visuo-spatial attention are implicated also in visual search tasks[65]. Indeed, it has been demonstrated that visual search abilities—without involving any phonological skills—are good predictors of future reading skills both in shallow and deep orthographies[26–29,34], and visuo-spatial attention training by using action video games improves both visual search efficiency and reading skills in children with and without dyslexia[42,44].

However, visual search tasks require not only distributed and focused visuo-spatial attention but also working memory for the visual target as well as a correct matching between the specific target and the focused candidate item (see[65,66] for a review). Visual working memory is impaired in children with dyslexia[67]. Importantly, in the

labyrinth task all elements (Cs) that compose the visual paths are sequential targets that should be processed without the involvement of working memory, minimizing the possible effect of visual working memory deficits in our visual task. Thus, our findings show that pure visuo-spatial attention difficulties—regardless of visual working memory skills—seem to characterize children with RD.

The possible causal relationship between visuo-spatial attention and reading acquisition has been critically discussed by Goswami[68], because reading experience could directly affect visuo-spatial attention development. However, the absence of exclusive left-to-right attentional shifting characterising the reading direction in western orthographies, and the necessity of continue re-orienting of attention in all the directions in the Cs labyrinth task, excluded the possibility that this difference could be due to a simple practice effect linked to the habitual left-to-right attentional shifting trained during reading acquisition and consolidation[69].

The selective difference in execution times between the two groups in the first and second labyrinth shows the importance of good visuo-spatial attention abilities, rather than a general speed of processing deficit. Indeed, in the first two labyrinths, participants were forced–for each C, or each chunk of Cs–to shift their visuo-spatial attention focus rapidly. Note that although the second labyrinth required a larger number of passages than the first (as indicated by slower execution times), the difference between the two groups was similar. It seems that the number of passages is not sensitive to the visuo-spatial attention impairment shown in children with RD. However, a more sensitive index of attentional shifting difficulty could be measured considering the ratio between the total number of passages and the number of passages that require a change in attentional shifting. The two labyrinths were similar in this attentional shifting difficulty index. These data could explain why the performance difference between the two groups was not different in labyrinths 1 and 2. To test this possible interpretation, we could increase the attentional shifting difficulty index in the Cs labyrinth task to improve the visuo-spatial attention sensitivity in the embedded visual condition[26,66].

Independent from the group analysis, in which we chose a critical cutoff to divide children with and without RD, the results of the partial correlation analyses confirmed the relationship between visuo-spatial attentional processing and reading skills. Correlations between the execution times of the labyrinth task, word and pseudoword reading speeds and errors were significant only for the first two labyrinths that requested a higher level of visuo-spatial attentional abilities, confirming the specific link between fronto-parietal visuo-spatial attention and specialized occipito-temporal visual word form area[70,71].

Finally, individual data analysis showed that about 40% of children with RD are impaired in visuo-spatial attentional mechanisms measured by labyrinths 1 and 2, indicating the presence of attentional dysfunction in children with RD. It should be noted that the sensitivity of our labyrinth task to visuo-spatial attentional disorder could be improved with regard to increasing lateral visual noise and stressing the specific orienting and zooming attentional mechanisms required during this simple paper-and-pencil task. Thus, the labyrinth task appears to be a good tool to detect the presence of visuo-spatial attentional deficits in primary school children with RD and in children with other neurodevelopmental disorders associated with RD[1].

In the third labyrinth, performance was not different in the two groups. Although they were not directly informed that this labyrinth was identical to the first one, children with RD were able to improve their performance (i.e., take advantage of their previous experience), as seen in the TRs group. This result suggests that our sample of children with RD, in this task, shows adequate procedural learning skills and that the visuo-motor skills did not play a critical role in the determination of between-group differences found in the first two labyrinths. We cannot exclude that in other tasks, children with RD should show a procedural learning deficit[55]. It should be noted that difficulties in procedural learning that involve motor abilities seem to characterize children with language impairments rather than children with RD[72]. It could be speculated that developmental coordination and language disorders share impairments in procedural learning that could be associated with additional cerebellar or motor cortex deficits[50]. However, further studies are necessary to test this specific prediction.

Developmental coordination disorder and DD are often present in comorbidities[46,47]. Performance in the Labyrinth task, largely involving motor coordination abilities, could be influenced by the presence of a disorder in this area. Nevertheless, the difference between the first and third labyrinth could help clinicians to estimate the possible presence of a specific difficulty in visuo-spatial attention, motor skills or procedural learning. As shown in the correlation section, the visuo-spatial attention deficit indexes (measured through the delta of the execution time between 1st and 2nd administration of the same labyrinth) control not only the procedural learning skills, but also the visuo-motor skills intrinsically captured in the performance of the third labyrinth. A difficulty exclusively in the first two labyrinths can indicate a specific visual attentional difficulty. The presence of a deficit in the execution of the first two labyrinths combined with an absence of improvement between the execution time in the first and third labyrinth, could indicate a deficit in procedural learning or in motor coordination.

We could not consider the observed visuo-attentional deficit to be causally linked to the RD because of the cross-sectional design of this research[68]. However, a large overlap between the brain networks associated with the dynamic pattern of executing both reading and visuo-spatial attentional tasks has been observed[12,71,73]. Importantly, the structural connectivity networks associated with different aspects of skilled reading showed that interconnectivity between left hemisphere language and right hemisphere attentional areas underlies both lexical and sublexical reading[12]. Moreover, both training[26,33,34,36,37–41]; see[43] for a recent review) and longitudinal[26,28,29,33,34,59] studies have previously demonstrated the causal links between visuo-attentional deficits and RD.

Another limitation of this study is the absence of additional tasks that measured other possible neurocognitive deficits associated with RD in developmental dyslexia. Nevertheless, both training[33,36,37,74] and longitudinal studies[26–28,33,34,59] have previously demonstrated that the link between visuo-attentional disorders and RD was present also controlling for other neurocognitive (e.g., RAN and auditory-phonological) deficits typically associated with developmental dyslexia.

Since visuo-spatial attention is relevant for reading acquisition, and it is frequently dysfunctional in children with RD, its clinical evaluation is crucial for the correct identification of a specific training designed to

improve RD in neurodevelopmental disorders. Considering that different visuo-spatial attention interventions can improve reading skills in children with RD[34,36,38,39,41,74–77], see[43] for a review), an efficient reading remediation program should integrate auditory-phonological and visuo-attentional interventions.

Finally, in the present study the possible role of IQ in reading acquisition was not considered. However, the results linking IQ and reading development in children with RD are inconsistent[78–80].

In sum, we show that children with RD, compared to those with typical reading skills, appear to be characterized by a visual attentional deficit independent of visual working memory and motor procedural learning. In particular, visual spatial attentional deficits captured by our labyrinth task highlight that both distributed and focused spatial attention could be impaired in children with RD. These visual attentional mechanisms are fundamental for both lexical and sublexical reading pathways development[12,71,81,82].

Data availability

Data will be share on request to corresponding Authors: sandrofranceschini@gmail.com; andreafacoetti@unipd.it.

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Competing interests

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