NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD AGOSTO 2020

ACS Chemical Neuroscience. 2020;11:2094-103.

GENETIC VARIANTS AND HAPLOTYPES OF TRYPTOPHAN HYDROXYLASE 2 AND REELIN GENES MAY BE LINKED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN EGYPTIAN CHILDREN.

Abo El Fotoh WMM, Bayomy NR, Kasemy ZA, et al.

Attention-deficit hyperactivity disorder (ADHD) has been proposed to stem from multiple etiologies, perhaps genetic in nature with biological and psychosocial motivates. Tryptophan hydroxylase 2 (TPH2) and Reelin (RELN) genes may play a key role in triggering ADHD. The purpose of this case-controlled study was to explore the linkage of the genetic variants of TPH2 and RELN genes with ADHD. One hundred Egyptian children with ADHD and 105 age and sex matched controls constituted the study samples. Genotyping was performed for TPH2 (rs11179027; rs1843809) and RELN (rs736707; rs362691) gene polymorphisms using real time PCR assay. The alleles and genotype frequencies of TPH2 and RELN gene polymorphisms were assessed in all study participants. The frequencies of the alleles of TPH2 rs11179027 (OR = 1.75, 95% CI = 1.08-2.85, p = 0.022), TPH2 rs1843809 (OR = 3.67, 95% CI = 1.82-7.43, p = <0.001), and RELN rs736707 (OR = 1.61, 95% CI = 1.03-2.51, p = 0.035) were significantly associated with ADHD, while there was no significant difference between ADHD patients and controls regarding the frequency of RELN rs362691 (OR = 1.34, 95% CI = 0.73-2.48, p = 0.34). The frequencies of CTAG, CTGG, CTAC, CTGC, and GTAC haplotypes were significantly higher in ADHD patients than in controls (p = 0.011, 0.005, 0.015, 0.001, and 0.027, respectively). In conclusion, TPH2 rs11179027, TPH2 rs1843809, and RELN rs736707 gene alleles and haplotypes might be significantly correlated with the genetic susceptibility to ADHD in Egyptian children

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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.

Am J Med Genet A. 2019 Dec;179:2433-46.

EMOTIONAL FUNCTIONING AMONG CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 OR NOONAN SYNDROME.

McNeill AM, Hudock RL, Foy AMH, et al.

While neurofibromatosis type 1 (NF1) and Noonan syndrome (NS) are clinically distinct genetic syndromes, they have overlapping features because they are caused by pathogenic variants in genes encoding molecules within the Ras-mitogen-activated protein kinase signaling pathway. Increased risk for emotional and behavioral challenges has been reported in both children and adults with these syndromes. The current study examined parent-report and self-report measures of emotional functioning among children with NF1 and NS as compared to their unaffected siblings. Parents and children with NS (n = 39), NF1 (n = 39), and their siblings without a genetic condition (n = 32) completed well-validated clinical symptom rating scales. Results from parent questionnaires indicated greater symptomatology on scales measuring internalizing behaviors and symptoms of attention deficit hyperactivity disorder (ADHD) in both syndrome groups as compared with unaffected children. Frequency and severity of emotional and behavioral symptoms were remarkably similar across the two clinical groups. Symptoms of depression and anxiety were higher in children who were also rated as meeting symptom criteria for ADHD. While self-report ratings by children generally correlated with parent ratings, symptom severity was less pronounced. Among unaffected siblings, parent ratings indicated higher than expected levels of anxiety. Study findings may assist with guiding family-based interventions to address emotional challenges

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Am J Orthod Dentofacial Orthop. 2020 Apr;157:466-73.

PEDIATRIC SLEEP-DISORDERED BREATHING IN THE ORTHODONTIC POPULATION: PREVALENCE OF POSITIVE RISK AND ASSOCIATIONS.

Abtahi S, Witmans M, Alsufyani NA, et al.

INTRODUCTION: Pediatric sleep-disordered breathing (SDB) describes a spectrum of disease ranging from snoring to upper airway resistance syndrome and obstructive sleep apnea (OSA). Anatomical features assessed during orthodontic exams are often associated with symptoms of SDB in children. Hence, we need to determine the prevalence of positive risk for SDB in the pediatric orthodontic population compared with a general pediatric population and understand comorbidities associated with SDB risk among orthodontic patients.

METHODS: Responses from Pediatric Sleep Questionnaires were collected from 390 patients between the ages of 5 and 16Â years, seeking orthodontic treatment. Prevalence of overall SDB risk, habitual snoring, and sleepiness were determined in the orthodontic population and compared with those previously reported by identical methods in the general pediatric population. Additional health history information was used to assess comorbidities associated with SDB risk in 130 of the patients.

RESULTS: At 10.8%, the prevalence of positive SDB risk was found to be significantly higher in the general pediatric orthodontic population than in a healthy pediatric population (5%). The prevalence of snoring and sleepiness in the orthodontic population was 13.3% and 17.9%, respectively. Among the comorbidities, nocturnal enuresis (13.6%), overweight (18.2%), and attention deficit hyperactivity disorder (31.8%) had a higher prevalence in orthodontic patients with higher SDB risk (PÂ <Â 0.05).

CONCLUSIONS: There is a higher pediatric SDB risk prevalence in the orthodontic population compared with a healthy pediatric population. Orthodontic practitioners should make SDB screening a routine part of their clinical practice

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Am J Med Genet Part A. 2020.

BEHAVIOR AND COGNITIVE FUNCTIONING IN WITTEVEENΓÇôKOLK SYNDROME.

van Dongen LCM, Wingberm++hle E, Dingemans AJM, et al.

Witteveen-Kolk syndrome (WITKOS) is a rare neurodevelopmental disorder characterized by developmental delay/intellectual disability, facial dysmorphisms, and short stature. The syndrome is caused by loss of function of switch-insensitive 3 transcription regulator family member A (SIN3A). Regarding behavioral

functioning, Autism Spectrum Disorders (ASD), obsessive-compulsive behaviors, as well as Attention-Deficit/Hyperactivity Disorder symptoms (ADHD) have been suggested. The present study explores various aspects of neurocognitive functioning in five individuals (age range 10-23) with WITKOS. Medical records and results of extensive neuropsychological assessment are used to describe developmental trajectories and neurocognitive profiles. Systematic analysis of medical records displays developmental difficulties described as ASD or ADHD in childhood, sleep problems and internalizing problems during adolescence. Results of cognitive assessments indicate profoundly disabled (n = 1), mildly disabled (n = 2), borderline (n = 1), and average (n = 1) levels of intelligence. Furthermore, results indicate weaknesses in speed of information processing/sustained attention in all participants, and difficulties in planning and maintaining overview in three participants. Furthermore, parent reports of behavioral functioning primarily suggest problems in social functioning. Implications of both cognitive problems and socialΓÇôemotional vulnerabilities for counseling are discussed and supplemented with suggestions for interventions

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Anticancer Res. 2020 Aug;40:4755-62.

USEFUL CASES OF PATIENTS WITH DEVELOPMENTAL DISORDERS IMPROVED BY ORAL ADMINISTRATION OF LPS DERIVED FROM PANTOEA AGGLOMERANS.

Morishima A, Zhang R, Nagaoka T, et al.

BACKGROUND: Developmental disorders are associated with microglial dysfunction. Oral administration of lipopolysaccharide derived from Pantoea agglomerans bacteria (LPSp) leads to normalization of phagocytic activity of microglia and suppression of inflammation in mice. In this article, we report on a successful trial in which we achieved a significant improvement of symptoms in patients with developmental disorders.

PATIENTS AND METHODS: Five pediatric patients diagnosed with autism spectrum disorders (ASD)/attention deficit hyperactivity disorder (ADHD) who visited our clinic received either 0.75 or 1 mg/day LPSp for 6 months or more, in addition to our usual therapy regimens (detoxification therapy, nutritional therapy, and vibration therapy). A survey questionnaire was completed by the patients' parents and evaluated using the Numerical Rating Scale.

RESULTS: Behavior, verbal ability, and communication disabilities associated with ASD/ADHD improved in all patients.

CONCLUSION: Oral administration of LPSp may represent a new treatment option in the area of developmental disorders where there is currently no treatment available

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Arch Iran Med. 2019 May;22:225-31.

EPIDEMIOLOGY OF PSYCHIATRIC DISORDERS IN CHILDREN AND ADOLESCENTS IN CHAHARMAHAL AND BAKHTIARI PROVINCE, IRAN, 2017.

Safavi P, Mohammadi MR, Khaleghi A, et al.

BACKGROUND: This study aimed to investigate the epidemiology of psychiatric disorders in children and adolescents in Chaharmahal and Bakhtiari Province of Iran.

METHODS: This community-based cross-sectional study included 1038 children and adolescents aged 6-18 years from Chaharmahal and Bakhtiari province selected by the multistage cluster sampling method. Samples were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children. Also, demographic data (gender, age, child education, parent education, and economic situation) were obtained. Binary logistic regression was used to analyze the data.

RESULTS: A total of 16.1% of participants were diagnosed to have psychiatric disorders. Total psychiatric disorders were significantly more prevalent in boys than in girls (P=0.025). Unemployment of fathers was significantly related to increased prevalence of psychiatric disorders in children (P=0.016). Other demographic variables had no significant correlation with prevalence of psychiatric disorders in children. Anxiety disorders were highly comorbid with behavioral problems (16.4%). Behavioral disorders also had high comorbidity with elimination disorders (16.7%) and substance use disorders (10%). Enuresis was the most frequent psychiatric disorder (5.8%), followed by epilepsy (3.5%), tobacco use (3.4%), and attention

deficit hyperactivity disorder (3%). Total anxiety disorders were the most prevalent group of psychiatric disorders in the sample (21.9%), followed by behavioral disorders (16.3%), elimination disorders (8.2%), and neurodevelopmental disorders (4.5%).
CONCLUSION: Our findings suggest that psychiatric disorders affect a significant number of children and adolescents. Prevalence estimates and identification of sources of heterogeneity have important implications to service providers and modifications are needed in mental health services in the community

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Arq Neuro-Psiquiatr. 2011;69:630-35.
QUALITY OF LIFE AND PSYCHOMOTOR PROFILE OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).
Goulardins JB, Marques JCFB, Casella EB.
The knowledge of psychomotor development of children with attention deficit hyperactivity disorder (ADHD) may help in defining therapeutic approaches in order to minimize losses in their quality of life. The study objectives were to evaluate the quality of life and psychomotor profile of children with ADHD and check your correlation. Fourteen children, from seven to ten years, with ADHD combined type were evaluate using the scales PedsQLΓäó and Motor Development Scale. Results showed adverse effects of ADHD on quality of life and a deficit in motor skills. Nine participants (64.2%) were classified in motor development as "Normal Medium", followed by the classification "Normal Low" in four (28.5%) and "Low" in one subject (7.1%). We observed a positive correlation between quality of life and psychomotor development of children with ADHD, especially in areas: fine motor and spatial organization with social and psychosocial aspects, gross motor control with the emotional and temporal organization with the emotional, psychosocial and overall quality of life

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Asia-Pacific Psychiatry. 2020.
CROSS-CULTURAL TRANSLATION AND VALIDATION OF THE MALAY VERSION OF THE SWANSON, NOLAN, AND PELHAM PARENT RATING SCALE OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS SYMPTOMS AMONG MALAYSIAN PROBANDS: A PRELIMINARY STUDY.
Jusoh M, Dzulkarnain AAA, Rahmat S, et al.
The aim of this study is to evaluate the psychometric properties of the Malay version of the Swanson, Nolan, and Pelham Parent Rating Scale of attention deficit hyperactivity disorders (ADHD) symptoms (M-SNAP-IV). For this purpose, the SNAP-IV scale was translated into the Malay language and was pilot-tested on 91 parents of children aged 8 to 11 years (ADHD [n = 36] and non-ADHD children [n = 55]). The findings depicted that the M-SNAP-IV has excellent content validity, internal consistency, and test-retest reliability. The M-SNAP-IV is a valid and reliable screening tool to detect ADHD symptoms in children and has the advantages to assess the specific presentation of ADHD

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Australas Psychiatry. 2020.
A COMMUNITY SURVEY OF ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND THEIR EXPERIENCE OF MEDICATION EFFECTIVENESS.
Sandhu A, Toll J, Poulton A.
Objective: Survey of ADHD-affected adult participants attending educational meetings of ADDults with ADHD, to ascertain age of diagnosis and treatment effects of psychostimulant medication on symptoms across functional and emotional domains.
Method: From 2016 to 2019, self-assessments of functional impairment were collected from ADHD-affected adults attending educational meetings of an Australian community support organisation (ADDults with ADHD). Participants were asked to rate their functioning on and off medication. Some demographic and treatment details were also collected.

Results: Questionnaires were collected from 117 attendees of five meetings. Their mean age was 42.5 (SD 15.0) years; their age of diagnosis and of starting treatment were 31.9 (SD 16.6) and 32.8 (SD 16.4) years, respectively, with no significant differences between men and women. Most (93%) reported symptom onset before age 18. Ninety (77%) had been treated medically, with self-ratings indicating significantly less impairment on treatment ($p < 0.001$).
Conclusion: Adults with ADHD reported substantial impairment but significant benefit from medication. Despite a mean age of over 30 at diagnosis, most recalled being symptomatic in childhood. This suggests many may experience a prolonged period of impaired function before starting treatment

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Behav Ther. 2020 Jan;51:27-41.
A Review of Pediatric Nonpharmacological Sleep Interventions: Effects on Sleep, Secondary Outcomes, and Populations With Co-occurring Mental Health Conditions.
Bourchtein E, Langberg JM, Eadeh HM.
Sleep problems are common in school-age children and linked to numerous negative outcomes. Sleep disturbances are particularly common in children with mental health disorders, such as attention-deficit/hyperactivity disorder, depression, and anxiety. Despite frequent use of nonpharmacological pediatric sleep interventions to treat common sleep problems, there is a paucity of research on whether these interventions are effective. Further, it is unclear whether by targeting sleep, these interventions lead to broader improvements in the domains of functioning that are commonly affected by poor sleep. The present review includes 20 studies that evaluated nonpharmacological sleep treatments for school-aged youth, including 5 studies specifically focused on youth with externalizing or internalizing problems. Multimodal approaches consisting of psychoeducation and sleep hygiene in combination with other components were effective at treating insomnia and general sleep problems in typically developing samples. The addition of behavioral parent training to sleep interventions was effective for youth with externalizing problems, whereas incorporating cognitive strategies into sleep interventions for youth with internalizing problems was found to be ineffective. A variety of secondary outcomes were examined, with the strongest support emerging for improvement in anxiety and behavioral problems. Implications for clinical practice and future research directions are discussed

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Biol Psychiatry. 2020.
Adolescent Attention-Deficit/Hyperactivity Disorder: Understanding Teenage Symptom Trajectories.
Shaw P, Sudre G.
Symptoms of attention-deficit/hyperactivity disorder (ADHD) run a variable course through adolescence. While most affected individuals show some improvement, particularly of hyperactivity-impulsivity, symptoms of inattention are more persistent, and some individuals may meet diagnostic criteria for the first time during adolescence. Genetic factors affect adolescent symptom trajectories; those showing persistence likely carry a greater burden of common risk alleles. Rare structural genomic variants, such as copy number variants and point mutations, might also play a role. Although psychostimulant medication is associated with better functional outcomes, an impact on underlying adolescent symptom trajectories has been hard to demonstrate. At a neural level, several studies report that adolescents whose childhood ADHD symptoms have remitted are indistinguishable from neurotypical individuals. This finding could reflect the carrying forward of relatively typical childhood neural features among those destined for adolescent remission or the correction of early childhood anomalies with a convergence toward typical dimensions. Other studies have noted unique, possibly compensatory patterns of neural activity among adolescents whose ADHD has improved. Finally, different neural processes might occur in different brain regions. Thus, some functional imaging studies find that subcortical anomalies reflect the onset of ADHD and remain throughout life regardless of symptom change, whereas the variable clinical course of adolescent ADHD is determined by

plasticity of the cerebral cortex. Integrating an understanding of the neural processes with genomic risk could elucidate the mechanisms underlying the complex course of adolescent ADHD

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Biol Psychiatry. 2020.

ESTIMATING THE HERITABILITY OF DEVELOPMENTAL CHANGE IN NEURAL CONNECTIVITY, AND ITS ASSOCIATION WITH CHANGING SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sudre G, Bouyssi-Kobar M, Norman L, et al.

Background: Twin studies show that age-related change in symptoms of attention-deficit/hyperactivity disorder (ADHD) is heritable. However, we do not know the heritability of the development of the neural substrates underlying the disorder. Here, we estimated the heritability of developmental change in white matter tracts and the brain's intrinsic functional connectivity using longitudinal data. We further determined associations with change in ADHD symptoms.

Methods: The study reports on 288 children, which included 127 siblings, 19 cousins, and 142 singletons; 150 (52%) had a diagnosis of ADHD (determined by clinician interview with parent); 188 were male. All had two clinical assessments (overall baseline mean age: 9.4 -¦ 2.4 years; follow-up: 12.5 -¦ 2.6 years). Diffusion tensor imaging estimated microstructural properties of white matter tracts on 252 participants. Resting-state functional magnetic resonance imaging estimated intrinsic connectivity within and between major brain networks on 226 participants. Total additive genetic heritability (h2) of the annual rate of change in these neural phenotypes was calculated using SOLAR (Sequential Oligogenic Linkage Analysis Routines).

Results: Significant heritability was found for the rates of change of 6 white matter tract microstructural properties and for change in the connectivity between the ventral attention network and both the cognitive control and dorsal attention networks. Change in hyperactivity-impulsivity was associated with heritable change in white matter tracts metrics and change in the connectivity between the ventral attention and cognitive networks.

Conclusions: The relatively small number of heritable, ADHD-associated developmental neural phenotypes can serve as phenotypes for future gene discovery and understanding

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Biol Psychiatry. 2020.

MICROSTRUCTURE OF THE DORSAL ANTERIOR CINGULUM BUNDLE IN VERY PRETERM NEONATES PREDICTS THE PRETERM BEHAVIORAL PHENOTYPE AT 5 YEARS OF AGE.

Brenner RG, Smyser CD, Lean RE, et al.

Background: The cingulum bundle (CB), specifically the dorsal anterior portion of the CB, plays an important role in psychiatric illnesses; however, its role during early development is unclear. This study investigated whether neonatal white matter microstructure in the CB and its subregions is associated with subsequent preterm behavioral phenotype symptoms (internalizing, inattention, and social deficits) in very preterm (VPT) children.

Methods: Diffusion magnetic resonance imaging data were obtained on a 3T scanner in 138 sleeping nonsedated neonates: 55 full-term neonates (gestational age ΓëÑ 36 weeks) and 83 VPT neonates (gestational age < 30 weeks). The CB was tracked using probabilistic tractography and split into anterior and posterior portions. When children were 5 years of age, parents (n = 80) and teachers (n = 63) of VPT children completed questionnaires of preterm behavioral phenotype symptoms. Linear regression models were used to relate measures of neonatal CB microstructure and childhood preterm behavioral phenotype symptoms (n = 56 parent report, n = 45 teacher report).

Results: Mean diffusivity in the anterior and posterior CB was increased in VPT neonates compared with full-term neonates. Increased fractional anisotropy and decreased mean diffusivity in the right anterior CB, but not in the posterior CB, were related to increased preterm behavioral phenotype symptoms in VPT children as reported by parents and teachers.

Conclusions: Aberrations in the anterior portion of the right CB may underlie the early development of the preterm behavioral phenotype. This finding provides the foundation for future mechanistic and therapeutic investigations into the role of the anterior cingulum in the development of psychopathology in VPT infants

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Biol Psychiatry. 2020.

DEVELOPMENT OF DISORDERED EATING BEHAVIORS AND COMORBID DEPRESSIVE SYMPTOMS IN ADOLESCENCE: NEURAL AND PSYCHOPATHOLOGICAL PREDICTORS.

Zhang Z, Robinson L, Jia T, et al.

Background: Eating disorders are common in adolescence and are devastating and strongly comorbid with other psychiatric disorders. Yet little is known about their etiology, knowing which would aid in developing effective preventive measures.

Methods: Longitudinal assessments of disordered eating behaviors (DEBs)ΓÇöbinge-eating, purging, and dieting-and comorbid psychopathology were measured in 1386 adolescents from the IMAGEN study. Development of DEBs and associated mental health problems was investigated by comparing participants who reported symptoms at ages 16 or 19 years, but not at age 14 years, with asymptomatic control participants. Voxel-based morphometry and psychopathological differences at age 14 were investigated to identify risk factors for the development of DEBs and associated mental health problems.

Results: DEBs and depressive symptoms developed together. Emotional and behavioral problems, including symptoms of attention-deficit/hyperactivity disorder and conduct disorder, predated their development. Alterations in frontostriatal brain areas also predated the development of DEBs and depressive symptoms. Specifically, development of binge-eating was predicted by higher gray matter volumes in the right putamen/globus pallidus at age 14. Conversely, development of purging and depressive symptoms was predicted by lower volumes in the medial orbitofrontal, dorsomedial, and dorsolateral prefrontal cortices. Lower gray matter volumes in the orbitofrontal and anterior cingulate cortices mediated the relationship between attention-deficit/hyperactivity disorder and conduct disorder symptoms and future purging and depressive symptoms.

Conclusions: These findings suggest that alterations in frontal brain circuits are part of the shared etiology among eating disorders, attention-deficit/hyperactivity disorder, conduct disorder, and depression and highlight the importance of a transdiagnostic approach to treating these conditions

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2020.

REDUCED ACTIVATION IN THE PALLIDAL-THALAMIC-MOTOR PATHWAY IS ASSOCIATED WITH DEFICITS IN REWARD-MODULATED INHIBITORY CONTROL IN ADULTS WITH A HISTORY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jones NP, Versace A, Lindstrom R, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) symptoms persist into adulthood and are associated with functional impairments. Neuroimaging studies of reward-modulated inhibitory control can identify potential objective markers of impairment and may deepen our understanding of why probands engage in costly behaviors leading to adverse outcomes. The study aimed to identify reward-modulated inhibitory control neural circuitries, their association with ADHD symptoms, and real-world implications of a decreased capacity to engage in reward-modulated inhibitory control.

Methods: A total of 106 adults (90% male) with rigorous childhood diagnoses of ADHD were scanned with functional magnetic resonance imaging during the Monetary Incentive Go/NoGo task. Adulthood symptoms of inattention and hyperactivity/impulsivity based on self- and informant report were assessed. The number of lifetime attempts taken to quit smoking were also assessed as an exemplar real-world outcome.

Results: Hyperactivity/impulsivity was negatively associated with activation in the pallidum and primary motor cortex when inhibiting a previously rewarded Go stimulus that yielded a small immediate reward in order to obtain a larger reward later on. Reduced recruitment of the pallidal-thalamic-motor circuit mediated the negative association between hyperactivity/impulsivity and reward-modulated inhibitory control accuracy.

Reduced pallidum activation, in response to reward-modulated inhibitory control, was also associated with more attempts made to successfully quit smoking.
Conclusions: Probands with persistent hyperactivity/impulsivity symptoms have alterations in brain regions that calculate the value of inhibiting an action that yields an immediate reward in order to obtain delayed larger rewards. This deficit results in poor inhibitory control on basic tasks and during real-world behaviors that rely on similar processes

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BMC Med Res Methodol. 2019 Aug;19:179.

HOW TO MEASURE THE NEED FOR TRANSITION TO ADULT SERVICES AMONG YOUNG PEOPLE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A COMPARISON OF SURVEILLANCE VERSUS CASE NOTE REVIEW METHODS.

Eke H, Janssens A, Downs J, et al.

BACKGROUND: Health services have not provided adequate support for young people with long term health conditions to transfer from child to adult services. National Institute of Health and Care (NICE) guidance on transition has been issued to address these gaps. However, data are often sparse about the number of young adults who might need to transition. Using Attention Deficit Hyperactivity Disorder (ADHD) as an exemplar, this study used an existing surveillance system and a case note review to capture the incidence of the transition process, and compared and contrasted the findings.
METHODS: The Child and Adolescent Psychiatry Surveillance System (CAPSS) was used to estimate the incident transition of young people with Attention Deficit Hyperactivity Disorder (ADHD) from child to adult services. This involves consultant child and adolescent psychiatrists from the United Kingdom (UK) and Republic of Ireland (ROI) reporting relevant young people as they are seen in clinics. In parallel, a case note review was conducted using the Maudsley Biomedical Research Centre (BRC) Clinical Records Interactive Search (CRIS). The study period ran for twelve months with a nine month follow up to see how the transition proceeded.
RESULTS: CRIS identified 76 cases in the study period, compared to 18 identified using surveillance via CAPSS. Methodological issues were experienced using both methods. Surveillance issues; eligibility criteria confusion, reporting errors, incomplete questionnaires, difficulties contacting clinicians, and surveillance systems do not cover non-doctors and psychiatrists who are not consultants. Case note review issues using CRIS included the need for researchers to interpret clinical notes, the availability and completeness of data in the notes, and data limited to the catchment of one particular mental health trust.
CONCLUSIONS: Both methods demonstrate strengths and weaknesses; the combination of both methods in the absence of strong routinely collected data, allowed a more robust estimate of the level of need for service planning and commissioning

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BMC Pediatr. 2019 Nov;19:406.

HETEROGENEOUS NEURODEVELOPMENTAL DISORDERS IN CHILDREN WITH KAWASAKI DISEASE: WHAT IS NEW TODAY?

Lin CH, Lin WD, Chou IC, et al.

BACKGROUND: Kawasaki disease (KD) is a common vasculitis of childhood in East Asia. The complications of KD ascribed to long-term cardiovascular sequelae are considerably diverse. Although studies have investigated neurodevelopmental problems following KD in the past few decades, they have reported inconsistent conclusions. This study investigated potential epilepsy and associated neurodevelopmental disorders (NDDs) following KD in Taiwanese children.
METHODS: We retrospectively analyzed the data of children aged <18 years with clinically diagnosed KD from January 1, 2005, to December 31, 2015. These patients were followed up to estimate the prevalence of epilepsy and associated NDDs in comparison with the prevalence in general pediatric population in Taiwan and worldwide.
RESULTS: A total of 612 patients with an average age of 1.6 years were included. The prevalence of associated NDDs was 16.8% (n=103/612) in the study group, which consisted of epilepsy, intellectual

disability (ID), autism spectrum disorders, Tourette syndrome (TS), attention deficit hyperactivity disorder, (ADHD), and others. Moreover, children with KD had a higher prevalence of epilepsy and TS in both Taiwan and worldwide (epilepsy: 2.61% in the KD group vs 0.33% in Taiwan and 0.05-0.8% in worldwide, $p<0.05$; TS: 2.77% in the KD group vs 0.56% in Taiwan and 0.3-1% in worldwide, $p<0.05$). The prevalence of ID, ADHD, and developmental language disorders was not significantly different between our study patients and those in Taiwan or worldwide.
CONCLUSIONS: Results revealed a higher prevalence rate of NDDs, especially epilepsy and TS, in Taiwanese children with KD than in the general pediatric population in Taiwan. However, these NDDs could be heterogeneous. Children diagnosed with KD were followed up because they had a higher risk of heterogeneous NDDs

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BMC Pediatr. 2019;19.

TRANSDIAGNOSTIC ASSOCIATIONS ACROSS COMMUNICATION, COGNITIVE, AND BEHAVIOURAL PROBLEMS IN A DEVELOPMENTALLY AT-RISK POPULATION: A NETWORK APPROACH.

Mareva S, Holmes J.

Background: Communication, behavioural, and executive function problems often co-occur in childhood. Previous attempts to identify the origins of these comorbidities have typically relied on comparisons of different deficit groups and/or latent variable models. Here we apply a network approach to a heterogeneous sample of struggling learners to conceptualise these comorbidities as a dynamic system of interacting difficulties.
Methods: 714 children struggling with attention, learning, and/or memory were included. The sample consisted of children with both diagnosed (41%) and undiagnosed difficulties. The conditional independence network of parent ratings of everyday behaviour, cognition, and communication was estimated.
Results: A clustering coefficient identified four interconnected areas of difficulty: (1) structural language and learning; (2) pragmatics and peer relationships; (3) behavioural and emotional problems; and (4) cognitive skills. Emotional and behavioural symptoms shared multiple direct connections with pragmatic abilities and cognitive problems, but not with structural language skills or learning problems. Poor structural language and cognitive skills were associated with learning problems. Centrality indices highlighted working memory and language coherence as symptoms bridging different problem areas.
Conclusion: The network model identified four areas of difficulty and potential bridging symptoms. Although the current analytic framework does not provide causal evidence, it is possible that bridging symptoms may be the origins of comorbidities observed on a dimensional level; problems in these areas may cascade and activate problems in other areas of the network. The potential value of applying a dynamic systems network approach to symptoms of developmental disorders is discussed

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BMC Psychiatry. 2019;19.

A REVIEW OF CHANGES TO THE ATTENTION DEFICIT/HYPERACTIVITY DISORDER AGE OF ONSET CRITERION USING THE CHECKLIST FOR MODIFYING DISEASE DEFINITIONS.

Sanders S, Thomas R, Glasziou P, et al.

Background: Widening definitions of health conditions have the potential to affect millions of people and should only occur when there is strong evidence of benefit. In the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the DSM-5 Committee changed the Attention Deficit Hyperactivity Disorder (ADHD) age of onset criterion in two ways: raising the age of symptom onset and removing the requirement for symptoms to cause impairment. Given concerns about ADHD prevalence and treatment rates, we aimed to evaluate the evidence available to support these changes using a recently developed Checklist for Modifying Disease Definitions.
Methods: We identified and analysed research informing changes to the DSM-IV-TR ADHD age of onset criterion. We compared this evidence to the evidence recommended in the Checklist for Modifying Disease Definitions.

Results: The changes to the DSM-IV-TR age of onset criterion were based on a literature review (publicly available as a 2 page document with online table of included studies), which we appraised as at high risk of bias. Estimates of the change in ADHD prevalence resulting from change to the age of onset criterion were based on a single study that included only a small number of children with ADHD (n = 68) and only assessed the impact of change to the age component of the criterion. No evidence was used by, or available to the Committee regarding the impact on prevalence of removal of the requirement for impairment, or the effect of the criterion changes on diagnostic precision, the prognosis of, or the potential benefits or harms for individuals diagnosed by the new, but not old criterion.
Conclusions: The changes to the age of onset criterion were based on minimal research evidence that suffered from either high risk of bias or poor applicability. The minimal documentation available makes it difficult to judge the rigor of the process behind the criterion changes. Use of the Checklist for Modifying Disease Definitions would assist future proposed modifications of the DSM ADHD criteria, provide guidance on the studies needed to inform potential changes and would improve the transparency and documentation of the process

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BMC Psychiatry. 2020;20.

THE ADHD TEEN INTEGRATIVE DATA ANALYSIS LONGITUDINAL (TIDAL) DATASET: BACKGROUND, METHODOLOGY, AND AIMS.

Sibley MH, Coxe SJ.

Background: The Attention Deficit Hyperactivity Disorder (ADHD) Teen Integrative Data Analysis Longitudinal (TIDAL) dataset integrates data from four randomized trials.
Method: Participants with ADHD (N = 854; 72.5% male, 92.5% racial/ethnic minority, ages 10-17) were assessed three times across 12 months. Data includes parent, self, and teacher ratings, observations, and school records. The battery was harmonized using an Integrative Data Analysis (IDA) approach to form variables that assign unique values to all participants.
Results: The data will be used to investigate: (1) profiles that organize the heterogeneous population into clinically meaningful subgroups, (2) whether these profiles predict treatment response, (3) heterogeneity in treatment response and variables that predict this response, (4) how treatment characteristics and adjunctive supports predict treatment response, and (5) mediators of treatment and whether these mechanisms are moderated by treatment characteristics.
Conclusions: The ADHD TIDAL Dataset will be openly shared with the field to maximize its utility

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Brain Sciences. 2020;10:1-14.

ACTIGRAPH-MEASURED MOVEMENT CORRELATES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS IN YOUNG PEOPLE WITH TUBEROUS SCLEROSIS COMPLEX (TSC) WITH AND WITHOUT INTELLECTUAL DISABILITY AND AUTISM SPECTRUM DISORDER (ASD).

Earnest T, Shephard E, Tye C, et al.

Actigraphy, an objective measure of motor activity, reliably indexes increased movement levels in attention-deficit/hyperactivity disorder (ADHD) and may be useful for diagnosis and treatment-monitoring. However, actigraphy has not been examined in complex neurodevelopmental conditions. This study used actigraphy to objectively measure movement levels in individuals with a complex neurodevelopmental genetic disorder, tuberous sclerosis (TSC). Thirty participants with TSC (11ΓÇô21 years, 20 females, IQ = 35ΓÇô108) underwent brief (approximately 1 h) daytime actigraph assessment during two settings: movie viewing and cognitive testing. Multiple linear regressions were used to test associations between movement measurements and parent-rated ADHD symptoms. Correlations were used to examine associations between actigraph measures and parent-rated ADHD symptoms and other characteristics of TSC (symptoms of autism spectrum disorder (ASD), intellectual ability (IQ), epilepsy severity, cortical tuber count). Higher movement levels during movies were associated with higher parent-rated ADHD symptoms. Higher ADHD symptoms and actigraph-measured movement levels during movies were positively associated with ASD

symptoms and negatively associated with IQ. Inter-individual variability of movement during movies was not associated with parent-rated hyperactivity or IQ but was negatively associated with ASD symptoms. There were no associations with tuber count or epilepsy. Our findings suggest that actigraph-measured movement provides a useful correlate of ADHD in TSC

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Brain Sciences. 2020;10:1-16.

THE ROLE OF EXECUTIVE FUNCTIONS IN THE DEVELOPMENT OF EMPATHY AND ITS ASSOCIATION WITH EXTERNALIZING BEHAVIORS IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS AND OTHER PSYCHIATRIC COMORBIDITIES.

Cristofani C, Sesso G, Cristofani P, et al.

Executive functions have been previously shown to correlate with empathic attitudes and prosocial behaviors. People with higher levels of executive functions, as a whole, may better regulate their emotions and reduce perceived distress during the empathetic processes. Our goal was to explore the relationship between empathy and executive functioning in a sample of children and adolescents diagnosed with Attention Deficit and Hyperactivity Disorder alone or associated with comorbid Disruptive Behavior Disorders and/or Autism Spectrum Disorder. We also aimed to examine the role of empathic dimensions and executive skills in regulating externalizing behaviors. The 151 participants with ADHD were assigned to four groups according to their psychiatric comorbidity (either ΓÇ£pureΓÇØ or with ASD and/or ODD/CD) and assessed by means of either parent-or self-reported questionnaires, namely the BRIEFΓêÆ2, the BES, and the IRI. No questionnaire was found to discriminate between the four groups. Affective Empathy was found to positively correlate with Emotional and Behavioral Regulation competences. Furthermore, Aggressiveness and Oppositional Defiant Problems were positively associated with Executive Emotional and Behavioral Regulation competences. On the other hand, Rule-Breaking Behaviors and Conduct Problems were negatively associated with Affective Empathy and with Behavioral skills. Our study provides an additional contribution for a better understanding of the complex relationship between empathic competence and executive functions, showing that executive functioning and empathic attitudes interact with each other to regulate aggressive behaviors. This study further corroborates developmental models of empathy and their clinical implications, for which externalizing behaviors could be attenuated by enhancing executive functioning skills

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Brain Behav Immun. 2020.

EVALUATION OF MATERNAL INFLAMMATION AS A MARKER OF FUTURE OFFSPRING ADHD SYMPTOMS: A PROSPECTIVE INVESTIGATION.

Gustafsson HC, Sullivan EL, Battison EAJ, et al.

Early life predictors of attention-deficit/hyperactivity disorder (ADHD) are critically needed; they could inform etiological theory and may help identify new prevention targets. The current study examined prospectively whether maternal cytokine levels during pregnancy predict offspring ADHD symptoms at age 4ΓÇô6 years. Secondarily, we evaluated maternal cytokine levels as a possible common pathway through which prenatal risks exert influence on child ADHD. Data came from a sample of women recruited during the 2nd trimester of pregnancy (N = 62) and followed postnatally until children were 4ΓÇô6 years old. Maternal inflammation was assessed using 3rd trimester plasma concentrations of three indicators of nuclear factor kappa B signaling: interleukin-6, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1 which were combined into a latent variable. Mothers and teachers reported on child ADHD symptoms, negative affect, and externalizing behaviors at 48ΓÇô72 months of age. Maternal inflammation in the 3rd trimester predicted ADHD symptoms when children were 4ΓÇô6 years old (+¦ = 0.53, 95% CI = 0.154, 0.905, p = 0.006). Further, maternal inflammation mediated the effect of prenatal distress on child ADHD (+¦ = 0.21, 95% CI = 0.007, 0.419, p = 0.04). The inflammation effect on ADHD was not explained by concurrent child negative affect, externalizing behavior, or familial ADHD status. This is the first human study to prospectively link maternal pregnancy cytokine levels and offspring ADHD symptoms, suggesting that cytokine levels are a possible

marker of ADHD risk. Results also provide new evidence that maternal prenatal inflammation may be one common pathway by which prenatal risk factors influence offspring mental health outcomes

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Can J Psychiatry. 2019 Apr;64:246-55.

SIX-MONTH PREVALENCE OF MENTAL DISORDERS AND SERVICE CONTACTS AMONG CHILDREN AND YOUTH IN ONTARIO: EVIDENCE FROM THE 2014 ONTARIO CHILD HEALTH STUDY.

Georgiades K, Duncan L, Wang L, et al.

OBJECTIVES: To present the 6-month prevalence and sociodemographic correlates of mental disorders and mental health-related service contacts in a sample of children (4 to 11 years) and youth (12 to 17 years) in Ontario.

METHODS: The 2014 Ontario Child Health Study is a provincially representative survey of 6537 families with children aged 4 to 17 years in Ontario. DSM-IV-TR mental disorders were assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) and included mood (major depressive episode), anxiety (generalized anxiety, separation anxiety, social phobia, specific phobia), and behaviour disorders (attention-deficit/hyperactivity disorder, oppositional-defiant disorder, conduct disorder).The MINI-KID was administered independently to the primary caregiver and youth aged 12 to 17 years in the family's home.

RESULTS: Past 6-month prevalence of any mental disorder ranged from 18.2% to 21.8% depending on age and informant. Behaviour disorders were the most common among children, and anxiety disorders were the most common among youth. Among children and youth with a parent-identified mental disorder, 25.6% of children and 33.7% of youth had contact with a mental health provider. However, 60% had contact with one or more of the providers or service settings assessed, most often through schools.

CONCLUSIONS: Between 18% and 22% of children and youth in Ontario met criteria for a mental disorder but less than one-third had contact with a mental health provider. These findings provide support for strengthening prevention and early intervention efforts and enhancing service capacity to meet the mental health needs of children and youth in Ontario

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Child Adolesc Psychiatr Clin North Am. 2020.

MEASUREMENT-BASED CARE IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DISRUPTIVE BEHAVIOR DISORDERS.

Higdon C, Blader J, Kalari VK, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric diagnoses. The core symptoms of ADHD include inattention, impulsivity, and hyperactivity. ADHD entails impairments that have extensive and profound detrimental effects on many critical developmental areas. As a valid neurobiologic condition that causes significant impairments in those affected, it is one of the best-researched disorders in medicine. Measurement-based care in treatment of ADHD is critical in establishing a diagnosis, determining a treatment target, and assessing treatment response. This article highlights the rationale for measurement-based care in ADHD, how to implement measurement-based care in clinical practice, and common challenges encountered

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Child Adolesc Psychiatry Ment Health. 2020;14.

SYMPTOMS AND LEVEL OF FUNCTIONING RELATED TO COMORBIDITY IN CHILDREN AND ADOLESCENTS WITH ADHD: A CROSS-SECTIONAL REGISTRY STUDY.

Elwin M, Elvin T, Larsson JO.

Background: It is well known that a wide range of psychiatric disorders co-occur with attention deficit hyperactivity disorder. In this study we aimed to examine the associations of psychiatric comorbidity in ADHD with symptom severity and level of functioning.

Methods: We used data from the Swedish National Quality Registry for ADHD Treatment Follow-up and identified comorbid diagnoses in a sample of 3246 Swedish children and adolescents with ADHD. We investigated the association of comorbidity with symptom severity and level of function by multiple linear regressions.
Results: Autism spectrum disorder, anxiety and affective disorders, oppositional defiant disorder or conduct disorder, learning disorders, and multiple comorbid disorders associate to lower levels of functioning compared to ADHD only. Multiple comorbidity, autism spectrum disorder, oppositional defiant or conduct disorders and tic disorders relate to ADHD symptom severity.
Conclusions: Comorbidity subgroups with ADHD differ in functional impairment and ADHD symptoms severity. Information on comorbidity profiles could be used for treatment planning more adapted to the individual. Especially those who have autism spectrum disorders and multiple comorbid disorders are at risk of severe ADHD symptoms and low level of functioning

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Child Care Health Dev. 2019 Sep;45:688-93.
THE ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER SEVERITY AND RISK OF MILD TRAUMATIC BRAIN INJURY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE UNITED STATES OF AMERICA: A CROSS-SECTIONAL STUDY OF DATA FROM THE NATIONAL SURVEY OF CHILDREN WITH SPECIAL HEALTH CARE NEEDS.
Karic S, DesRosiers M, Mizrahi B, et al.
BACKGROUND: As children with attention deficit hyperactivity disorder (ADHD) have shown to be at higher risk of accidents and injury, one may assume that they may also bear a higher likelihood of mild traumatic brain injuries (mTBI). However, the current scientific evidence whether ADHD severity is associated with traumatic brain injuries is controversial. The objective of this study was too assess the association between the severity of ADHD and prevalence of mTBI in 0- to 18-year-old children with ADHD in the United States.
METHODS: Cross-sectional study using secondary data gathered in 2009/10 from the National Survey of Children with Special Healthcare Needs. After excluding comorbidity and those with nonspecific attention deficits, the final study population consisted of 10,739 children with ADHD from 40,052 households. The main exposure variable was self-reported ADHD severity (mild, moderate, or severe). The main outcome was mTBI, defined as head injury, traumatic brain injury, and/or concussion). Covariates included age, gender and race, medication status. Unadjusted and adjusted logistic regression analysis were used.
RESULTS: Children with more severe ADHD had consistently increased incidences of mTBI. Adjusted logistic regression analysis revealed a statistically significant association between severity of ADHD and occurrence of mTBI. The corresponding odds ratios were 1.57 (95% confidence interval (CI) [1.13, 2.18] for moderate, and 1.79 (95% CI [1.18, 2.72]) for severe ADHD, respectively, compared with mild ADHD. In males, children with moderate and severe ADHD had increased odds of mTBI. The corresponding odds ratio for mTBI in those with moderate ADHD was 1.60 (95% CI [1.07, 2.39]) and 1.86 (95% CI [1.15, 3.00]) for severe ADHD, respectively. No associations between severity and mTBI were found in girls.
CONCLUSIONS: As ADHD severity was associated with incidence of mTBI, it is important to identify those who need increased attention and counselling to prevent injury

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Child Neuropsychol. 2020.
TIME PERCEPTION IN CHILDREN WITH ATTENTION DEFICITΓÇôHYPERACTIVITY DISORDER (ADHD): DOES TASK MATTER? A META-ANALYSIS STUDY.
Nejati V, Yazdani S.
We aimed to assess the effects of the nature of the task on time perception deficit (TPD) in children with attention deficitΓÇôhyperactivity disorder (ADHD). The inconsistent results from 12 studies in children with ADHD revealed that the problem of time estimation was more obvious in prospective tasks in long-duration intervals. The modality is not a decisive factor. Only two studies reported the subtypes of ADHD that showed TPD in all subtypes. Children with ADHD have difficulties in time perception (TP). The problem is obvious in

different types of modality including visual and auditory, in different types of task time estimation, time reproduction, and especially in longer duration

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Clin Child Fam Psychol Rev. 2019 Dec;22:527-48.

A Systematic Review and Evaluation of Clinical Practice Guidelines for Children and Youth with Disruptive Behavior: Rigor of Development and Recommendations for Use.

Andrade BF, Courtney D, Duda S, et al.

Clinical practice guidelines (CPG) provide a framework for evidence-based practice; however, few studies have assessed the methodological quality of CPGs relevant to child and youth mental health. This study was a systematic review of CPGs for the assessment, prevention and treatment of disruptive behavior, including attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD) and aggression in children and youth. Systematic review identified 29 CPGs meeting inclusion criteria that were appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) validated tool. Twenty-two guidelines addressed ADHD, 2 CD, 1 ODD, 2 for Behavior Disorders collectively and 2 for Aggression. Among the 29 guidelines, two that were developed for ADHD (NICE 2013a; Spanish Ministry of Health, 2010) and one practice guideline developed for CD (NICE 2013b) met high quality criteria; one guideline for behavior disorders (Gorman et al. 2015), two for ADHD (AAP 2011a, b; SIGN 2009a, b, c, d, e), and two for aggression (Knapp et al. 2012; Scotto Rosato et al. 2012a, b) met minimum quality criteria. Findings from this review provide important information for clinicians and organizations who want to utilize guidelines to implement best-practice clinical services for children and youth with disruptive behavior

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Clin Neuropharmacol. 2020;43:114-15.

Skin Picking Successfully Treated with Atomoxetine in Comorbid Skin Picking and Attention-Deficit/Hyperactivity Disorder: A Case Report.

Yurteri N, Sarigedik E.

"Skin picking disorder"(SPD: also known as neurotic excoriation, psychogenic excoriation, or dermatillomania) is classified in the "obsessive-compulsive and related disorders"category in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and characterized by unintentional, repetitive skin picking behaviors. Atomoxetine is a selective noradrenaline reuptake inhibitor used in the treatment of attention-deficit/hyperactivity disorder (ADHD). In this case report, we present a 9-year-old girl with the comorbid diagnosis of ADHD and SPD treated successfully with atomoxetine. To our knowledge, this is the first report of skin picking treated with atomoxetine in a patient with ADHD. We discussed possible explanations of mechanisms. Further studies are required on the effectiveness of atomoxetine for the treatment of SPD in the presence and absence of comorbid ADHD

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Clin Psychopharmacol Neurosci. 2020;18:249-60.

Associations between the Mismatch-negativity Potential and Symptom Severity in Medication- naïve Children and Adolescents with Symptoms of Attention Deficit/hyperactivity Disorder.

Lee YJ, Jeong MY, Kim JH, et al.

Objective The mismatch negativity (MMN) event-related potential is an index of the pre-attentive stage of neural auditory information processing and an electrophysiological signal indicative of the integrity of auditory information processing with regard to the attention deficit symptom of attention deficit hyperactivity disorder (ADHD). We investigated the association between the MMN amplitude and latency in frontal brain regions and symptom severity in children with ADHD and subclinical ADHD symptoms.

Methods This study included 29 children: 16 (10 boys; mean age, 13.06 ± 3.67 years) with ADHD (ADHD group) and 13 (eight boys; mean age, 13.40 ± 3.31 years) with sub-clinical ADHD symptoms (subclinical ADHD group). We performed the following assessments: Korean ADHD rating scale-IV (K-ARS-IV), children

depression inventory, state/trait anxiety inventory for children, and MMN (measured at Fz, FCz, Cz, and CPz).
Results There were no sex or mean age differences between the groups (c2 = −0.01, p = 0.958; Z = −1.88, p = 0.060, respectively). The ADHD group had a significantly higher mean K-ARS-IV score (26.13 ± 9.56 vs. 17.15 ± 11.73, Z = −2.11, p = 0.035). Significant differences were found according to symptom severity in the MMN amplitude at FCz (Z = −2.11, p = 0.035) and MMN latency at Fz and FCz (Z = −2.48, p = 0.013; Z = −2.57, p = 0.010). The K-ARS-IV, K-ARS inattention subscale, and K-ARS hyperactivity-impulsivity subscale scores in the ADHD group correlated significantly with the MMN amplitude at Cz and CPz.
Conclusion This study found differences in the MMN amplitude and latency according to the severity of ADHD symptoms and identified MMN as a potential adjunct to the diagnosis of ADHD

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Clin Ther. 2020.

A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO ASSESS THE EFFICACY AND SAFETY OF ONCE-DAILY SPN-812 (VILOXAZINE EXTENDED-RELEASE) IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOL-AGE CHILDREN.

Nasser A, Liranso T, Adewole T, et al.

Purpose: The limitations of current US Food and Drug Administration (FDA) approved medications for the treatment of attention-deficit/hyperactivity disorder (ADHD) set the need for the development of novel, effective, and tolerable medications to treat this disorder. The purpose of this study was to evaluate whether treatment with SPN-812 (viloxazine extended-release) significantly reduces symptoms of ADHD in children.
Methods: This study was a randomized, double-blind, placebo-controlled 6-week trial to assess the efficacy and safety of once-daily 100- and 200-mg SPN-812 in the treatment of ADHD in male and female children 6-11 years of age. Inclusion criteria required subjects to have a confirmed Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ADHD diagnosis, an ADHD-Rating Scale-5 (ADHD-RS-5) score 28, a Clinical Global Impression-Severity score 4, and for subjects to be free of ADHD medication 1 week before randomization. The primary efficacy endpoint was the change from baseline (CFB) at end of study (EOS) in ADHD-RS-5 Total score. Key secondary endpoints included Clinical Global Impression-Improvement (CGI-I) scores at EOS and CFB at EOS in the Conners 3 Parent Short Form (Conners 3 PS) Composite T-score and the Weiss Functional Impairment Rating ScaleΓÇôParent (WFIRSΓÇôP) Total average score. Safety assessments included adverse events (AEs), laboratory tests, vital signs, physical examinations, ECGs, and the Columbia-Suicide Severity Rating Scale. The primary efficacy endpoint was analyzed by using a mixed model for repeated measures; all secondary measures were analyzed by using an ANCOVA model.
Results: A total of 477 subjects were randomized to treatment (intent-to-treat population, n = 460). The majority of subjects were male (63%) and either White (51.3%) or African American (43.7%). The demographic and baseline characteristics between the groups were similar. Statistically significant improvements in ADHD-RS-5 Total score were observed in both the 100- and 200-mg/day SPN-812 treatment groups compared to placebo at week 1 of treatment (P = 0.0004 and P = 0.0244, respectively), which was maintained through EOS (P = 0.0004 and P < 0.0001). Significant improvements were also observed at EOS in the CGI-I scale (P = 0.0020 and P < 0.0001), Conners 3 PS Composite T-score (P = 0.0003 and P = 0.0002), and WFIRS P Total average score (P = 0.0019 and P = 0.0002) versus placebo. Treatment-related AEs reported in 5% of subjects included somnolence, decreased appetite, and headache. The discontinuation rate due to AEs was <5%.
Implications: SPN-812 significantly reduced ADHD symptoms in children and was well tolerated. SPN-812 may prove to be an effective treatment for children with ADHD.
ClinicalTrials.gov identifier: NCT03247530

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CNS Neurosci Ther. 2020.

BRAIN MORPHOMETRIC ABNORMALITIES IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER REVEALED BY SULCAL PITS-BASED ANALYSES.

Li XW, Jiang YH, Wang W, et al.

Aim: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder associated with widespread brain morphological abnormalities. Here, we utilized a sulcal pits-based method to provide new insight into the atypical cortical folding morphology in ADHD.

Methods: Sulcal pits, the locally deepest points in each fold, were first extracted from magnetic resonance imaging data of 183 boys with ADHD (10.62-¦-1.96 years) and 167 age- and gender-matched typically developing controls (10.70-á-¦-á1.73-áyears). Then, the geometrical properties of sulcal pits were statistically compared between ADHD and controls.

Results: Our results demonstrated that the number of sulcal pits was reduced and confined to the superficial secondary sulci in the ADHD group relative to controls (P<.05). We also found that ADHD boys were associated with significantly increased pit depth in the left superior frontal junction, circular insular sulcus, right inferior frontal junction, and bilateral cingulate sulcus, as well as significantly decreased pit depth in the bilateral orbital sulcus (P<.05, corrected).

Conclusion: The experimental findings reveal atypical sulcal anatomy in boys with ADHD and support the feasibility of sulcal pits as anatomic landmarks for disease diagnosis

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CNS Spectr. 2019 Oct;24:518-25.

EXAMINING THE VALIDITY OF THE ADHD CONCEPT IN ADULTS AND OLDER ADULTS.

Callahan BL, Plamondon A.

OBJECTIVE: It is crucial to clarify the structure of attention-deficit/hyperactivity disorder (ADHD) symptomatology in all age groups to determine how to best conceptualize this disorder across the lifespan. We tested the ADHD factor structure across adulthood and investigated independent associations with executive functions.

METHOD: Data from 645 adults aged 18-59 and 233 adults aged 60-85 were drawn from the Nathan Kline Institute Rockland Sample. Participants completed the Conners Adult ADHD Rating Scale and tests of executive functioning. Invariance of the ADHD factor structure was investigated using confirmatory factor analyses. Associations with cognition were explored using multiple linear regression.

RESULTS: Results confirmed a bifactor model with 3 specific factors (inattention, hyperactivity, and impulsivity). Factor loadings and item intercepts were invariant across ages. Levels of hyperactivity and impulsivity were lower in older adults. Inattentive symptoms in young adults were positively related to cognitive flexibility. In older adults, ADHD symptoms predicted poorer working memory.

CONCLUSION: ADHD symptoms manifest similarly across adulthood. The lack of robust associations between ADHD symptomatology and executive functions raises concerns about the usefulness of neuropsychological measures in diagnosing adult ADHD. These results support the validity of the ADHD concept in older adults but suggest a need for age-appropriate normative criteria

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Cold Spring Harb Mol Case Stud. 2019 Dec;5.

22Q11.2 DUPLICATION: A REVIEW OF NEUROPSYCHIATRIC CORRELATES AND A NEWLY OBSERVED CASE OF PROTOTYPIC SOCIOPATHY.

Vyas S, Constantino JN, Baldridge D.

Callous-unemotional (CU) traits are highly disabling behavioral characteristics, common predictors of delinquency and criminality, and pathognomonic for antisocial personality disorder. They are highly heritable, but their specific molecular genetic causes are unknown. Here, we briefly review the literature on neuropsychiatric correlates of 22q11.2 duplication and describe a newly identified case of a 737-kb microduplication within the low copy repeat (LCR) B-D region, involving a 13-yr-old early adoptee with mild developmental delay and severe, chronic antisocial behavior of early childhood onset. When psychiatric

symptoms have been reported in relation to duplications in this specific region, 19% of the reports feature aggression-but never previously CU traits-as a component of the phenotype. We discuss the potential implications of gain of function in this chromosomal region for heritable origins of sociopathy and their possible relation to genetic influences on aggression

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Cold Spring Harb Mol Case Stud. 2019 Dec;5.

THREE RARE DISEASE DIAGNOSES IN ONE PATIENT THROUGH EXOME SEQUENCING.

Ferrer A, Schultz-Rogers L, Kaiwar C, et al.

Diagnostic exome sequencing yields a single genetic diagnosis in âˆ¼30% of cases, and according to recent studies the prevalence of identifying two genetic conditions in a single individual range between 4.6% and 7%. We present a patient diagnosed with three different rare conditions, each explained by a pathogenic variant in a different gene. A 17-yr-old female was evaluated for a history of motor and speech delay, scoliosis, distinctive craniofacial features, and dry skin in the Department of Clinical Genomics at Mayo Clinic. Her distinctive features included prominent forehead, epicanthus, depressed nasal bridge, narrow mouth, prognathism, malar flattening, and oligodontia. Family history was notable for dry skin in her mother and missing teeth in the paternal grandmother. Previous diagnostic testing was unrevealing including biochemical testing, echocardiogram, abdominal ultrasound, and electroencephalogram. Previous genetic testing included a microarray-based comparative genomic hybridization that was reported normal. Three pathogenic loss-of-function heterozygous variants were identified by exome trio sequencing, each linked to different genetic conditions: SIN3A (Witteveen-Kolk syndrome), FLG (dermatitis), and EDAR (ectodermal dysplasia). Together, these three genetic alterations could explain the patient's overall phenotype. This patient demonstrates the importance of performing a thorough curation of exome data when presented with a complex phenotype. Although phenotypic variability can explain some of these situations, the hypothesis of multiple diseases coexisting in a single patient should never be disregarded completely

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Dev Psychopathol. 2020 Aug;32:909-21.

MODERATION OF PARENTING BY INHIBITORY CONTROL IN THE PREDICTION OF THE COMMON AND UNIQUE VARIANCE OF HYPERACTIVITY-IMPULSIVITY AND INATTENTION.

Rioux C, Murray J, Castellanos-Ryan N, et al.

This study examined whether the interaction between parenting and inhibitory control predicts hyperactivity-impulsivity and inattention in 195 children. Observation data of positive parenting were collected at 4 years, and mother reports of coercive parenting at 5 years, inhibitory control at 6 years, and hyperactivity-impulsivity/inattention at 7 years were obtained. The common and unique variance of hyperactivity-impulsivity and inattention symptoms were examined as outcomes using a bifactor model. Results indicated that positive parenting practices predicted lower levels of hyperactivity-impulsivity/inattention behaviors at age 7 only when children's inhibitory control was high. These results support the vantage sensitivity model, which posits that some individuals show an increased sensitivity to positive experiences exclusively, and support the appropriateness of a targeted prevention approach in early childhood

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Dev Psychopathol. 2020 Aug;32:791-802.

EARLY LIFE PREDICTORS OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMATOLOGY PROFILES FROM EARLY THROUGH MIDDLE CHILDHOOD.

Willoughby MT, Williams J, Mills-Koonce WR, et al.

This study used repeated measures data to identify developmental profiles of elevated risk for ADHD (i.e., six or more inattentive and/or hyperactive-impulsive symptoms), with an interest in the age at which ADHD risk first emerged. Risk factors that were measured across the first 3 years of life were used to predict profile membership. Participants included 1,173 children who were drawn from the Family Life Project, an ongoing

longitudinal study of children's development in low-income, nonmetropolitan communities. Four heuristic profiles of ADHD risk were identified. Approximately two thirds of children never exhibited elevated risk for ADHD. The remaining children were characterized by early childhood onset and persistent risk (5%), early childhood limited risk (10%), and middle childhood onset risk (19%). Pregnancy and delivery complications and harsh-intrusive caregiving behaviors operated as general risk for all ADHD profiles. Parental history of ADHD was uniquely predictive of early onset and persistent ADHD risk, and low primary caregiver education was uniquely predictive of early childhood limited ADHD risk. Results are discussed with respect to how changes to the age of onset criterion for ADHD in DSM5 may affect etiological research and the need for developmental models of ADHD that inform ADHD symptom persistence and desistance

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Disabil Health J. 2020.

MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND BEHAVIORAL OUTCOMES IN ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: THE ROLE OF SLEEP.

Li C, Haegele JA, Wang L.

Background: Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental disorder that has a worldwide prevalence of 7.2%. Individuals with ADHD often have sleep and behavioral problems.

Objective: This cross-sectional survey aims to investigate the relationships between moderate-to-vigorous physical activity (MVPA), sleep, bullying, and school engagement in adolescents with ADHD.

Methods: Data were obtained from the 2011ΓÇô2012 National Survey of Children's Health. A subsample (n = 272) that fit the inclusion criteria was included. Path analysis was used to test the hypothesized model (i.e., MVPA sleep bullying/school engagement).

Results: The proposed model fit the data well. MVPA was found to be associated with sleep, bullying, and school engagement. In addition, sleep mediated the relationship between MVPA and bullying/school engagement.

Conclusions: MVPA and sleep play an important role in understanding behavioral outcomes in adolescents with ADHD. Longitudinal or intervention studies are needed to support the present findings

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East Mediterr Health J. 2020;26:834-38.

DIFFERENCES IN IDENTIFICATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN BETWEEN TEACHERS AND PARENTS.

Nafi O, Shahin A, Tarawneh A, et al.

Background: The worldwide prevalence estimates for attention deficit hyperactive disorder (ADHD) are extremely heterogeneous. Diagnosis in children demands symptoms be present in at least 2 different settings, mainly school and home. The proportion of children estimated to have ADHD can vary based on whether the symptoms are evaluated by parents or teachers.

Aims: This study determined whether ADHD and its subtypes are better recognized by parents or teachers.

Methods: Our study included 1326 schoolchildren (boys = 712, girls = 614; age range: 6-12 years). We prepared 2 questionnaires for each student enrolled in the study; one was completed by the student’s parents and the other by the teacher. We included students who attended 3 selected schools in the cities of Amman and Karak in Jordan during the first term of 2017. The Arabic version of the Diagnostic and statistical manual of mental disorders, 4th edition, was used for the diagnosis and classification of ADHD.

Results: Of the 1326 students included in this study, 254 (19.2%) were considered to have ADHD by the teachers and 172 (13.0%) by the parents. The Wilcoxon signed-ranks test showed that teachers gave statistically higher scores on the questionnaire than parents. However, overall agreement between parents and teachers, as measured by the +¦-value, reached 77.2%.

Conclusions: Although both teachers and parents recognized ADHD symptoms, they were generally more recognized by teachers than by parents

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Environ Sci Pollut Res Int. 2020 Sep;27:31233-42.

ASSOCIATION BETWEEN 10 URINARY HEAVY METAL EXPOSURE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER FOR CHILDREN.

Li Y, Cha C, Lv X, et al.

Attention deficit hyperactivity disorder (ADHD) is associated with heavy metal exposure during adolescent development. However, the direct clinical evidence is limited. To investigate the possible association between environmental heavy metal exposure and ADHD, a case-control study was conducted with children aged 6-14 years in Guangzhou, China. Results showed that median concentrations of chromium (Cr), manganese (Mn), cobalt (Co), nickel (Ni), copper (Cu), molybdenum (Mo), tin (Sn), barium (Ba), and lead (Pb) in the urine of the case group were significantly higher than those of the control group. Children with ADHD had significantly higher levels of 8-OHdG and MDA compared with those from the control group. In addition, correlations between urinary Co, Ni, Cu, Mo, and Sn were significantly correlated with 8-OHdG and MDA concentrations in urine. After the case and control groups were combined together and the first quartile was used as the reference category, odds ratios (ORs) of ADHD for children increased significantly with the quartile increasing of urinary Co, Cu, and Sn. Our study provides a clinical evidence that Co, Cu, and Sn exposure, particularly Sn exposure, may be an environmental risk of the incurrence of ADHD for children. Furthermore, Co, Ni, Cu, Mo, and Sn exposures were significantly correlated with DNA and lipid damage

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Environmental Pollution. 2020;266.

ASSOCIATION BETWEEN SHORT-TERM AIR POLLUTION EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER-RELATED HOSPITAL ADMISSIONS AMONG ADOLESCENTS: A NATIONWIDE TIME-SERIES STUDY.

Park J, Sohn JH, Cho SJ, et al.

Long-term air pollution exposure has been suggested to increase the risk of attention-deficit/hyperactivity disorder (ADHD). However, the association between short-term air pollution exposure and ADHD-related outcomes is still unknown. We investigated the associations between short-term exposure to particulate matter with an aerodynamic diameter Γëñ10 ++m (PM10), nitrogen oxide (NO2), and sulfur dioxide (SO2) and hospital admissions with a principal diagnosis of ADHD among adolescents (age 10ΓÇô19 years) in 16 regions of the Republic of Korea from 2013 to 2015. We estimated the region-specific relative risks (RRs) and 95% confidence intervals (CIs) from quasi-Poisson regressions adjusted for potential confounders, considering single-day and moving average lag. Consequently, we performed meta-analyses to pool the region-specific estimates. The risks of ADHD-related hospital admissions were increased in the single-day and moving average lag models for PM10 (largest association for lag 1 in the single-day lag model, RR = 1.12, 95% CI: 1.05, 1.20; lag 0-2 in the moving average lag model, RR = 1.17, 95% CI: 1.07, 1.27), NO2 (lag 3, RR = 1.47, 95% CI: 1.25, 1.73; lag 1-3, RR = 1.68, 95% CI: 1.38, 2.04), and SO2 (lag 1, RR = 1.27, 95% CI: 1.14, 1.41; lag 1-3, RR = 1.29, 95% CI: 1.12, 1.49). The associations were similar between boys and girls, but they were stronger among adolescents aged 15-19 years than those aged 10–14 years for NO2 and SO2. In conclusion, the results indicate that short-term exposure to PM10, NO2, and SO2 may be a risk factor for the exacerbation of ADHD symptoms, leading to hospitalization

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Eur Child Adolesc Psychiatry. 2020 Aug;29:1035-48.

EFFECTIVENESS AND SIDE EFFECTS OF PSYCHOPHARMACOTHERAPY IN INDIVIDUALS WITH 22Q11.2 DELETION SYNDROME WITH COMORBID PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW.

Mosheva M, Korotkin L, Gur RE, et al.

22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion in humans and is associated with high rates of attention deficit/hyperactivity disorder (ADHD), psychotic spectrum disorders and mood and anxiety disorders. The objective of the study was to systematically review studies regarding pharmacological treatments for psychiatric disorders in individuals with 22q11.2DS and to provide practical guidelines for the psychiatric management and side effect monitoring in 22q11.2DS. A literature search was conducted using the databases PubMed, PsycINFO and Embase. Information regarding study population,

drug treatment, side effect profile and efficacy for each trial was extracted. Data collection was completed on May 2018. The search identified 705 studies. A total of seven studies, describing 182 individuals, were included. Pharmacological interventions included three studies for antipsychotic treatment, two studies for stimulants, one study for selective serotonin reuptake inhibitors (SSRIs), one study for S-adenosyl-L-methionine (SAMe), and one case series for metyrosine. The presented data support the clinical impression that individuals with 22q11.2DS and comorbid psychiatric disorders are treated in a manner comparable to non-22q11.2DS individuals. However, distinct medical comorbidities common in individuals with 22q11.2DS may complicate the administration of pharmacotherapy. Further trials with RCT design, larger sample sizes and more syndrome-specific pharmacological agents are needed to improve evidence-based psychiatric care of 22q11.2DS individuals with comorbid mental disorders

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Eur Child Adolesc Psychiatry. 2020 Jul;29:903-16.

EARLY MOTOR SIGNS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Athanasiadou A, Buitelaar JK, Brovedani P, et al.

ADHD is a common neurodevelopmental disorder with onset of symptoms typically in early childhood. First signs of the disorder, including language delay, motor delay and temperament characteristics, may be evident as early as infancy. The present review describes published evidence about early motor signs of either children with later symptoms of ADHD or a later diagnosis of the disorder. Nine published cohort studies were included after a systematic search of related terms in PubMed and PsycInfo databases. Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participants' assessment by/at 12Â months of age; (3) report of a later presence of ADHD symptoms. The limited number of reports included suggests an association between mild early neurological markers and later developmental coordination disorder and motor overflow movements. Unfortunately, due to their small sample sizes and focus on group reports rather than individuals, they have limited power to find strong associations. Early motor indicators of ADHD, if present, appear to be non-specific, and therefore not yet useful in clinical screening. Spontaneous motility seems to be a promising measure for early ADHD detection, although further studies with large cohorts are recommended to determine its clinical role in children at risk for ADHD

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Eur Addict Res. 2020.

INTERNATIONAL CONSENSUS STATEMENT FOR THE SCREENING, DIAGNOSIS, AND TREATMENT OF ADOLESCENTS WITH CONCURRENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SUBSTANCE USE DISORDER.

Ozgen H, Spijkerman R, Noack M, et al.

Background: Childhood attention-deficit/hyperactivity disorder (ADHD) is a risk factor for substance misuse and substance use disorder (SUD) in adolescence and (early) adulthood. ADHD and SUD also frequently co-occur in treatment-seeking adolescents, which complicates diagnosis and treatment and is associated with poor treatment outcomes. Research on the effect of treatment of childhood ADHD on the prevention of adolescent SUD is inconclusive, and studies on the diagnosis and treatment of adolescents with ADHD and SUD are scarce. Thus, the available evidence is generally not sufficient to justify robust treatment recommendations.

Objective: The aim of the study was to obtain a consensus statement based on a combination of scientific data and clinical experience. Method: A modified Delphi study to reach consensus based upon the combination of scientific data and clinical experience with a multidisciplinary group of 55 experts from 17 countries. The experts were asked to rate a set of statements on the effect of treatment of childhood ADHD on adolescent SUD and on the screening, diagnosis, and treatment of adolescents with comorbid ADHD and SUD.

Results: After 3 iterative rounds of rating and adapting 37 statements, consensus was reached on 36 of these statements representing 6 domains: general (n = 4), risk of developing SUD (n = 3), screening and diagnosis (n = 7), psychosocial treatment (n = 5), pharmacological treatment (n = 11), and complementary

treatments (n = 7). Routine screening is recommended for ADHD in adolescent patients in substance abuse treatment and for SUD in adolescent patients with ADHD in mental healthcare settings. Long-acting stimulants are recommended as the first-line treatment of ADHD in adolescents with concurrent ADHD and SUD, and pharmacotherapy should preferably be embedded in psychosocial treatment. The only remaining no-consensus statement concerned the requirement of abstinence before starting pharmacological treatment in adolescents with ADHD and concurrent SUD. In contrast to the majority, some experts required full abstinence before starting any pharmacological treatment, some were against the use of stimulants in the treatment of these patients (independent of abstinence), while some were against the alternative use of bupropion.

Conclusion: This international consensus statement can be used by clinicians and patients together in a shared decision-making process to select the best interventions and to reach optimal outcomes in adolescent patients with concurrent ADHD and SUD

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Eur Arch Psychiatry Clin Neurosci. 2020.

ADHD SYMPTOM PROFILES, INTERMITTENT EXPLOSIVE DISORDER, ADVERSE CHILDHOOD EXPERIENCES, AND INTERNALIZING/EXTERNALIZING PROBLEMS IN YOUNG OFFENDERS.

Barra S, Turner D, M++ller M, et al.

Attention-deficit/hyperactivity disorder (ADHD) and co-existing psychiatric/psychological impairments as well as adverse childhood experiences (ACEs) are common among young offenders. Research on their associations is of major importance for early intervention and crime prevention. Intermittent explosive disorder (IED) warrants specific consideration in this regard. To gain sophisticated insights into the occurrence and associations of ADHD, IED, ACEs, and further psychiatric/psychological impairments in young (male and female) offenders, we used latent profile analysis (LPA) to empirically derive subtypes among 156 young offenders who were at an early stage of crime development based on their self-reported ADHD symptoms, and combined those with the presence of IED. We found four distinct ADHD subtypes that differed rather quantitatively than qualitatively (very low, low, moderate, and severe symptomatology). Additional IED, ACEs, and further internalizing and externalizing problems were found most frequently in the severe ADHD subtype. Furthermore, females were over-represented in the severe ADHD subtype. Finally, ACEs predicted high ADHD symptomatology with co-existing IED, but not without IED. Because ACEs were positively associated with the occurrence of ADHD/IED and ADHD is one important risk factor for on-going criminal behaviors, our findings highlight the need for early identification of ACEs and ADHD/IED in young offenders to identify those adolescents who are at increased risk for long-lasting criminal careers. Furthermore, they contribute to the debate about how to best conceptualize ADHD regarding further emotional and behavioral disturbances

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Eur Child Adolesc Psychiatry. 2020.

AGGRESSION SUBTYPES RELATE TO DISTINCT RESTING STATE FUNCTIONAL CONNECTIVITY IN CHILDREN AND ADOLESCENTS WITH DISRUPTIVE BEHAVIOR.

Werhahn JE, Mohl S, Willinger D, et al.

There is increasing evidence for altered brain resting state functional connectivity in adolescents with disruptive behavior. While a considerable body of behavioral research points to differences between reactive and proactive aggression, it remains unknown whether these two subtypes have dissociable effects on connectivity. Additionally, callous-unemotional traits are important specifiers in subtyping aggressive behavior along the affective dimension. Accordingly, we examined associations between two aggression subtypes along with callous-unemotional traits using a seed-to-voxel approach. Six functionally relevant seeds were selected to probe the salience and the default mode network, based on their presumed role in aggression. The resting state sequence was acquired from 207 children and adolescents of both sexes [mean age (standard deviation) = 13.30 (2.60); range = 8.02ΓÇô18.35] as part of a Europe-based multi-center study. One hundred eighteen individuals exhibiting disruptive behavior (conduct disorder/oppositional

defiant disorder) with varying comorbid attention-deficit/hyperactivity disorder (ADHD) symptoms were studied, together with 89 healthy controls. Proactive aggression was associated with increased left amygdala-precuneus coupling, while reactive aggression related to hyper-connectivities of the posterior cingulate cortex (PCC) to the parahippocampus, the left amygdala to the precuneus and to hypo-connectivity between the right anterior insula and the-ánucleus caudate. Callous-unemotional traits were linked to distinct hyper-connectivities to frontal, parietal, and cingulate areas. Additionally, compared to controls, cases demonstrated reduced connectivity of the PCC and left anterior insula to left frontal areas, the latter only when controlling for ADHD scores. Taken together, this study revealed aggression-subtype-specific patterns involving areas associated with emotion, empathy, morality, and cognitive control

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Eur Child Adolesc Psychiatry. 2020.

THE ASSOCIATION BETWEEN ADVERSE CHILDHOOD EXPERIENCES AND MENTAL HEALTH PROBLEMS IN YOUNG OFFENDERS.

Turner D, Wolf AJ, Barra S, et al.

High rates of adverse childhood experiences (ACEs, e.g., abuse and neglect) have been found in young offenders. Furthermore, ACEs seem to increase the risk of developing relevant mental health problems, in non-offending juveniles and adults. However, this association has only seldomly been addressed in offending juveniles and young adults. The present study aimed at evaluating the prevalence of ACEs and mental health problems as well as their association within a sample of male and female young offenders. Altogether, 161 adolescent and young adult offenders (16.8% females) from the youth detention center Worms (Germany) filled out questionnaires concerning ACEs and mental health problems with a focus on attention-deficit/hyperactivity disorder and intermittent explosive disorder. Considerable rates of mental health problems were found, e.g., a prevalence of 35.9% was found for intermittent explosive disorder. Furthermore, a greater proportion of the female offenders fell into the clinically significant category for somatic complaints, anxiety/depression, and attention problems than the male offenders. Female young offenders also reported more frequently about all forms of ACEs compared to the male offenders. Latent class analysis defined three subtypes of young offenders depending on their individual ACE patterns: (1) low ACEs, (2) mainly neglectful ACEs, and (3) multiple ACEs. ACEs were significantly associated with the occurrence of both internalizing and externalizing mental health disturbances, with the multiple-ACE subtype being most likely to report about significant mental health problems. The results of the present study point towards the relevance to routinely assess ACEs in young offenders to identify possible precursors of mental health problems and of future criminal behaviors

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Eur J Clin Pharmacol. 2020.

THE 10-YEAR TREND IN DRUG PRESCRIPTIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN GERMANY.

Grimmsmann T, Himmel W.

Purpose: The aim of this study was to analyse whether the global trend in drug prescriptions for attention-deficit hyperactivity disorders (ADHD), as observed during the last years and often criticized as medicalization, have remained stable or shifted.

Methods: This observational study was based on a secondary analysis of data from a large German database including patients with an ADHD diagnosis between 2008 and 2018. Prescription data comprised all important ADHD drugs.

Results: A total of 620 practices delivered data from a total of 77,504 patients (31% of them females) with a diagnosis of AHDH. Nearly 38% (29,396/77,504) of all patients received, at least, one prescription for an ADHS medicine between 2008 and 2018. The number of patients receiving a drug steadily increased annually until 2012 and then slowly fell, but unevenly distributed across the age groups. While the number of younger patients (16 years) receiving a prescription fell by 24% and the defined daily doses (DDDs) remained stable, the number of patients between 17 and 24-áyears receiving a prescription increased by

113% and the DDDs by 150%. Respectively, the number of older adults (25 years) with a prescription-áincreased by 355% and the DDDs by 515%. Nearly one-third of older adults received an ADHD medicine only once.
Conclusion: The ever-increasing prescription of ADHD medicines stopped some years ago for children. ADHS and its pharmacological management are increasingly observed among older adolescents and adults, with a different pattern of drug persistence compared with children

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Eur J Hum Genet. 2020;28:1098-110.
WHOLE EXOME SEQUENCING IN ADHD TRIOS FROM SINGLE AND MULTI-INCIDENT FAMILIES IMPLICATES NEW CANDIDATE GENES AND HIGHLIGHTS POLYGENIC TRANSMISSION.
Al-Mubarak BR, Omar A, Baz B, et al.
Several types of genetic alterations occurring at numerous loci have been described in attention deficit hyperactivity disorder (ADHD). However, the role of rare single nucleotide variants (SNVs) remains under investigated. Here, we sought to identify rare SNVs with predicted deleterious effect that may contribute to ADHD risk. We chose to study ADHD families (including multi-incident) from a population with a high rate of consanguinity in which genetic risk factors tend to accumulate and therefore increasing the chance of detecting risk alleles. We employed whole exome sequencing (WES) to interrogate the entire coding region of 16 trios with ADHD. We also performed enrichment analysis on our final list of genes to identify the overrepresented biological processes. A total of 32 rare variants with predicted damaging effect were identified in 31 genes. At least two variants were detected per proband, most of which were not exclusive to the affected individuals. In addition, the majority of our candidate genes have not been previously described in ADHD including five genes (NEK4, NLE1, PSRC1, PTP4A3, and TMEM183A) that were not previously described in any human condition. Moreover, enrichment analysis highlighted brain-relevant biological themes such as Glutamatergic synapse, Cytoskeleton organization, and Ca2+ pathway. In conclusion, our findings are in keeping with prior studies demonstrating the highly challenging genetic architecture of ADHD involving low penetrance, variable expressivity and locus heterogeneity

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Eur J Neurol. 2020;27:819.
EVALUATION OF PARENT SUPPORT PROGRAM ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN YOUNG CHILDREN: A RANDOMIZED CONTROLLED TRIAL.
Sharma N, Sharma S, Singh D, et al.
Background and aims: Attention Deficit Hyperactivity Disorder (ADHD) is a chronic condition affecting millions of children worldwide. There has been no cure but with medication and behavioural management, symptoms can be managed with great effect. Previous studies explored the effect of parent training intervention in children aged 5 and 8 years old and found beneficial effects in children and parents.
Methods: Present study evaluated parent support program (L.E.A.D) in ADHD-risk children. 75 children aged between 8 to 12 years old were having ADHD symptoms were recruited from community clinic. Parents were enrolled in support groups where they were skilled to manage their children's challenging behaviour. Intervention consisted of 60mins group session followed by parenting one to one support. Children were assessed before and after the 3 months of intervention. Outcome measures were parent ratings of ADHD symptoms, behavior, mood, attitude and understanding toward peers.
Results: Post data included seventy parents. AT the end of intervention, parents reported significant decrease in ADHD symptoms: $p<0.001$; oppositional symptoms: $p<0.001$; mood symptoms; $p<0.01$. Parents reported better behavior towards peers but that did not reach significance levels.
Conclusion: To our knowledge, this is the 1st randomized trial to address parent support intervention for an ADHDrisk sample. This study provides significant evidence on the beneficial effect of parent support program on at-risk ADHD Children

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Front Psychiatry. 2020;11.

A Deep Learning Approach for Missing Data Imputation of Rating Scales Assessing Attention-Deficit Hyperactivity Disorder.

Cheng CY, Tseng WL, Chang CF, et al.

A variety of tools and methods have been used to measure behavioral symptoms of attention-deficit/hyperactivity disorder (ADHD). Missing data is a major concern in ADHD behavioral studies. This study used a deep learning method to impute missing data in ADHD rating scales and evaluated the ability of the imputed dataset (i.e., the imputed data replacing the original missing values) to distinguish youths with ADHD from youths without ADHD. The data were collected from 1220 youths, 799 of whom had an ADHD diagnosis, and 421 were typically developing (TD) youths without ADHD, recruited in Northern Taiwan. Participants were assessed using the ConnersΓÇÖ Continuous Performance Test, the Chinese versions of the ConnersΓÇÖ rating scale-revised: short form for parent and teacher reports, and the Swanson, Nolan, and Pelham, version IV scale for parent and teacher reports. We used deep learning, with information from the original complete dataset (referred to as the reference dataset), to perform missing data imputation and generate an imputation order according to the imputed accuracy of each question. We evaluated the effectiveness of imputation using support vector machine to classify the ADHD and TD groups in the imputed dataset. The imputed dataset can classify ADHD vs. TD up to 89% accuracy, which did not differ from the classification accuracy (89%) using the reference dataset. Most of the behaviors related to oppositional behaviors rated by teachers and hyperactivity/impulsivity rated by both parents and teachers showed high discriminatory accuracy to distinguish ADHD from non-ADHD. Our findings support a deep learning solution for missing data imputation without introducing bias to the data

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Gazi Medical Journal. 2020;31:345-48.

Early cardiovascular evaluation after methylphenidate in children with attention-deficit hyperactivity disorder.

Cilsal E, Yurtcu E, Elatas A.

Objective: Rare cardiovascular side effects may be observed in patients after treatment with methylphenidate for Attention Deficiency and Hyperactivity Disorder (ADHD). In this study, we aimed to evaluate the cardiac effects of methylphenidate before and after treatment in our center in children with ADHD.

Method: This study included 253 ADHD patients who underwent methylphenidate treatment and involved a retrospective comparison of their demographic data, heart rate, systolic, diastolic blood pressure, corrected QT (QTc) interval with electrocardiography and echocardiographic examinations from before and two weeks after treatment.

Results: The median age of the patients was 11.8 3.3 years, palpitations were observed in 18 (7%) patients, and blood pressure elevation was observed in 5 (1.9%) patients after methylphenidate treatment. Sinus tachycardia was observed in all patients with palpitation symptoms, and echocardiography revealed an atrial septal defect in four patients, valvular pulmonary stenosis in two patients, ventricular septal defect and patent ductus arteriosus in one patient. No significant difference in heart rate, systolic and diastolic blood pressure values were identified after treatment. Although the QTc intervals recorded after treatment were significantly longer, these values did not exceed pathological levels.

Conclusion: The findings of evaluations of children with ADHD after methylphenidate treatment vary according to the characteristics of the patients. Patients with structural heart disease or with arterial hypertension should be monitored more carefully before the use of methylphenidate in the diagnosis of ADHD. Our findings suggests that both blood pressure measurement and electrocardiographic assessment appear to be useful and appropriate in the detection of side effects after methylphenidate treatment

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Indian Journal of Public Health Research and Development. 2020;11:1037-44.

EFFECT OF VIDEO BASED TEACHING ON KNOWLEDGE AND ATTITUDE REGARDING ADHD OF CHILDREN AMONG PRIMARY SCHOOL TEACHERS.

Bhasin V, Srinivasan P, Deaver UJ, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is the most pervasive disorder of childhood affecting about 3% to 5%. Early identification and intervention of this problem are very important to address issues at early age.

Materials and method: Quantitative approach and quasi experimental non equivalent control group pretest-posttest design was used. Total 100 primary school teachers (54 in experimental group and 46 in comparison group) were recruited by convenience sampling technique. Tools in the study were selected variables, structured knowledge questionnaire and structured attitude scale.

Results: Mean post-test knowledge score (t= 5.24, p=0.00) and mean posttest attitude score (t=4.10, p=0.00) was higher than mean pretest knowledge and attitude score in experimental group. There was a weak positive correlation (r=0.282) in experimental and a moderate positive correlation (r=0.406) in comparison group. There was no significant association of knowledge except gender (p=0.03) and teaching experience (p=0.04) in experimental group and except religion (p=0.03) in comparison group. There was no significant association of attitude in experimental group and except age (p=0.03) in comparison group. Regression shows teaching experience having predictability, R= 30.10% (0.301) on knowledge and qualification having predictability on attitude, R= 34.20% (0.342) in experimental group. In comparison group, number of children having predictability, R= 32.70% (0.327) on attitude. It was concluded that Video based teaching was effective to improve the knowledge and attitude regarding ADHD of children

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Int J Eat Disord. 2020 Mar;53:349-61.

PREVALENCE, CORRELATES AND COMORBIDITIES OF FEEDING AND EATING DISORDERS IN A NATIONALLY REPRESENTATIVE SAMPLE OF IRANIAN CHILDREN AND ADOLESCENTS.

Mohammadi MR, Mostafavi SA, Hooshyari Z, et al.

OBJECTIVE: This study investigated the prevalence of feeding and eating disorders, and identified their correlates and comorbidities among children and adolescents.

METHOD: We used the nationally representative sample of the Iranian Children and Adolescents' Psychiatric disorders (IRCAP) survey, with 30,532 participants randomly selected by a multistage cluster sampling method. We employed the kiddie schedule for affective disorders and schizophrenia-present and lifetime version (K-SADS-PL) semi-structured face-to-face interview to screen for any psychiatric disorders, including feeding and eating disorders, and associated factors. We used multivariate binary logistic regression to analyze the data.

RESULTS: Valid data from 27,111 participants were analyzed. The total prevalence of feeding and eating disorders among children and adolescents was 0.89 (0.81-1.10). In all types of feeding and eating disorders, the adjusted odds ratio was higher among girls (except binge-eating disorder) and older adolescents but was lower among rural residents. The most common psychiatric comorbidities observed in children and adolescents with feeding and eating disorders were obsessive-compulsive disorder (20.2%), agoraphobia (20.2%), depressive disorder (16.4%), social phobia (10.1%), oppositional defiant disorder (10.1%), generalized anxiety disorder (9.4%), attention deficit hyperactivity disorder (7.5%), and conduct disorder (5.7%), which were significantly more common compared to their peers without feeding and eating disorders.

DISCUSSION: Older age, female gender and living in an urban area are predisposing factors in feeding and eating disorders (in binge-eating disorder, the male gender is a positive correlate). We suggest that future works pay attention to the role of gender, comorbidities and predisposing factors

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Int J Environ Res Public Health. 2020;17:1-13.

SLEEP AND PROSPECTIVE MEMORY: A RETROSPECTIVE STUDY IN DIFFERENT CLINICAL POPULATIONS.

Tonetti L, Occhionero M, Boreggiani M, et al.

Prospective memory (PM) is essential in everyday life because it concerns the ability to remember to perform an intended action in the future. This ability could be influenced by poor sleep quality, the role of which, however, is still being debated. To examine the role of sleep quality in PM in depth, we decided to perform a retrospective naturalistic study examining different clinical populations with a primary sleep disorder or comorbid low sleep quality. If sleep is important for PM function, we could expect poor sleep to affect PM performance tasks both directly and indirectly. We examined a total of 3600 nights, recorded using actigraphy in participants belonging to the following groups: primary insomnia (731 nights); narcolepsy type 1 (1069 nights); attention deficit hyperactivity disorder (152 nights in children and 239 in adults); severe obesity (232 nights); essential hypertension (226 nights); menopause (143 nights); healthy controls (808 nights). In a naturalistic activity-based PM task, each participant originally wore an actigraph around the non-dominant wrist and was requested to push the event-marker button at two specific times of day: bedtime (activity 1) and get-up time (activity 2). Each clinical group showed significantly lower sleep quality in comparison to the control group. However, only narcolepsy type 1 patients presented a significantly impaired PM performance at get-up time, remembering to push the event-marker button around half the time compared not only to healthy controls but also to the other clinical groups. Overall, the present results seem to point to sleep quality having no effect on the efficiency of a naturalistic activity-based PM task. Moreover, the data indicated that narcolepsy type 1 patients may show a disease-specific cognitive deficit of PM

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Int J Environ Res Public Health. 2020;17:1-13.

MULTIDIMENSIONAL CORRELATES OF PARENTAL SELF-EFFICACY IN MANAGING ADOLESCENT INTERNET USE AMONG PARENTS OF ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hsieh YP, Wu CF, Chou WJ, et al.

Given the growing concerns of problematic Internet use and online safety, it is critical to address parental self-efficacy in managing adolescent Internet use and to examine associated factors, especially in parents of adolescents with attention-deficit/hyperactivity disorder (ADHD). We examined the roles of adolescentsΓÇÖ hyperactivity/impulsivity, inattention and oppositional defiant disorder (ODD) symptoms, parentsΓÇÖ depressive symptoms, parenting behavior (parental care and indifference), and child behavior (Internet addiction) in relation to parental self-efficacy in managing adolescent Internet use. We recruited 237 Taiwanese parents of adolescents with ADHD (ages 11ΓÇô18). Hierarchical linear regression was performed in four steps to test the study hypotheses. The results indicated that childΓÇÖs age, ODD symptoms, and Internet addiction of adolescents were negatively associated, and parental care was positively associated with parental self-efficacy in managing adolescent Internet use. The final model was significant and explained 43% of the variance. The present study demonstrated that parenting and child behaviors contribute to parental self-efficacy in managing adolescent Internet use. Moreover, childrenΓÇÖs ODD symptoms were identified as the risk factor for reduced parental self-efficacy

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Int J Environ Res Public Health. 2020;17:1-12.

EXCESSIVE WEIGHT GAIN AND DENTAL CARIES EXPERIENCE AMONG CHILDREN AFFECTED BY ADHD.

Paszynska E, Dmitrzak-W-Öglarz M, Perczak A, et al.

In recent years, attention has been paid to the co-occurrence of attention deficit hyperactivity disorder (ADHD) and obesity, but results in relation to dental caries outcomes differ. The study was conducted to determine obesity/overweight and dental caries in children suffering from ADHD and to draw comparisons with non-ADHD children. A total of 119 children under 11 years old (8.2 -¦ 1.2) were enrolled into a cross-sectional study: those with confirmed ADHD (n = 39), and healthy controls (n = 80). The behavioral evaluation included a parent interview directed at sweetened food/drink habits. The clinical evaluation included physical measurements (height, waist, hip circumference, body weight, body mass index (BMI), and dental

examination (International Caries Detection and Assessment SystemΓÇöICDAS). Results showed a higher prevalence of abnormal body weight, hip circumference, and BMI, and a higher frequency of caries (84.6%) in the ADHD group. Significant caries differences for primary (ICDAS 0, 1, 2, 5, 6 scores) and permanent teeth (ICDAS 1, 3 scores) were recorded. The questionnaire pinpointed interplays between sugar consumption and tooth decay, especially for primary dentition. It can be concluded that the consumption of sweetened foods/drinks among ADHD children may lead to an increased rate of overweight, but may also affect oral health. Limiting sugar consumption might be one of the important elements in prevention programmes against dental caries and overweight/obesity

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Int J Neuropsychopharmacol. 2020;23:349-55.

TREATMENT EFFICACY OF INTERNET GAMING DISORDER WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND EMOTIONAL DYSREGULATON.

Chang CH, Chang YC, Cheng H, et al.

Background: Recent youth with Attention Deficit Hyperactivity Disorder (ADHD) noticed emotional dysregulation if they had Internet Gaming Disorder (IGD). This study aims to understand the treatment efficacy of IGD with ADHD and emotional dysregulaton.

Method: A total of 101 ADHD youths were recruited. We used the Chen Internet Addiction Scale and IGD criteria of the diagnotsic statistical manual (DSM)-5 to confirm IGD. The Swanson, Nolan, and Pelham questionnaire Version IV was used for symptoms of ADHD and oppositional defiant disorder. Disruptive mood dysregulation disorder was assessed by psychiatrist.

Results: There is a new phenomenon that emotional dysregulation has been frequently noticed in severely gaming-addicted ADHD youth. Treatment efficacy of IGD is good when the underlying symptom of ADHD is controlled. Symptom scores of disruptive mood dysregulation (DMDD) were significantly reduced by 71.9%, 74.8%, and 84.4% at week 2, 3, and 4, respectively (P 001) after adjusting baseline symptom severity.

Conclusion: IGD may strongly arouse emotional dysregulation. Future DSM criteria could consider these gaming-addicted youth as a specific subclass of ADHD

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Int J Psychiatry Clin Pract. 2020.

SERUM ZONULIN AND CLAUDIN-5 LEVELS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Aydogan Avsar P, et al.

Objective: This study aimed to investigate serum zonulin and claudin-5 levels of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and healthy controls by controlling the parameters such as age, sex and body mass index (BMI) percentile which are known to affect these parameters.

Method: A total of 80 treatment-naive children and adolescents with ADHD and 40 healthy volunteer controls aged 8-12 years were enrolled in this study. The severities of ADHD symptoms were assessed via parent- and teacher-rated questionnaires. The severity of anxiety and depression symptoms of the children were assessed by the self-report inventories. Serum levels of zonulin and claudin-5 were measured using commercial enzyme-linked immunosorbent assay kits.

Results: The multivariate analysis of covariance (MANCOVA) revealed a significant main effect of groups in the serum zonulin and claudin-5 levels, an effect that was independent of age, sex and BMI percentile. Significant differences were found between the study groups in terms of serum log-claudin-5 levels. However, there was no significant difference between the study groups in terms of serum zonulin levels

Conclusion: These findings provide additional evidence for dysregulation of the blood-brain barrier, especially abnormalities in claudin-5 function, which may be involved in the aetiology of ADHD.Key points ADHD is one of the most common neurodevelopmental disorders of childhood. Although ADHD is quite common, its aetiology has yet to be fully explained. In recent years, studies on the relationship between

intestinal and blood-brain brain barrier permeability and psychiatric disorders have increased. In our study, serum claudin-5 levels were higher in the ADHD group compared to the control group, while serum zonulin levels did not differ between the groups

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Int J Psychiatry Clin Pract. 2020.

ELEVATED NEUTROPHIL-TO-LYMPHOCYTE RATIO IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Onder A, et al.

Objective: Inflammation is reported to play a substantial role in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are inexpensive and potentially interesting biomarkers of inflammation. In this cross-sectional and retrospective study, we investigated the relationship between NLR, PLR and ADHD.

Methods: This study consisted of 100 children and adolescents with ADHD (85 of those receiving psychopharmacological treatment), and 99 physically and mentally healthy children.

Results: The mean NLR and PLR were significantly higher in patients than in controls. There was no significant difference between patients who received psychopharmacological treatment for ADHD and patient that did not with regard to NLR and PLR. No associations were found between NLR and PLR and ADHD symptom severity. The significance of NLR is not influenced by medication use, age and sex.

Conclusions: Our findings suggest that NLR and PLR may be inflammation biomarkers in children and adolescents with ADHD. Moreover, the significance of NLR is not influenced by medication use, age and sex. Prospective studies that address alterations in NLR and PLR and other pro-inflammatory cytokines following ADHD treatment may provide additional information about the inflammatory mechanisms in ADHD.Key points The mean NLR and PLR were significantly higher in patients than in controls. The significance of NLR is not influenced by medication use, age and sex. No associations were found between NLR and PLR and ADHD symptom severity. Prospective studies that address alterations in NLR and PLR and other pro-inflammatory cytokines following psychopharmacological treatment of ADHD may provide additional information about the inflammatory mechanisms in ADHD

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Iran J Pediatr. 2020;30:1-6.

EFFECTS OF BALANCE TRAINING ON POSTURAL CONTROL OF CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Moradi J, Jalali S, Bucci MP.

Background: Children with attention-deficit/hyperactivity disorder (ADHD) have shown deficiencies in many physical activities in comparison with normally developing children. One of the problems of these children is the balance and postural control.

Objectives: The aim of this study was to investigate the effects of balance training on postural control of children with ADHD.

Methods: Thirty children with ADHD participated in this study and were divided randomly into experimental and control groups. The experimental group performed balance training three times per week for seven weeks. During this period, the control group did not experience any exercises but continued their normal activities. The Biodex balance system (BBS) was used to evaluate static and dynamic balance.

Results: The balance training significantly increased static and dynamic balance in the experimental group ($P < 0.001$), while the balance scores of children with ADHD in the control group did not change. Participants in the experimental group also performed static and dynamic balance tests significantly better than members of the control group ($P < 0.001$).

Conclusions: The results showed that specific balance training improves postural control of children with ADHD. These balance trainings probably lead to an adaptive mechanism in the sensory process and cerebellar integration of children with ADHD

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J Abnorm Child Psychol. 2019 Apr;47:589-603.

RESPONSE INHIBITION, RESPONSE EXECUTION, AND EMOTION REGULATION AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Tenenbaum RB, Musser ED, Morris S, et al.

Attention-deficit/hyperactivity disorder (ADHD) is associated with deficits in response inhibition, response execution, and emotion regulation. However, the nature of the associations among these deficits remains unclear. Thus, this study examines these associations using a multi-method design. One hundred sixty-six children (aged 5-13Â years; 66.3% male; 75 with ADHD) completed two conditions (i.e., neutral and fear) of an emotional go/no-go task. Parasympathetic-based regulation was indexed via respiratory sinus arrhythmia (RSA), and sympathetic-based reactivity was indexed via cardiac pre-ejection period (PEP). Overall, children exhibited more difficulty with response execution (i.e., more omission errors, fewer correct go responses) and less difficulty with response inhibition (i.e., fewer commission errors, more correct no-go responses) during the fear condition than the neutral condition. Children with ADHD displayed more difficulty with response execution during the fear condition compared to typically developing youth. Additionally, children with ADHD displayed parasympathetic-based dysregulation (i.e., RSA increase from baseline) and reduced sympathetic-based reactivity (i.e., PEP lengthening) compared to typically developing youth across task conditions. In sum, children with ADHD demonstrate greater difficulty with response execution during emotionally salient contexts, as well as parasympathetic-based emotion dysregulation. Future work should examine these associations longitudinally with the aim of predicting impairment and treatment response in youth with ADHD

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J Abnorm Child Psychol. 2019 Apr;47:671-81.

POSTTRAUMATIC STRESS DISORDER AND PSYCHIATRIC COMORBIDITY AMONG ADOLESCENT EARTHQUAKE SURVIVORS: A LONGITUDINAL COHORT STUDY.

Geng F, Zhou Y, Liang Y, et al.

Although posttraumatic stress disorder (PTSD) is highly comorbid with psychiatric disorders, little longitudinal research has been conducted to determine the potentially causal links. This study aimed to investigate the prevalence and comorbidity patterns of posttraumatic stress disorder symptoms and psychiatric symptoms among adolescents exposed to the 2008 Wenchuan earthquake in China and to examine the bidirectional prospective associations between PTSD symptoms and other psychiatric symptoms. A sample of 1573 adolescent survivors (45.8% male; mean age at initial survey was 15.0Â years, SDâ€‰=â€‰1.3) completed a battery of standardized measures assessing symptoms of PTSD, depression, panic disorder, generalized anxiety disorder (GAD), separation anxiety disorder (SAD), social phobia, conduct disorder, and attention deficit hyperactivity disorder at 6 and 18Â months post-earthquake. Among participants with PTSD symptoms, 91.9 and 94.0% had at least one comorbid psychiatric disorder at 6 and 18Â months post-earthquake, respectively; however, among those without PTSD symptoms, 54.3 and 50.4% had at least one psychiatric disorder. PTSD symptoms were more likely to co-occur with subtypes of anxiety or depression symptoms than with behavior problems. Participants who were screened as having PTSD comorbid with depression or SAD at 6Â months were less likely to recover from PTSD over time. Longitudinal analyses showed that symptoms of depression, GAD and SAD predicted increases in PTSD symptoms. In turn, PTSD symptoms predicted increases in GAD and panic disorder symptoms. Overall, our results support causal hypotheses of PTSD comorbidity. Specific multi-modal assessments and treatments targeting to both PTSD and its comorbidity disorders are warranted

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J Am Acad Child Adolesc Psychiatry. 2019 Oct;58:936-38.

DEBATE: ARE STIMULANT MEDICATIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER EFFECTIVE IN THE LONG TERM? (AGAINST).

Swanson JM.

Definition of terms is necessary to address the motion. First, "psychostimulants" are defined as methylphenidate and amphetamine, which inherently are short-acting drugs characterized by pharmacokinetic and pharmacodynamic properties of immediate-release formulations that act for a few hours. Sustained effects across the day can be achieved by controlled-release formulations, but positive carry-over to the next day is not significant, so on subsequent days these medications must be administered again to reinstate pharmacological effects. Second, "effective" refers to treatment-as-usual, whereas "efficacious" refers to enhanced or optimized treatment (that may set a maximum for effectiveness). Magnitude of effectiveness (eg, small, medium, or large effect size) depends on who is treated, how treatment is delivered, what outcome is evaluated, and other factors (including treatment adherence and study design). Third, "long term" refers to a given time frame (eg, 1 year), which can be applied to specify duration of treatment, length of follow-up, or both. Some studies evaluate long-term effectiveness of treatment while it is continued, whereas others evaluate long-term effectiveness of treatment during the follow-up after it is discontinued. Given these definitions, the following questions address long-term effectiveness of stimulant medication

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J Am Acad Child Adolesc Psychiatry. 2019 Oct;58:938-39.

DEBATE: ARE STIMULANT MEDICATIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER EFFECTIVE IN THE LONG TERM? (FOR).

Coghill D.

Long-term effectiveness studies for ADHD medications are complicated to design well, and no single study design will capture the entire picture. Although randomized controlled trials are the highest level of evidence, most authorities agree that, when you have treatments as efficacious as the ADHD medications (methylphenidate and amphetamine derivatives and prodrugs, atomoxetine, guanfacine, and clonidine), it is neither practical nor ethical to conduct long-term placebo-controlled RCTs. As a consequence, almost all of the RCT evidence for ADHD medications relates to short-term studies. Although these provide strong evidence for short-term efficacy,(1) they do not speak to long-term effectiveness. The European Medicines Agency (EMA) recognized the need for additional evidence of long-term effects before granting licenses for medications that will usually be required to be taken forÂ several years. They therefore introduced a requirement for companies to demonstrate longer-term efficacy. This has generally been done through the use of randomized withdrawal designs that are designed to demonstrate continued efficacy over a period of 6 to 12 months. Several of these have been completed and published, all of which, as expected, demonstrate continued efficacy.(2) The EMA also insisted that all new ADHD medications demonstrate continued effectiveness, and that adverse effects and safety be assessed up to 2 years. Again the studies completed so far support continued effectiveness, and, although highlighting the presence of common, expected adverse effects, have not identified any new safety signals or unexpected problems in targeted areas such as growth and cognition.(3)

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J Am Acad Child Adolesc Psychiatry. 2019 Oct;58:936.

DEBATE: ARE STIMULANT MEDICATIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER EFFECTIVE IN THE LONG TERM?

Cortese S.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common diagnoses in child and adolescent mental health services, in the United States as well as in many other countries. Medication, including stimulant and nonstimulant options, is an important element of the multimodal approach to ADHD management. Stimulants are recommended as the first-line pharmacological treatment.(1) A recent study

including data from more than 150Â million individuals in 13 countries showed an increase in the prevalence of ADHD medications use over the past 15 years in all countries, albeit with large variations across countries.(2) One of the aspects that remains controversial in relation to stimulants pertains to their long-term effectiveness

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J Child Adolesc Psychopharmacol. 2019 Jun;29:324-39.

NEW FORMULATIONS OF STIMULANTS: AN UPDATE FOR CLINICIANS.

Steingard R, Taskiran S, Connor DF, et al.

In the last 15 years, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets, chewable tablets, extended-release liquid formulations, transdermal patches, and novel "beaded" technology. All of these formulations involve changes to the pharmaceutical delivery systems of the two existing compounds most commonly employed to treat attention-deficit/hyperactivity disorder (ADHD), amphetamine (AMP) and methylphenidate (MPH). In addition to these new formulations, our knowledge about the individual differences in response has advanced and contributes to a more nuanced approach to treatment. The clinician can now make increasingly informed choices about these formulations and more effectively individualize treatment in a way that had not been possible before. In the absence of reliable biomarkers that can predict individualized response to ADHD treatment, clinical knowledge about differences in MPH and AMP pharmacodynamics, pharmacokinetics, and metabolism can be utilized to personalize treatment and optimize response. Different properties of these new formulations (delivery modality, onset of action, duration of response, safety, and tolerability) will most likely weigh heavily into the clinician's choice of formulation. To manage the broad range of options that are now available, clinicians should familiarize themselves in each of these categories for both stimulant compounds. This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties

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J Child Adolesc Psychopharmacol. 2019 Dec;29:764-72.

POPULATION-BASED EPIDEMIOLOGY OF PEDIATRIC PATIENTS WITH TREATED TIC DISORDERS FROM REAL-WORLD EVIDENCE IN KOREA.

Choi S, Lee H, Song DH, et al.

Objectives: Although tic disorder (TD) is a common mental disorder in children and adolescents, epidemiological data based on real-world evidence (RWE) are insufficient. Using RWE, this study sought to examine the prevalence of treated TD, use of medical utilization, and use of prescription drugs among patients with TD with respect to TD type and comorbid psychiatric illness.

Methods: We performed a retrospective cross-sectional study. Using the Korean Health Insurance Review and Assessment Service Pediatric Patient Sample data from 2009 to 2016, we analyzed 20,599 patients with TD (Korean Standard Classification of Diseases-6/7 code: F95.x) aged 2-19 years.

Results: The annual average TD prevalence was 2.6/1000 population (95% confidence interval, 2.3-2.8/1000). Between 2009 and 2016, a slight increase in TD prevalence was observed from 1.9 to 2.9/1000 population. The TD prevalence rate in male patients was four times higher than that in female patients. Differences were observed in health care utilization and drug prescription types between patients with Tourette syndrome and chronic or transient TD. In addition, more than half of patients with TD had comorbid psychiatric disorders, and one-third of patients with TD had attention-deficit/hyperactivity disorder (ADHD). Patients with TD without comorbidities were frequently prescribed aripiprazole, while patients with TD and comorbid ADHD were frequently prescribed atomoxetine, methylphenidate, risperidone, and aripiprazole.

Conclusion: This study described the epidemiological characteristics of TD based on recent RWE from Korea, and its findings can help establish future TD evidence-based clinical guidelines and related policies

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J Child Adolesc Psychopharmacol. 2019 Dec;29:740-45.

THE PHARMACOEPIDEMIOLOGY OF PSYCHOTROPIC MEDICATION USE IN CANADIAN CHILDREN FROM 2012 TO 2016.

Pringsheim T, Stewart DG, Chan P, et al.

Objective: The goal of this study was to characterize the frequency and trends of psychotropic drug prescribing in Canadian children from 2010 to 2016 and to compare these results with a previous study conducted between 2005 and 2009.

Methods: Using a national physician panel survey database from IQVIA Canada, aggregated frequencies of written prescriptions and therapeutic indications for antipsychotics, attention-deficit/hyperactivity disorder (ADHD) medications (psychostimulants and nonstimulants), and antidepressants were analyzed in children. Changes in frequency of written prescriptions and therapeutic indications are presented using descriptive statistics.

Results: Written prescriptions for antipsychotics decreased by 10% from 2010 to 2016, in contrast to a 114% increase in written prescriptions for antipsychotics observed between 2005 and 2009. Written prescriptions for psychostimulants and antidepressants rose by 35% and 27%, respectively, between 2012 and 2016, comparable with previous results. The most common reasons for recommending an antipsychotic were ADHD and conduct disorder, although there appears to be a downward trend for ADHD compared with other conditions. In contrast, the share of written prescriptions for antipsychotics for autism increased 34% over the study period. Within the second-generation antipsychotics, written prescriptions for aripiprazole increased. An increase in the use of guanfacine extended release for ADHD was also observed.

Conclusion: Several factors may be involved in stabilization and small decrease in antipsychotic use in recent years, including physician and patient awareness of adverse effects related to antipsychotic use, knowledge implementation strategies advocating short-term and judicious use of antipsychotics in children, and the approval of guanfacine extended release for use in Canada for ADHD in 2013

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J Child Adolesc Psychopharmacol. 2019 Aug;29:516-25.

REWARD PROCESSING IN DRUG-NAIVE YOUTH WITH VARIOUS LEVELS OF RISK FOR SUBSTANCE USE DISORDERS: A PILOT STUDY.

Ivanov I, Schulz K, Li X, et al.

Background: It has been hypothesized that attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) share common neurobiological features. When abnormalities in the mesolimbic reward system are characteristic of children with ADHD, it is unclear whether youth at particularly elevated risk for SUD may exhibit any further disturbances. The objective of this pilot study is to examine possible neurobiological differences among youth with different levels of SUD risk before exposure to any abusable substances.

Methods: We recruited 47 drug-naive children aged 8-13 divided into (1) Low Risk (LR)-ADHD only (‰=16); (2) High Risk (HR)-ADHD+familial SUD (n=17); and (3) healthy controls (HC, n=14) who underwent one functional magnetic resonance imaging scan while performing a hybrid task. We used the omnibus analysis of covariance model to assess for group differences in brain activation in regions linked to the brain reward and behavioral control systems.

Results: Behavioral analysis showed significant Cue and Flanker main effects, but no significant main effect for Group. Whole-brain analysis showed significant differences in widely distributed networks related to both reward processing and behavioral control. Region of interest (ROI) activations showed that the HR group had the highest activation in the right putamen during both expected rewards and unexpected nonreward outcomes and in the anterior cingulate cortex (ACC) during unexpected nonreward outcomes, while LR and HC youth showed similarly low activation during these contrasts. Furthermore, the LR and HR groups showed lower activation than HC in the right ACC and the right caudate during flanker contrasts.

Conclusions: These are the first preliminary results to demonstrate that the magnitude of activation during reward notification differs as a function of reward outcome in youth at high versus LR for SUD, such that youth at LR for SUD exhibit the highest activation for positive rewards, whereas those at HR for SUD exhibit the highest activation during negative rewards

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J Commun Disord. 2019 Nov;82:105935.

SLEEP PROBLEMS IN CHILDREN WHO STUTTER: EVIDENCE FROM POPULATION DATA.

Merlo S, Briley PM.

Purpose Previous research has identified seizures, intellectual disability, learning disability, pervasive developmental disorder, and attention deficit hyperactivity disorder as coexisting disabilities frequently seen in children who stutter (CWS). The observation that those conditions are affected by sleep has incited the present study, which aimed to explore if sleep problems are also more frequent in CWS.

Method Data was obtained from the 2012 National Health Interview Survey. Children included in the analysis were those whose caregivers answered definitively whether or not the sample child stuttered in the last 12 months and whose caregivers definitively answered questions regarding insomnia or trouble sleeping, sleepiness during the day, and fatigue during the day in the last 12 months. This sample included 203 CWS and 10,005 children who do not stutter (CWNS).

Results CWS were at greater odds of presenting insomnia or trouble sleeping (OR=3.72, p<.001), sleepiness during the day (OR=2.20, p<.001), and fatigue during the day (OR=2.87, p<.001) when compared to CWNS. Moreover, CWS with coexisting disabilities were at greater odds of presenting with sleep problems when compared to CWS without coexisting disabilities. Finally, CWS without coexisting disabilities were at greater odds of presenting insomnia when compared to CWNS without coexisting disabilities.

Conclusion CWS are at risk for presenting with sleep problems. Additionally, sleep problems persist from early childhood to adolescence. The implications of these findings are unclear, though future studies should look to explore the impact of sleep problems on stuttering

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J Dev Behav Pediatr. 2019 Jun;40:321-29.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER RISK: INTERACTION BETWEEN PARENTAL AGE AND MATERNAL HISTORY OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Wang X, Martinez MP, Chow T, et al.

OBJECTIVE: To assess the interaction between maternal attention-deficit/hyperactivity disorder (ADHD) history and young parental age on child's ADHD risk.

METHODS: The study included 321,272 singleton children born between 1995 and 2012 from hospitals within a single integrated health care organization. The children were prospectively followed up through electronic medical record systems from birth until the first date of the following: date of clinical diagnosis of ADHD, last date of continuous health plan membership, death due to any cause, or December 31, 2017. Risks of ADHD associated with a maternal history of ADHD before pregnancy and young parental age were assessed by using Cox regression adjusting for potential confounders.

RESULTS: The children were followed up for a median (interquartile range) of 8.9 (6.2, 13.6) years from birth. Among them, 5.1% had ADHD diagnosis, 1.8% had a maternal history of ADHD before the pregnancy, and 4.4% had mothers <20 years and 2.3% had fathers <20 years at date of birth. The hazard ratio (HR) of ADHD in children associated with parental age <20 years varied by maternal history of ADHD ($p < 0.005$ for both multiplicative and additive interactions). For children without a maternal history of ADHD, the HR associated with at least 1 parent <20 years was 1.14 (95% confidence interval 1.04-1.24). However, for children with a maternal history of ADHD, the HR associated with at least 1 parent <20 years was 1.92 (95% confidence interval 1.31-2.82).

CONCLUSION: High ADHD risk in offspring associated with young parenthood was predominantly observed among children with a maternal history of ADHD

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J Dev Behav Pediatr. 2019 Oct;40:581-88.

CHARACTERIZING THE LEARNING-TO-DRIVE PERIOD FOR TEENS WITH ATTENTION DEFICITS.

Bishop HJ, Curry AE, Stavrinos D, et al.

OBJECTIVE: Motor vehicle collisions are the leading cause of death among teenagers, accounting for approximately 1 in 3 deaths for this age group. A number of factors increase crash risk for teen drivers,

including vulnerability to distraction, poor judgment, propensity to engage in risky driving behaviors, and inexperience. These factors may be of particular concern and exacerbated among teens learning to drive with attention deficits. To our knowledge, our study is among the first to systematically investigate the experiences of novice adolescent drivers with attention deficits during the learner period of a Graduated Drivers Licensing program.
METHOD: Survey and on-road driving assessment (ODA) data were used to examine parent and teen confidence in the teens' driving ability, driving practice frequency, diversity of driving practice environments, and driving errors among teens with attention deficits as defined by attention-deficit/hyperactivity disorder (ADHD) diagnosis or parent-reported trouble staying focused (TSF).
RESULTS: When teens' driving skill was evaluated at the conclusion of the learner period, teens with ADHD exhibited more driving errors than their typically developing (TD) counterparts ($p = 0.034$). Teens with TSF were more likely to have their ODA terminated ($p = 0.019$), had marginally lower overall driving scores ($p = 0.098$), and exhibited more critical driving errors ($p = 0.01$) compared with TD teens.
CONCLUSION: These findings may have implications on the learning-to-drive period for adolescents with attention deficits. Adjustments may need to be made to the learner period for teens with attention deficits to account for attention impairments and to better instill safe driving behavior

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J Dev Behav Pediatr. 2019 Sep;40:563-65.
TRANSITIONS, SUICIDALITY, AND UNDERAPPRECIATED AUTISM SPECTRUM DISORDER IN A HIGH SCHOOL STUDENT.
Ignaszewski MJ, Munshi K, Fogler J, et al.
Alex is a 14-year-old Portuguese-American boy with a psychiatric history starting at age 5 who presents to your primary care practice after an insurance change.He was delivered prematurely at 32 weeks and diagnosed with congenital hypothyroidism at the age of 6 weeks and growth hormone deficiency at the age of 2 years; he is in active treatment for both. He otherwise met developmental milestones on time yet continues to have significant fatigue despite adequate sleep and vitamin D supplementation.His family history is remarkable for maternal anxiety, depression, suicidal thoughts, and previous attempted suicide, as well as anxiety, alcoholism, depression, and attention-deficit/hyperactivity disorder (ADHD) in the extended family.Alex has had multiple psychiatric diagnoses by sequential providers. He was diagnosed with generalized anxiety disorder and ADHD by 5 years of age, major depressive disorder by 11 years of age, persistent depressive disorder by 12 years of age, and ultimately disruptive mood dysregulation disorder because of severe and persistent temper outbursts associated with negative mood and behavioral dysregulation, leading to recurrent crisis evaluations. He has been psychiatrically hospitalized twice, in the fifth and seventh grade, for suicidal ideation (SI) and elopement from home, respectively. He recently completed a 2-week acute residential placement, during which no medication changes were made. Current medications include escitalopram 20 mg daily, guanfacine 1 mg 3 times daily, sustained release bupropion 100 mg twice daily, levothyroxine, vitamin D, and a weekly somatropin injection. He has not been able to tolerate psychostimulants or nonstimulant agents because of treatment-emergent SI.Now in the ninth grade, he continues to be easily distracted by peers, with impulsive behaviors and reduced self-regulation. Despite receiving special education services since the fifth grade, his academic performance has been poor, and he has limited motivation. Previous testing indicated average in an intelligence quotient test, with relative deficits in working memory compared with above average strength in fluid reasoning. He dislikes school and has few friends. He has always been noted to be "immature." He displays temper tantrums at home and school around transitions and behavioral expectations and has complained of feeling "different" and misunderstood by peers in addition to having difficulty reading social cues. His interests include acting and playing Fortnite and other video/computer games. His screen time is limited to 1 to 2 hr/d by the family.As the new clinician, you raise the possibility of undiagnosed autism spectrum disorder as a unifying/underlying diagnosis with his mother, who disagrees and does not consent to additional workup despite your recommendations. How would you proceed with next steps to best support your patient and his family in obtaining further clarifying evaluation?

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J Dev Behav Pediatr. 2019 Jun;40:397-99.

CARING FOR THE TRANSGENDER ADOLESCENT: IT TAKES A VILLAGE.

Agana M, Apple R, Alavi Z, et al.

Christa is a 15-year-old male-to-female (MTF) transgender patient who comes to your Developmental-Behavioral Pediatrics office for consultation on attention deficit/hyperactivity disorder (ADHD) management and concerns about worsening anxiety. Review of medical history included mild persistent asthma managed with steroid inhaler and leukotriene antagonist. She was diagnosed with ADHD at 12 years and has been placed on methylphenidate and clonidine over the years with little improvement. She struggles in school, with barely passing grades, and feels that she cannot focus on her assignments.She was diagnosed with MTF transition gender dysphoria, social anxiety disorder, and depressive disorder at 13 years by a psychiatrist and was treated with sertraline with some mood improvement. More recently, she reports having thoughts of wanting to hurt people and "wanting to watch them wither away." She expressed being terrified by these thoughts, which lasted for a couple of days but have since resolved. She denied any suicidal thoughts recently and gives credit to her "best girlfriend" for her overall improved mood, improved sleep pattern, and increased energy level. She expressed having deepening feelings for this girlfriend but admitted to not having acted on these feelings as she is afraid of the consequences. She currently uses the pronouns she/her/hers.Family history is pertinent for paternal bipolar disorder. There is considerable psychosocial stress as Christa is estranged from her father, who is not supportive of her transition, although mother is. Unfortunately, she is dependent on her father for medical insurance coverage, and he is refusing to give authorization to proceed with the evaluations and diagnostic workup for the transformation. Christa has been repeatedly encouraged to seek counseling but has declined because of previous poor experiences with counselors. Her primary care clinician in Family Medicine has been administering hormonal replacement therapy because she cannot access the regional center of excellence because of above-mentioned insurance issues. She presents to you now with her mother for management suggestions and diagnostic clarification. What is your next step?

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J Dev Behav Pediatr. 2019 Jun;40:330-34.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS: CLINICAL OUTCOMES AND DIABETES CONTROL.

Vinker-Shuster M, Golan-Cohen A, Merhasin I, et al.

OBJECTIVE: To assess the interactions between attention-deficit hyperactivity disorder (ADHD) and type 1 diabetes mellitus (T1DM), including diabetes outcomes and patients' general health status.

METHODS: Primary care and hospital records of patients aged 5 to 18 years with T1DM were analyzed using the Leumit Health Services database. The diabetic control and general health of patients with T1DM and ADHD diagnoses were compared with those of patients with T1DM alone in a cross-sectional study. The ADHD group included patients with ADHD diagnosis who purchased at least 3 prescriptions of psychostimulant agents and nootropics. Parameters including demographic, clinical, and laboratory data were collected and assessed.

RESULTS: The study included 230 patients with T1DM; of them, 24 had ADHD (10.4%). Twenty of 24 patients with ADHD (83.3%) had hemoglobin A1C of 9% and higher versus 87 of 206 patients with diabetes alone (43.3%) ($p < 0.05$). The ADHD group had significantly higher annual emergency department admissions [15/24 (62.5%) vs 77/201 (37.4%); $p < 0.05$], higher annual hospitalization rates [18/24 (75%) vs 78/206 (37.9%); $p < 0.05$], and longer hospitalization stays (mean, 2.21 vs 0.65 days; $p < 0.05$). The total medical annual costs per patient were twice as high in the ADHD group ($p < 0.05$). In multivariate analysis, these unfavorable outcomes of the ADHD group were preserved.

CONCLUSION: In this study, having ADHD and T1DM comorbidity was associated with a higher complications rate and poorer diabetes control in comparison to having T1DM alone. Although further research is needed, our data suggest that this group requires special care and attention of the medical staff

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J Dev Behav Pediatr. 2019 Oct;40:573-80.

ADVERSE CHILDHOOD EXPERIENCES AND FAMILY RESILIENCE AMONG CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schneider M, VanOrmer J, Zlomke K.

OBJECTIVES: The purpose of the present study was to (1) examine the differences in adverse childhood experiences (ACEs) among children with autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and comorbid ASD/ADHD and healthy neurodevelopmental controls; (2) explore the levels of family resilience across diagnostic categories; (3) identify the differences in family resilience by the number of ACEs; and (4) explore the interaction between ACEs and the diagnostic category on family resilience.
METHOD: Participants were 2083 children between the ages of 6 and 17 years (M = 12.23, SD = 3.36) from the 2016 National Survey of Children's Health. The majority of the sample were male (68.7%) and white (78.6%).
RESULTS: Overall, youth diagnosed with solely ADHD had the highest number of ACEs (Madj = 1.94). In addition, individuals who endorsed exposure to 1 ACE reported higher levels of family resilience in comparison to those who reported 0 ACEs or 2 or more ACEs. Family resilience did not differ between youth who experienced 2 or more ACEs and youth who experienced 0 ACEs. Youth diagnosed with comorbid ASD/ADHD had the lowest levels of family resilience. Interestingly, family resilience did not differ between ADHD and neurotypical youth.
CONCLUSION: Youth diagnosed with ADHD seem to be at the highest risk for ACEs. Those with comorbid ASD/ADHD report the lowest levels of family resilience when controlling for exposure to ACEs. Families of youth with ASD had lower levels of family resilience than those of neurotypical youth when controlling for exposure to ACEs, whereas families of youth with solely ADHD displayed similar levels of family resilience in comparison to neurotypical youth and their families. Results have implications for prevention and intervention with ASD and/or ADHD youth and their families

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J Dev Behav Pediatr. 2019 May;40:249-56.

CHILDREN'S INATTENTION AND HYPERACTIVITY, MOTHER'S PARENTING, AND RISK BEHAVIORS IN ADOLESCENCE: A 10-YEAR LONGITUDINAL STUDY OF CHILEAN CHILDREN.

Nelson T, East P, Delva J, et al.

OBJECTIVE: To examine how mothers' nurturant and, separately, hostile parenting mediate the effects of young children's inattentiveness and hyperactivity on risk behaviors in adolescence.
METHOD: Data were analyzed from 920 healthy Chilean children, studied at 5.5, 10 years, and adolescence. Children's hyperactivity and inattentiveness at 5.5 years were assessed by mother ratings on the Children's Adaptive Behavior Inventory. Mothers' nurturance and hostility toward the child at 10 years were assessed by maternal interview on the Home Observation for Measurement of the Environment. Youth's delinquent and aggressive behaviors in adolescence were compiled from the Youth Self-Report questionnaire, and youth's substance use in adolescence was assessed by an extensive self-report substance use inventory. Structural equation modeling was used to identify direct and indirect effects.
RESULTS: Findings supported a mediating effect, with more severe child hyperactivity at 5.5 years leading to mothers' greater hostility toward her child at age 10, which, in turn, led to greater delinquency and aggression in adolescence. Marginal mediating effects were also found from child hyperactivity and inattention at 5.5 years to mothers' lower nurturance at 10 years to youth substance use in adolescence.
CONCLUSION: Mothers' hostile treatment of children with hyperactive or inattentive behaviors contributed to adolescent risk behaviors and is an area of intervention

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J Dev Behav Pediatr. 2019 Oct;40:651-53.

MAINTAINING SAFETY AND PLANNING FOR THE FUTURE.

Allen C, Fehr KK, Nyp SS.

Kevin is a 12-year-old boy with autism spectrum disorder, intellectual disability (nonverbal IQ scores in mid-40s), and attention-deficit/hyperactivity disorder who has been followed up by a developmental-behavioral pediatrician (DBP) and a child psychologist for medication and behavioral management since he was 4 years old. Kevin was placed in the care of his great-great-aunt shortly after he turned 2 years of age because of concerns of neglect. She is now his legal guardian.Kevin is predominately nonverbal but does use a few single words to make requests or label items. He attends a public school and receives full-time special education support. He has a personal care assistant (PCA) who provides in-home support 5 to 6 days/wk for 3 to 4 hours at a time. The PCA is working on toilet training, using a "clock-training" approach, and also takes Kevin outdoors to play or on short outings during her visits. In his free time, Kevin prefers to watch cooking shows on television.Over the past year, Kevin's behaviors have become more concerning. There have been several episodes of Kevin waking up during the early morning hours and going to the kitchen to "cook." After one of these episodes, his guardian was not aware that Kevin had woken up until the next morning when she found a concoction of corn starch, coffee grounds, cottage cheese, and powdered drink mix in the blender. Kevin had also woken up during the night and ventured out of the house into the back yard. His guardian had woken up immediately as the alarm system sounded when he opened the outer door from the house to the yard.A door alarm was added to Kevin's bedroom door so that his guardian would be alerted when he leaves his bedroom; however, the alarm is not used consistently because there are times when the alarm cannot be found at bedtime. Kevin's guardian was able to obtain a GPS device for him to wear on his shoe from the local police department. He wears this without resistance every day.Kevin's guardian is in her mid-70s, and she has had several health issues over the past 2 to 3 years. There are no other family members who are willing or able to care for Kevin if his guardian were no longer able to. The DBP and child psychologist have encouraged Kevin's guardian to explore long-term residential care options with the state agency that provides support for individuals with intellectual disabilities and with Kevin's insurance provider, but the guardian is very reluctant to do this. She fears that Kevin will be removed from her care or placed in a "home" where someone will "do bad things to him."What else would you recommend or actions would you take to support Kevin's guardian in ensuring Kevin's safety and planning for his future care?

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J Intellect Disabil Res. 2019 May;63:408-17.

FACTORS ASSOCIATED WITH DEPRESSION AND ANXIETY IN CHILDREN WITH INTELLECTUAL DISABILITIES.

Whitney DG, Shapiro DN, Peterson MD, et al.

BACKGROUND: Individuals with intellectual disabilities (ID) are at increased risk for depression and anxiety disorders; however, there is a paucity of research that pertains to associative factors for these mental health disorders in this population. The objective of this investigation was to determine factors associated with depression and anxiety problems in children with ID.

METHODS: Children 6-17Â years with ID (nÂ =Â 423; 63% male) from the 2016 National Survey of Children's Health were included in this cross-sectional study. Outcome measures included depression and anxiety problems. Predictor variables included sociodemographics, ID severity, co-morbid conditions (autism spectrum disorders, epilepsy, cerebral palsy, Down syndrome and attention-deficit/hyperactivity disorder), physical factors (i.e. physical activity, sleep duration and pain) and social factors (e.g. participation in activities and bully victimisation). Multivariable logistic regression was performed to determine the association between all factors and depression and/or anxiety problems among children with ID.

RESULTS: The prevalence of depression and/or anxiety problems was 35.4%. After adjusting for sociodemographics, Hispanic race was associated with lower odds [odds ratio (OR), 0.3; 95% confidence interval (CI), 0.1-0.8] of depression and/or anxiety problems. After adjusting for race, co-morbid conditions, and physical and social factors, autism spectrum disorders (OR, 4.4; 95% CI, 1.1-10.1), Down syndrome (OR, 0.2; 95% CI, 0.1-0.8), attention-deficit/hyperactivity disorder (OR, 5.9; 95% CI, 2.5-14.3), pain (OR, 7.0; 95% CI, 2.9-17.1) and bully victimisation (OR 2.3; 95% CI, 1.0-5.3) were each associated with depression and/or anxiety problems.

CONCLUSIONS: The present study identified both treatable and modifiable, as well as unmodifiable, factors associated with depression and/or anxiety problems in children with ID

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J Magn Reson Imaging. 2019 May;49:1347-55.

ROLE OF RESTING STATE MRI TEMPORAL LATENCY IN REFRACTORY PEDIATRIC EXTRATEMPORAL EPILEPSY LATERALIZATION.

Shah MN, Nguyen RD, Pao LP, et al.

BACKGROUND: Pediatric epilepsy affects 0.5-1% of children, with 10-30% of these children refractory to medical anticonvulsant therapy and potentially requiring surgical intervention. Analysis of resting state functional MRI (rsMRI) signal temporal differences (latency) has been proposed to study the pathological cognitive processes.

PURPOSE/HYPOTHESIS: To quantitatively and qualitatively analyze the correlation of rsMRI signal latency to pediatric refractory extratemporal epilepsy seizure foci lateralization.

STUDY TYPE: Retrospective review.

POPULATION: With Institutional Review Board approval, rsMRI and anatomical MRI scans were obtained from 38 registered pediatric epilepsy surgery patients from Washington University and 259 healthy control patients from the ADHD-200 dataset.

FIELD STRENGTH/SEQUENCE: 3 T echo planar imaging (EPI) blood oxygenation level-dependent (BOLD) sequence.

ASSESSMENT: The images were transformed to pediatric atlases in Talairach space. Preoperative voxelwise latency maps were generated with parabolic interpolation of the rsMRI signal lateness or earliness when compared with the global mean signal (GMS) using cross-covariance analysis.

STATISTICAL TESTS: Latency z-score maps were created for each epilepsy patient by voxelwise calculation using healthy control mean and standard deviation maps. Voxelwise hypothesis testing was performed via multiple comparisons corrected (false discovery and familywise error rate) and uncorrected methods to determine significantly late and early voxels. Significantly late and/or early voxels were counted for the right and left hemisphere separately. The hemisphere with the greater proportion of significantly late and/or early voxels was hypothesized to contain the seizure focus. Preoperative rsMRI latency analysis hypotheses were compared with postoperative seizure foci lateralization determined by resection images.

RESULTS: Preoperative rsMRI latency analysis correctly identified seizure foci lateralization of 64-85% of postoperative epilepsy resections with the proposed methods. RsMRI latency lateralization analysis was 77-100% sensitive and 58-79% specific. In some patients, qualitative analysis yielded preoperative rsMRI latency patterns specific to procedure performed.

DATA CONCLUSION: Preoperative rsMRI signal latency of pediatric epilepsy patients was correlated with seizure foci lateralization

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J Neurodev Disord. 2019 Jun;11:8.

USING KINEMATIC ANALYSES TO EXPLORE SENSORIMOTOR CONTROL IMPAIRMENTS IN CHILDREN WITH 22Q11.2 DELETION SYNDROME.

Cunningham AC, Hill L, Mon-Williams M, et al.

BACKGROUND: The 22q11.2 deletion is associated with psychiatric and behavioural disorders, intellectual disability and multiple physical abnormalities. Recent research also indicates impaired coordination skills may be part of the clinical phenotype. This study aimed to characterise sensorimotor control abilities in children with 22q11.2 deletion syndrome (22q11.2DS) and investigate their relationships with co-occurring IQ impairments and psychopathology.

METHODS: Fifty-four children with 22q11.2DS and 24 unaffected sibling controls, comparable in age and gender, underwent kinematic analysis of their hand movements, whilst performing a battery of three visuo-manual coordination tasks that measured their tracking, aiming and steering abilities. Additionally,

standardised assessments of full-scale IQ (FSIQ), attention deficit hyperactivity disorder, indicative autism spectrum disorder (ASD) and anxiety disorder symptomatology were conducted.
RESULTS: Children with 22q11.2DS showed deficits on seven of eight kinematic descriptors of movement quality across the three coordination tasks, compared to controls. Within 22q11.2DS cases, the extent of impairment on only three kinematic descriptors was significantly related to FSIQ after correction for multiple testing. Moreover, only error whilst visuo-manually tracking was nominally associated with ADHD symptom counts.
CONCLUSIONS: Impairments in sensorimotor control are seen on a range of visuo-manual tasks in children with 22q11.2DS but the extent of these impairments are largely unrelated to the severity of other psychopathological and intellectual impairments commonly found in children with 22q11.2DS

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J Neurodev Disord. 2019 Feb;11:3.
RARE COPY NUMBER VARIATIONS AFFECTING THE SYNAPTIC GENE DMXL2 IN NEURODEVELOPMENTAL DISORDERS.
Costain G, Walker S, Argiropoulos B, et al.
BACKGROUND: Ultra-rare genetic variants, including non-recurrent copy number variations (CNVs) affecting important dosage-sensitive genes, are important contributors to the etiology of neurodevelopmental disorders (NDDs). Pairing family-based whole-genome sequencing (WGS) with detailed phenotype data can enable novel gene associations in NDDs.
METHODS: We performed WGS of six members from a three-generation family, where three individuals each had a spectrum of features suggestive of a NDD. CNVs and sequence-level variants were identified and further investigated in disease and control databases.
RESULTS: We identified a novel 252-kb deletion at 15q21 that overlaps the synaptic gene DMXL2 and the gene GLDN. The microdeletion segregated in NDD-affected individuals. Additional rare inherited and de novo sequence-level variants were found that may also be involved, including a missense change in GRIK5. Multiple CNVs and loss-of-function sequence variants affecting DMXL2 were discovered in additional unrelated individuals with a range of NDDs.
CONCLUSIONS: Disruption of DMXL2 may predispose to NDDs including autism spectrum disorder. The robust interpretation of private variants requires a multifaceted approach that incorporates multigenerational pedigrees and genome-wide and population-scale data

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J Neurodev Disord. 2019 Aug;11:19.
MAGNETOENCEPHALOGRAPHIC (MEG) BRAIN ACTIVITY DURING A MENTAL FLEXIBILITY TASK SUGGESTS SOME SHARED NEUROBIOLOGY IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.
Mogadam A, Keller AE, Arnold PD, et al.
BACKGROUND: Children with neurodevelopmental disorders (NDDs) exhibit a shared phenotype that involves executive dysfunctions including impairments in mental flexibility (MF). It is of interest to understand if this phenotype stems from some shared neurobiology.
METHODS: To investigate this possibility, we used magnetoencephalography (MEG) neuroimaging to compare brain activity in children (n=88; 8-15 years) with autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), as they completed a set-shifting/mental flexibility task.
RESULTS: Neuroimaging results revealed a similar parietal activation profile across the NDD, groups suggesting a link to their shared phenotype. Differences in frontal activity differentiated the three clinical groups. Brain-behaviour analyses showed a link with repetitive behaviours suggesting shared dysfunction in the associative loop of the corticostriatal system.
CONCLUSION: Our study supports the notion that NDDs may exist along a complex phenotypic/biological continuum. All NDD groups showed a sustained parietal activity profile suggesting that they share a strong reliance on the posterior parietal cortices to complete the mental flexibility task; future studies could elucidate whether this is due to delayed brain development or compensatory functioning. The differences in frontal

activity may play a role in differentiating the NDDs. The OCD group showed sustained prefrontal activity that may be reflective of hyperfrontality. The ASD group showed reduced frontal activation suggestive of frontal dysfunction and the ADHD group showed an extensive hypoactivity that included frontal and parietal regions. Brain-behaviour analyses showed a significant correlation with repetitive behaviours which may reflect dysfunction in the associative loop of the corticostriatal system, linked to inflexible behaviours

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J Neuroendocrinol. 2019 Nov;31:e12803.

HYPOGONADOTROPHIC HYPOGONADISM, DELAYED PUBERTY AND RISK FOR NEURODEVELOPMENTAL DISORDERS.

Ohlsson G, V, SÃ¶der O, et al.

Hypogonadotrophic hypogonadism (HH) is a rare disorder that manifests absent puberty and infertility. Genetic syndromes with hypogonadism, such as Klinefelter syndrome, are associated with an increased risk of neurodevelopmental disorders (NDDs). However, it is not clear whether patients with HH or transient delayed puberty in general, have an increased risk of NDDs. We performed a register-based study on a national cohort of 264 patients with HH and 7447 patients diagnosed with delayed puberty that was matched with 2640 and 74Â 470 controls, respectively. The outcome was defined as having any of the following NDD diagnoses: (i) autism spectrum disorder (ASD); (ii) attention deficit hyperactivity disorder (ADHD); or (iii) intellectual disability (ID). Additional sensitivity analyses were performed to control for different parental and birth variables, as well as diagnosed malformation syndromes and chromosomal anomalies (ie, Down's and Turner syndromes). Patients with HH had increased risk for being diagnosed with ASD (odds ratio [OR]Â =Â 5.7; 95% confidence interval [CI]Â =Â 2.6-12.6), ADHD (ORÂ =Â 3.0; 95% CIÂ =Â 1.8-5.1) and ID (ORÂ =Â 18.0; 95% CIÂ =Â 8.9-36.3) compared to controls. Patients with delayed puberty also had a significantly increased risk of being diagnosed with an NDD. These associations remained significant after adjustments. This is the first study to demonstrate a significant association between HH, delayed puberty and NDDs in a population-based cohort. Clinicians should be aware of the overlap between these disorders. Further studies should explore the mechanisms behind these associations

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J Postgrad Med. 2019 Oct;65:219-26.

ECONOMIC BURDEN OF SLOW LEARNERS: A PREVALENCE-BASED COST OF ILLNESS STUDY OF ITS DIRECT, INDIRECT, AND INTANGIBLE COSTS.

Karande S, Ramadoss D, Gogtay N.

AIMS: The primary objective of this study was to evaluate the economic burden of slow learners (students with "borderline intellectual functioning") by estimating its direct, indirect, and intangible costs. The secondary objective was to assess the impact of variables on the economic burden.

SETTINGS AND DESIGN: Cross-sectional, single-arm descriptive study.

SETTING: Learning disability clinic in a public medical college in Mumbai.

MATERIALS AND METHODS: The study cases (age 5 - 18 years) were recruited by nonprobability sampling. A structured questionnaire was used to interview the parent to collect data related to direct and indirect costs. Intangible costs data were collected by documenting the willingness-to-pay value using the contingent valuation technique.

STATISTICAL ANALYSIS USED: A quantile regression model was used to assess the impact of predictor variables on the costs.

RESULTS: The direct, indirect, and intangible costs of slow learners were INR 6,065,915, 10,298,613, and 145,172,800, respectively. Indirect costs comprised 62.9% of the total costs. Expenditure on tuitions, medications, and remedial education comprised 57.38%, 16.18%, and 10.30% of the direct costs, respectively. The average annual total costs of slow learners were INR 3,544,880. The average annual learning disability clinic costs were INR 2,250,194. The average annual total costs per student were INR 57,951. Longer duration of poor school performance was predictive of higher direct and total costs.

CONCLUSION: The economic burden of slow learners is enormous (intangible > indirect > direct costs). Tuitions are the most costly component of direct costs. Parental loss of earnings is the most costly component of indirect costs

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JAMA Netw Open. 2020 Feb;3:e1920787.

ASSOCIATIONS OF DIFFERENT TYPES OF MATERNAL DIABETES AND BODY MASS INDEX WITH OFFSPRING PSYCHIATRIC DISORDERS.

Kong L, Nilsson IAK, Brismar K, et al.

IMPORTANCE: Maternal obesity, pregestational type 1 and 2 diabetes, and gestational diabetes have been reported to increase the risk of autism spectrum disorder and attention-deficit/hyperactivity disorder in the mothers' offspring. However, the associations of maternal diabetes disorders and body mass index jointly with psychiatric disorders among offspring are less well documented, especially for type 2 diabetes.

OBJECTIVE: To examine the associations of different types of maternal diabetes, separately and together with maternal obesity, with psychiatric disorders in the mothers' offspring.

DESIGN, SETTING, AND PARTICIPANTS: This population-based cohort study used data from nationwide registries in Finland encompassing all 649 043 live births occurring between 2004 and 2014. The study and data analysis were conducted from January 1, 2019, to July 5, 2019.

EXPOSURES: Maternal prepregnancy body mass index, insulin-treated pregestational diabetes, and pregestational type 2 diabetes and gestational diabetes without insulin treatment.

MAIN OUTCOMES AND MEASURES: Psychiatric diagnoses and prescription of psychotropic drugs among the mothers' offspring. Cox proportional hazards models were adjusted for birth year, sex, mode of delivery, maternal age, number of fetuses, parity, mother's country of birth, mother's marital status, maternal smoking, maternal psychiatric disorder, and maternal systemic inflammatory disease.

RESULTS: The mean (SD) age of mothers was 30.20 (5.37) years; 357 238 of 394-302 mothers (90.6%) were born in Finland. Of the 647 099 births studied, 4000 fetuses (0.62%) were exposed to maternal insulin-treated pregestational diabetes, 3724 (0.57%) were exposed to type 2 diabetes, and 98 242 (15.18%) were exposed to gestational diabetes; 34 892 offspring (5.39%) later received a diagnosis of a mild neurodevelopmental or psychiatric disorder. Non-insulin-treated type 2 diabetes in severely obese mothers, compared with normal-weight mothers without diabetes, was associated with psychiatric disorders in the offspring (hazard ratio, 1.97; 95% CI, 1.64-2.37), although with a lower effect size than that for severely obese mothers with insulin-treated pregestational diabetes (hazard ratio, 2.71; 95% CI, 2.03-3.61). The largest effect sizes were found for mood disorders, attention-deficit/hyperactivity disorder and conduct disorders, and autism. Gestational diabetes in severely obese mothers had a lower overall effect size (hazard ratio, 1.61; 95% CI, 1.50-1.72). Diabetes in normal-weight mothers was not associated with psychopathologic disorders in the offspring.

CONCLUSIONS AND RELEVANCE: Severe obesity in mothers with diabetes was associated with an increased overall risk for psychiatric disorders in their offspring. The risk was highest for those exposed to insulin-treated pregestational diabetes, followed by non-insulin-treated type 2 diabetes and gestational diabetes. These findings may have implications for managing pregnancies

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J Abnorm Child Psychol. 2020 Sep;48:1129-41.

RISK TAKING BY ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A BEHAVIORAL AND PSYCHOPHYSIOLOGICAL INVESTIGATION OF PEER INFLUENCE.

Dekkers TJ, Popma A, Sonuga-Barke Edmund JS, et al.

Adolescents with ADHD demonstrate increased risk-taking behavior (RTB) like substance abuse and dangerous traffic conduct. RTB in adolescence is more likely under peer influence. The current investigation (1) tests the hypothesis that adolescents with ADHD are particularly susceptible to such influence and (2) tests whether groups differed in autonomic reactivity to peer influence. Adolescent boys between 12 and 19Â years with (n=81) and without (n=99) ADHD performed the Balloon Analogue Risk Task twice. In the

peer condition, a highly credible virtual peer manipulation that encouraged risk taking was added, in the solo condition this was absent. Autonomic reactivity was indexed by heart rate (HR), pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA). All adolescents engaged in more risk taking in the peer condition relative to solo condition. Autonomic differences between groups were only found on PEP: a stronger sympathetic response to peer influence was observed in typically developing adolescents relative to adolescents with ADHD. Increased physiological stress (as indexed by PEP) in the peer relative to the solo condition predicted peer-induced risk taking in all adolescents. We conclude that susceptibility to peer influence is not exaggerated in ADHD but rather reflects a general tendency of adolescents. As adolescents experiencing peer influence as stressful are most susceptible to peer influence, we suggest that increasing resistance to peer influence may be an important treatment aim for these adolescents specifically

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J Affective Disord. 2020;277:109-14.

ASSOCIATION OF PARENTAL DEPRESSION WITH OFFSPRING ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER: A NATIONWIDE BIRTH COHORT STUDY.

Chen LC, Chen MH, Hsu JW, et al.

Background: Studies have indicated that parental depression was slightly related to the increased risk of offspring attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). However, the association between exposure to parental depression at different neurodevelopmental stages (i.e., perinatal or postnatal period) and subsequent ADHD and ASD development remained uncertain.

Method: 708,515 children born between 2001 and 2008 were screened for ADHD and ASD based on ICD-9-CM codes of 314 and 299 given by psychiatrists from their birth to the end of 2011. Paternal and maternal depression was separately assessed during five periods, namely those before pregnancy (pre-pregnancy), during pregnancy (perinatal), and <1, 1 3, and >3 years after childbirth (postnatal). Cox regression analyses were performed.

Results: Both paternal and maternal depression occurring in the pre-pregnancy, perinatal and postnatal periods were significantly associated with subsequent ADHD and ASD in the offspring, with hazard ratios between 1.42 (95% confidence interval [CI]: 1.35-1.49) and 2.25 (2.09-2.41). The chronicity and additive effect of paternal and maternal depression were related to increased risks of offspring ADHD and ASD. The effects of maternal depression were stronger than the effects of paternal depression for offspring ADHD (HR: 1.35, 95% CI: 1.27ΓÇô1.45) and ASD (HR: 1.23, 95% CI: 1.05ΓÇô1.46) risks.

Conclusion: Both paternal depression and maternal depression in the pre-pregnancy, perinatal and postnatal periods increases offspring ADHD and ASD risks, and these risks increase further with increases in the duration of parental depression and with the additive effect of parental and maternal depression

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J Autism Dev Disord. 2020.

BRIEF REPORT: PREDICTORS OF SCHOOL REFUSAL DUE TO BULLYING IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McClemont AJ, Morton HE, Gillis JM, et al.

Children with Autism Spectrum Disorder (ASD) or Attention-Deficit/Hyperactivity Disorder (ADHD) are at increased risk for bullying victimization. School refusal is a red flag for identification of bullying in children with ASD and/or ADHD. This study examined the impact of diagnoses, demographics, and school variables on school refusal due to bullying. Participants were 97 parents of 154 children with ASD, ADHD, ASD + ADHD, other diagnoses, or no diagnosis. Children with ASD + ADHD were most likely to refuse school due to bullying. Classroom aides and behavior problems were protective and risk factors, respectively. In the final regression model, child diagnosis no longer predicted school refusal. School refusal and problem behavior warrant consideration as a marker of distress for victimized children

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J Autism Dev Disord. 2020.

THE SELF OF ADOLESCENTS WITH AUTISM SPECTRUM DISORDER OR ATTENTION DEFICIT HYPERACTIVITY DISORDER: A QUALITATIVE STUDY.

Hanai F, Narama M, Tamakoshi K.

Self-development is a central developmental issue in adolescence, there are few studies describing the experiences related to the self in adolescents with autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). We conducted semi-structural interviews with 14 adolescents with ASD and three with ADHD to describe the self. As a result of inductive continuous comparison analysis, three concepts Interest in self and self-realization, Intentionality and self-transformation, Unrealized/unnoticed self were generated. It was suggested that the characteristic perceptions may tend to have difficulty realizing subjective selves. Otherwise, most adolescents realized various sense of self through interaction with others. Nurses should know adolescents inner world and share their emotions related to their self-recognition in order to provide care that meets important youth developmental needs

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Journal of Behavioral Addictions. 2020;9:401-09.

LOW SELF-CONTROL AND AGGRESSION EXERT SERIAL MEDIATION BETWEEN INATTENTION/HYPERACTIVITY PROBLEMS AND SEVERITY OF INTERNET GAMING DISORDER FEATURES LONGITUDINALLY AMONG ADOLESCENTS.

Jeong H, Yim HW, Lee SY, et al.

Objectives: We examined serial mediating roles of low self-control and aggression in explaining relationships between levels of inattention and hyperactivity problems (IHPs) and severity of Internet gaming disorder (IGD) features when exposed to online games among adolescents without Attention deficit hyperactivity disorder (ADHD) stratified by gender using three-wave longitudinal study.

Method: The sample comprised a total of 1,732 family dyads from a study that was conducted among seventh graders without diagnoses of ADHD at baseline. Levels of IHPs were assessed by the parent reported Korean version of the ADHD rating scale at baseline (wave1). Severity of IGD features was assessed by the Internet Game Use-Elicited Symptom Screen (IGUESS) at wave3. Both levels of selfcontrol (wave1) and aggression (wave2) were assessed by self-report. The mediating role of low selfcontrol and aggression in the relationships between level of IHPs and severity of IGD were evaluated using serial mediation analysis separately for each gender.

Results: Levels of IHPs were related directly to severity of IGD features in both genders. The indirect effects via low self-control were also significant in both genders, however, the indirect effects via aggression was significant only in women. The serial mediation effect via low self-control and aggression between levels of IHPs and IGD features was significant in both genders (men, coefficient:0.009, 95%CI 0.005-0.019; women, coefficient:0.010, 95%CI:0.005-0.026).

Conclusion: We revealed a possible mechanism underlying a serial mediation chain from low self-control to aggression explaining the effects of IHPs on severity of IGD features. However, this conclusion should be taken with a caution, because the effect sizes were very low

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J Child Psychol Psychiatry. 2020 Sep;61:1009-18.

MECHANISMS LINKING PARENTAL EDUCATIONAL ATTAINMENT WITH CHILD ADHD, DEPRESSION, AND ACADEMIC PROBLEMS: A STUDY OF EXTENDED FAMILIES IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY.

Fartein AT, Espen ME, McAdams TA, et al.

Background Low educational attainment in parents is associated with child psychopathology. It is not clear whether the associations are due to risk factors that family members share or due to effects of maternal or paternal education on the offspring. We investigate whether associations between maternal and paternal educational attainment and child symptoms of attention deficit/hyperactivity disorder (ADHD), depression, and academic problems are due to shared genetic factors, shared family environmental factors, or effects of the parental phenotype educational attainment itself.

Methods This study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa). The sample comprised 34,958 children (17,128 girls) in 28,372 extended-family units. We used data from related nuclear families linked by siblings in the parent generation. We applied a quasi experimental extended children of twins design that included siblings in both generations and took account of nonrandom mating by including partners. Educational attainment was self-reported by mothers and fathers. Mothers reported children's symptoms of ADHD, symptoms of depression, and academic problems by questionnaire when the children were 8Â years old.
Results Children of lowly educated parents scored higher on all outcomes and had an approximate doubling of the risk of high symptom levels. The association between maternal and paternal educational attainment and child symptoms of ADHD and academic problems persisted after controlling for shared genetic and family environmental factors. Phenotypic transmission to depression was weaker and in the best fitting model fully explained by genetic factors shared by the two generations.
Conclusions Associations between educational attainment of mothers and fathers and child symptoms of ADHD and academic problems could not be ascribed to shared familial risk factors, whereas associations with symptoms of depression could. Parental education or resources and behaviors resulting from low education might be targets of interventions aimed at reducing symptoms of ADHD and academic problems

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J Clin Diagn Res. 2020;14:YC01-YC04.

COMPARATIVE EFFICACY OF STRUCTURED GAMES AND BEHAVIOURAL PARENT TRAINING ON WORKING MEMORY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PILOT STUDY.

Raghuveer R, Ruchi.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) may develop during the preschool years of the child and extend into adulthood. ADHD also leads to impaired Working Memory (WM) creating problems in various functions. Aim: To compare the effectiveness of behavioural parent training and structured games on WM of children with ADHD.
Materials and Methods: This prospective interventional study was conducted in 18 schools of Ghaziabad city, Uttar Pradesh, India. Seventy subjects were selected based on Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. Group A (n=35) received structured games and Group B (n=35) received Behavioural Parent Training (BPT). Seguin Form Board Test Time (SFBTT) was recorded as outcome on baseline and 5th week. Student's paired and unpaired t-test was done. SPSS 22.0 version was the software used and $p<0.05$ was considered as level of significance.
Results: Analysed data showed significant results within structured games group with $t=2.355$, $p<0.05$, and no significant result within BPT group with $t=-0.776$, $p>0.05$. Between group comparison showed significant difference with $t=-2.804$, $p<0.05$.
Conclusion: Training of WM in form of structured games can be an effective method when compared to BPT in children with ADHD

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Journal of Clinical Medicine. 2020;9:1-17.

METHYLPHENIDATE IN AUTISM SPECTRUM DISORDER: A LONG-TERM FOLLOW UP NATURALISTIC STUDY.

Ventura P, de Giambattista C, Spagnoletta L, et al.

Autism spectrum disorder (ASD) often co-occurs with attention deficit/hyperactivity disorder (ADHD). Although methylphenidate (MPH) efficacy and safety are well-demonstrated for ADHD, evidences are scant in the context of ASD. This naturalistic study aimed to analyze long-term MPH efficacy and safety in 40 ADHD children and adolescents with comorbid ASD, comparing them with 40 ones affected by ADHD without ASD. Treatment lasted from 6 to 156 months (longer than 24 months in more than three quarters of patients). Efficacy and safety were measured by clinical global impression and children global assessment scales; influence of intellectual functioning was examined. Comparisons between groups were made by Wilcoxon or Friedmann tests; relationships between functioning scores and other characteristics were analyzed by ordinal logistic and linear regression. Results demonstrated that MPH in patients with ASD was associated with

significative reduction of illness severity, clinical improvement and amelioration of global functioning, without significant differences with patients having ADHD without ASD. The trend of reduction of illness severity and increase of global functioning were favorably related with intellectual functioning. No serious adverse events were reported. The findings showed that long-term MPH was effective and well-tolerated in ADHD children and adolescents with comorbid high functioning ASD

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Journal of Experimental Psychology. 2020 Sep;149:1615.

PARTICIPANT' EXPERIMENTER RAPPORT IN EXPERIMENTAL SETTINGS: A TEST CASE OF EXECUTIVE FUNCTIONS AMONG CHILDREN WITH ADHD.

Gidron M, Sabag M, Yarmolovsky J, et al.

There is a growing interest in the effects of social engagement on cognition, yet, research on the effects of social engagement with the experimenter in empirical contexts has been sparse. During an experiment, the experimenter and participant form a dyad, establishing a certain level of rapport-a sense of a positive and congruent relationship. This rapport is thought to promote performance by providing a comfortable testing environment, thereby reducing resource demand, and enhancing participant engagement and willingness to exert effort to perform. The current study sought to better understand the role of rapport by examining the effects of perceived rapport on effortful control, that is, inhibition and shifting, in an experimental setting among children with and without attention-deficit/hyperactivity disorder (ADHD). Forty-nine children (9 to 12 years old) were divided into two groups based on ADHD classification (i.e., typically developing children, n = 27; children with ADHD, n = 22). Participants completed the day/night Stroop task and the Wisconsin Card Sorting Task following a short rapport-building conversation with the experimenter. Later, both participant and experimenter filled the CHARM questionnaire reporting the rapport constructed during the experiment. Results show moderating effects of ADHD on the relationship between perceived rapport quality and congruency, and participant's executive functions performance. Specifically, children with ADHD showed higher susceptibility to rapport quality and were impervious to the effects of rapport congruency. Results highlight the importance of rapport with the experimenter in experimental research and suggest incorporating considerations concerning rapport, both in designing the experimental paradigm as well as an independent factor affecting task performance and outcome

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J Indian Assoc Child Adolesc Ment Health. 2020;16:13-32.

TOBACCO USE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN EXPLORATORY STUDY.

Mathur R, Jhanjee S, Sagar R, et al.

Background: Substance use disorders are now conceptualized as having their developmental roots in childhood. The risk of substance use has been reported to be higher among children with Attention Deficit Hyperactivity Disorder (ADHD) as compared to the normal population. We aimed to examine the proportion of tobacco use in children and adolescents with ADHD and compare it with healthy age-matched controls.

Methodology: Cross-sectional observational study, with a sample size of 50 male cases of ADHD and 50 healthy age-matched controls. Following informed consent from parents and assent from children, participants and parents were interviewed using a semi-structured questionnaire and MINI Kid. The severity of ADHD was assessed using Conner's parent rating scale-short form (CPRS-S).

Results: Tobacco use was present significantly more among the cases of ADHD as compared to the control group (34% versus 4%, $p < 0.001$). The most common tobacco product used by the case group was chewable (smokeless) tobacco. No differences were found in the tobacco use pattern among those with ADHD alone and those with ADHD and comorbid conduct/oppositional defiant disorder.

Conclusion: There is an increased risk of tobacco use in children and adolescents with ADHD. This underscores the importance of incorporating screening for tobacco use as a necessary component of the evaluation of cases with ADHD

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Journal of Nutrition. 2020;150:1516-28.

MATERNAL IODINE STATUS DURING PREGNANCY IS NOT CONSISTENTLY ASSOCIATED WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER OR AUTISTIC TRAITS IN CHILDREN.

Levie D, Bath SC, Guxens M, et al.

Severe iodine deficiency during pregnancy can cause intellectual disability, presumably through inadequate placental transfer of maternal thyroid hormone to the fetus. The association between mild-to-moderate iodine deficiency and child neurodevelopmental problems is not well understood. Objectives: We investigated the association of maternal iodine status during pregnancy with child attention-deficit hyperactivity disorder (ADHD) and autistic traits. Methods: This was a collaborative study of 3 population-based birth cohorts: Generation R (n = 1634), INfancia y Medio Ambiente (n = 1293), and the Avon Longitudinal Study of Parents and Children (n = 2619). Exclusion criteria were multiple fetuses, fertility treatment, thyroid-interfering medication use, and pre-existing thyroid disease. The mean age of assessment in the cohorts was between 4.4 and 7.7 y for ADHD symptoms and 4.5 and 7.6 y for autistic traits. We studied the association of the urinary iodine-to-creatinine ratio (UI/Creat) <150 ++g/g - in all mother-child pairs, and in those with a urinary-iodine measurement at Γëñ18 weeks and Γëñ14 weeks of gestation - with the risk of ADHD or a high autistic-trait score (93rd percentile cutoff), using logistic regression. The cohort-specific effect estimates were combined by random-effects meta-analyses. We also investigated whether UI/Creat modified the associations of maternal free thyroxine (FT4) or thyroid-stimulating hormone concentrations with ADHD or autistic traits. Results: UI/Creat <150 ++g/g was not associated with ADHD (OR: 1.2; 95% CI: 0.7, 2.2; P = 0.56) or with a high autistic-trait score (OR: 0.8; 95% CI: 0.6, 1.1; P = 0.22). UI/Creat <150 ++g/g in early pregnancy (i.e., Γëñ18 weeks or Γëñ14 weeks of gestation) was not associated with a higher risk of behavioral problems. The association between a higher FT4 and a greater risk of ADHD (OR: 1.3; 95% CI: 1.0, 1.6; P = 0.017) was not modified by iodine status. Conclusions: There is no consistent evidence to support an association of mild-to-moderate iodine deficiency during pregnancy with child ADHD or autistic traits

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J Am Acad Child Adolesc Psychiatry. 2020.

EFFECT OF PARENT TRAINING ON HEALTH-RELATED QUALITY OF LIFE IN PRESCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SECONDARY ANALYSIS OF DATA FROM A RANDOMIZED CONTROLLED TRIAL.

Larsen LB, Daley D, Lange AM, et al.

Objective: School-age children with attention-deficit/hyperactivity disorder (ADHD) have reduced health-related quality of life (HRQoL), but it is unclear whether this is also true for preschool children. It is unknown whether parent training (PT) improves HRQoL. This study compared HRQoL in preschool children with ADHD with age-matched children from the general population; examined whether PT improves HRQoL; and tested if treatment-related changes in HRQoL were mediated by improvements in ADHD, parent efficacy, and family stress.

Method: Parents of 164 children age 3ΓÇô7 years with an ADHD diagnosis participated in a randomized controlled trial comparing the New Forest Parenting Programme and treatment as usual. Measures of HRQoL, ADHD, parent efficacy, and family stress were completed at baseline, posttreatment, and 36-week follow-up. Child baseline HRQoL was compared with two general population-based reference groups. PT effects were analyzed using linear models and mediation analyses.

Results: Preschoolers with ADHD had lower HRQoL than the reference groups. The New Forest Parenting Programme, but not treatment as usual, was associated with improvement in psychosocial HRQoL at posttreatment (change 2.28, 95% CI [0.78, 3.77]) and at 36-week follow-up (change 2.05, 95% CI [0.56, 3.54]). This difference between treatment arms was not statistically significant. Parent efficacy and family stress scores at posttreatment significantly mediated improvements in HRQoL at 36-week follow-up; ADHD scores at posttreatment did not.

Conclusion: ADHD negatively impacts HRQoL in early childhood. PT for ADHD has the potential to improve HRQoL independently of its effects on ADHD symptoms.

Clinical trial registration information: A Controlled Study of Parent Training in the Treatment of ADHD in Young Children (D'SNAPP); http://clinicaltrial.gov/; NCT01684644

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J Can Acad Child Adolesc Psychiatry. 2020;29:188-201.

FACING THE METHODOLOGICAL CHALLENGE IN DISSECTING THE GENETICS OF ADHD: A CASE FOR DEEP PHENOTYPING AND HETEROGENEITY REDUCTION.

Sengupta SM, Grizenko N, Fortier M+, et al.

Objective: The aetiology of ADHD is complex, with genetic and environmental factors both implicated in the disorder. The most recent ADHD genome-wide association study identified 12 loci that showed significant association with the disorder. However, as highlighted by the authors, these loci only capture a tiny fraction of the risk for ADHD. It has been suggested that it may be important to disentangle: (1) the clinical complexity of the disorder, and (2) the complex interaction between genetic and environmental factors, in order to better dissect the aetiology of the disorder.

Method: We have conducted a clinically-relevant Pharmaco-Behavioural Genetic study in a large group of children with ADHD (~850 families) over the last 15 years. The study includes detailed evaluation of quantitative behavioural and neuropsychological phenotypes, as well as short-term response of these phenotypes to treatment with a fixed dose of methylphenidate (0.5mg/kg in a b.i.d. dose). Specific genetic markers and environmental factors were examined for their association with these dimensions.

Results: Here we present results that highlight the importance of examining genetic association with quantitative traits, including those constructs having relevance to Research Domain Criteria (RDoC). Further, we demonstrate that by conducting association analysis in groups of children stratified based on exposure to key environmental exposure (maternal smoking or stress during pregnancy), we are able to increase the sensitivity for finding genes involved in the disorder.

Conclusion: These results suggest that deep phenotyping and heterogeneity reduction may be imperative in order to uncover the missing heritability of the disorder

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J Can Acad Child Adolesc Psychiatry. 2020;29:177-87.

BARRIERS AND FACILITATORS ASSOCIATED WITH THE MANAGEMENT OF AGGRESSIVE AND DISRUPTIVE BEHAVIOUR IN CHILDREN: A QUALITATIVE STUDY WITH PEDIATRICIANS.

Speranzini N, Goodarzi Z, Casselman L, et al.

Background: Aggressive and disruptive behaviours are frequently observed in children. Short-term use of antipsychotics with monitoring for adverse effects is recommended when first-line interventions fail (e.g. psychosocial therapies and psychostimulants for ADHD). This study aimed to understand the barriers and facilitators to behavioural change for the management of aggressive and disruptive behaviours by pediatricians.

Methods: This was a qualitative study with twenty community-based pediatricians. An interview guide was developed to elicit beliefs associated with practice behaviours. We used thematic content analysis with the Theoretical Domains Framework to inform knowledge translation interventions, by helping to determine what behavioural barriers and facilitators to practice exist. Key domains which influenced behaviour were identified by evaluating the frequency of beliefs across interviews, conflicting beliefs, and the strength of beliefs impacting behaviour.

Results: Pediatricians described evaluating the impact of aggressive and disruptive behaviours, attempting to determine their cause, and using an approach that prioritized psychosocial therapies and psychostimulants. Pediatricians reported that antipsychotics were effective but that they experienced anxiety about harms, and there was a need to accept the adverse effects as a trade-off for improved function. Discontinuing antipsychotics was problematic. Despite awareness of antipsychotic-induced movement disorders and metabolic effects, there were limitations in physician skills, knowledge and resources and social influences that were a barrier to routine implementation of recommended monitoring procedures.

Conclusions: This study identifies barriers and facilitators to evidence-based practice that can be used for knowledge translation interventions to ensure a high standard of care for children prescribed antipsychotics

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Journal of the International Neuropsychological Society : JINS. 2020 Aug;26:725-32.

PRELIMINARY PSYCHOMETRICS FOR THE EXECUTIVE FUNCTION CHALLENGE TASK: A NOVEL, â€œHOTâ€• FLEXIBILITY, AND PLANNING TASK FOR YOUTH.

Kenworthy L, Freeman A, Ratto A, et al.

Objective: Executive functions (EF) drive health and educational outcomes and therefore are increasingly common treatment targets. Most treatment trials rely on questionnaires to capture meaningful change because ecologically valid, pediatric performance-based EF tasks are lacking. The Executive Function Challenge Task (EFCT) is a standardized, treatment-sensitive, objective measure which assesses flexibility and planning in the context of provocative social interactions, making it a hot EF task.

Method: We investigate the structure, reliability, and validity of the EFCT in youth with autism (Autism Spectrum Disorder; n = 129), or attention deficit hyperactivity disorder with flexibility problems (n = 93), and typically developing (TD; n = 52) youth.

Results: The EFCT can be coded reliably, has a two-factor structure (flexibility and planning), and adequate internal consistency and consistency across forms. Unlike a traditional performance-based EF task (verbal fluency), it shows significant correlations with parent-reported EF, indicating ecological validity. EFCT performance distinguishes youth with known EF problems from TD youth and is not significantly related to visual pattern recognition, or social communication/understanding in autistic children.

Conclusions: The EFCT demonstrates adequate reliability and validity and may provide developmentally appropriate, treatment-sensitive, and ecologically valid assessment of hot EF in youth. It can be administered in controlled settings by masked administrators

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Language, Speech & Hearing Services in Schools (Online). 2020 Jul;51:795-806.

EXAMINING THE ROLE OF LANGUAGE IN PLAY AMONG CHILDREN WITH AND WITHOUT DEVELOPMENTAL DISABILITIES.

Short EJ, Schindler RC, Obeid R, et al.

Purpose: Play is a critical aspect of children's development, and researchers have long argued that symbolic deficits in play may be diagnostic of developmental disabilities. This study examined whether deficits in play emerge as a function of developmental disabilities and whether our perceptions of play are colored by differences in language and behavioral presentations.

Method: Ninety-three children participated in this study (typically developing [TD]; n = 23, developmental language disorders [DlD]; n = 24, attention-deficit/ hyperactivity disorder [ADHD]; n = 26, and autism spectrum disorder [ASD]; n = 20). Children were videotaped engaging in free-play. Children's symbolic play (imagination, organization, elaboration, and comfort) was scored under conditions of both audible language and no audible language to assess diagnostic group differences in play and whether audible language impacted raters' perception of play.

Results: Significant differences in play were evident across diagnostic groups. The presence of language did not alter play ratings for the TD group, but differences were found among the other diagnostic groups. When language was audible, children with DLD and ASD (but not ADHD) were scored poorly on play compared to their TD peers. When language was not audible, children with DLD were perceived to play better than when language was audible. Conversely, children with ADHD showed organizational deficits when language was not available to support their play. Finally, children with ASD demonstrated poor play performance regardless of whether language was audible or not.

Conclusions: Language affects our understanding of play skills in some young children. Parents, researchers, and clinicians must be careful not to underestimate or overestimate play based on language presentation. Differential skills in language have the potential to unduly influence our perceptions of play for children with developmental disabilities

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Nat Med J China. 2020;100:2446-51.

CHARACTERISTICS OF EXECUTIVE FUNCTION IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER COMORBID WITH HIGH FUNCTIONING AUTISM.

Zhang S, Wang P, Yang B, et al.

Objective: To explore the characteristics of executive function in children with attention-deficit/hyperactivity disorder comorbid with high functioning autism.

Methods: A total of 165 children with attention-deficit/hyperactivity disorder (ADHD group), 65 children with attention-deficit/Hyperactivity disorder comorbid with high functioning autism (ADHD-HFA group), and 84 healthy controls (control group) (based on the criteria of DSM-5) were recruited from the Outpatient Clinic of Child Healthcare Department of Shen Zhen Children's Hospital. The Rey complex figure test (RCFT), trail making test (TMT), Stroop color-word test were used to assess working memory, shifting and inhibition.

Results: ADHD group (2.1-¦1.9, 7-¦5, 2.1-¦2.0 and 7-¦5) and ADHD-HFA group (2.0-¦2.0, 7-¦6, 2.0-¦2.1 and 6-¦5) performed worse than control group (3.4-¦2.0, 10-¦5, 3.4-¦2.0 and 10-¦6) in Rey complex figure test (all P<0.05). ADHD group ((171-¦8) s, (27.40-¦0.82) s and (52.29-¦1.62) s) and ADHD-HFA group ((197-¦11) s, (29.7-¦1.1) s and (58.6-¦2.1) s) group took longer time on the TMT-2, Stroop2 and Stroop4 test than control group ((135-¦18) s, (22.4-¦1.9) s and (38.7-¦3.8) s) (all P<0.05). In children with low intelligence quotient (IQ), ADHD group ((30-¦8) s) and ADHD-HFA group ((34-¦9) s) performed worse on Stroop3 test than control group ((20-¦4) s) (all P<0.05). In children with average IQ, ADHD group ((19-¦5) s and (24-¦8) s) took longer time on the Stroop1 and Stroop3 test than control group ((16-¦3) s and (19-¦4) s) (all P<0.05). In children with high IQ, ADHD-HFA group ((20-¦8) s) spent more time on Stroop1 than control group ((15-¦4) s) (P<0.05). Inattention symptoms were associated with the time on TMT-2 of ADHD-HFA group (r=0.275 and 0.329, all P<0.05). The score of item 1 in autism spectrum screening questionnaire (ASSQ) was negatively correlated with immediate recall structure and detail scores as well as delay structure scores of Rey complex figure test (r=-0.358, -0.326 and -0.306, all P<0.05). The score of item 4 was positively correlated with errors of Stroop4 (r=0.296, P<0.05). The score of item 22 was positively correlated with time of color interference (r=0.279, P<0.05).

Conclusions: Children with ADHD-HFA are likely to demonstrate the spatial working memory, shifting and inhibition deficits associated with ADHD alone. Some domains of executive function impairment in ADHD-HFA group are related with symptoms of inattention/hyperactivity and autism

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Neuroscience. 2020.

DOMAIN-SPECIFIC INVOLVEMENT OF THE RIGHT POSTERIOR PARIETAL CORTEX IN ATTENTION NETWORK AND ATTENTIONAL CONTROL OF ADHD: A RANDOMIZED, CROSS-OVER, SHAM-CONTROLLED TDCS STUDY .

Salehinejad MA, Ghayerin E, Nejati V, et al.

Transcranial direct current stimulation (tDCS) has been increasingly used in attention-deficit hyperactivity disorder (ADHD) with mixed results. Previous tDCS studies merely targeted the dorsolateral prefrontal cortex and right inferior frontal gyrus with partial or no improving effects on cognitive deficits respectively. Posterior parietal cortex is another region involved in attentional functioning of ADHD, however, its contribution to ADHD attention functions has not been explored in tDCS studies. Moreover, attention networks are not investigated in the previous tDCS studies in ADHD neither. Here, we explored the effects of anodal tDCS over the right posterior parietal cortex (r-PPC) on attentional functioning (i.e., attention networks, selective attention, shifting attention) and response inhibition in ADHD children. 19 children with ADHD were recruited and underwent anodal/sham r-PPC tDCS (1 mA, 20 min) during task performance in a randomized cross-over design. Our results show an improving effect of anodal r-PPC tDCS specifically on the orienting but alerting or executive networks, in line with findings of healthy populations. Furthermore, activation of the r-PPC had a deteriorating effect on the top-down attentional control required for selective attention measured by the Stroop test. Modeling of the current flow showed a stronger electrical field induced in the inferior PPC (BA 39,40) which mediates bottom-up attentional control. No significant effect on shifting attention and response inhibition was found. Our findings indicate a domain-specific involvement of the r-PPC in attention

orienting network of ADHD children. Activation of the r-PPC improves bottom-up but hinders top-down attentional control suggesting a critical role of the r-PPC in ADHD bottom-up attentional control

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NeuroToxicology. 2020;81:11-17.

ASSOCIATIONS OF THE BEHAVIORAL ASSESSMENT AND RESEARCH SYSTEM (BARS) NEUROBEHAVIORAL OUTCOMES WITH ATTENTION PROBLEMS IN CHILDREN LIVING NEAR COAL ASH STORAGE SITES.

Sears L, Sears CG, Myers JV, et al.

Environmental exposures have been linked to childhood problems with overactivity, attention, and impulse control, and an increased risk of attention deficit hyperactivity disorder (ADHD) diagnosis. Two approaches to identify these types of exposure-related neurobehavioral problems include the use of computerized tests, such as the Behavioral Assessment and Research System (BARS), as well as the use of behavior rating scales. To assess comparability of these two types of measures, we analyzed data from 281 children aged 6 to 14 years enrolled in a 5-year research study investigating coal ash exposure and neurobehavioral health. All children lived in proximity of coal ash storage sites. We administered six computer tests from the BARS and obtained behavior measures from the parent-completed Child Behavior Checklist (CBCL) ADHD DSM oriented scale. BARS test performance was associated with age indicating that the tests could be used to evaluate neurodevelopmental changes over time or across a wide age range. Tests within the BARS including Continuous Performance (CPT) false alarm (standardized estimate 1.57, 95% confidence interval (CI) (0.67, 2.48), adjusted p = 0.006), Selective Attention (SAT) wrong count (standardized estimate 2.8, 95% CI (1.17, 4.44), adjusted p = 0.006), and SAT proportion correct (standardized estimate -2.45, 95% CI (-4.01, -0.88), adjusted p = 0.01) were associated with attention and impulse control problems on the CBCL after adjustment for multiple comparisons. Findings support that the BARS can contribute to research on environmental exposures by assessing subclinical behaviors related to ADHD such as sustained attention, impulse control, response inhibition, associative learning, and short-term memory. Future research can examine relationships of these BARS measures with biomarkers of neurotoxic exposures related to living near coal ash storage sites to better identify the potential risk for ADHD-related behaviors among children living near coal ash storage sites

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Nord J Psychiatry. 2020.

PSYCHOMETRIC PROPERTIES OF THE WEISS FUNCTIONAL IMPAIRMENT RATING SCALE PARENT AND SELF-REPORTS IN A NORWEGIAN CLINICAL SAMPLE OF ADOLESCENTS TREATED FOR ADHD.

Haugan ALJ, Sund AM, Thomsen PH, et al.

Objective: To analyze the psychometric properties of the Norwegian version of the Weiss Functional Impairment Rating Scale parent and self-reports (WFIRS-P and WFIRS-S) in adolescents with ADHD.

Methods: 102 clinically referred patients, of which 86% were enrolled in an ongoing RCT program (Clinical trials NCT02937142), were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV). The conceptual framework of the WFIRS-P and the WFIRS-S was evaluated using confirmatory factor analysis (CFA), reliability was estimated using CronbachΓÇÖs alpha, convergent and divergent validity was assessed using correlations with the ChildrenΓÇÖs Global Assessment Scale (C-GAS) and the ADHD Rating Scale-IV (ADHD-RS-IV).

Results: CFA supported the original factor structure of the questionnaires, both a first-order and a second-order model revealed acceptable model fit. Internal consistency was satisfactory across domains. The parent-adolescent agreement was moderate. The correlations between the C-GAS and the total scores of the WFIRS-P and WFIRS-S were low to moderate (r = ΓÇô0.29 to ΓêÆ0.38). The ADHD-RS-IV correlated moderately (r = 0.49) with WFIRS-P, the correlation with WFIRS-S was weak (r = 0.28) supporting divergent validity. In multiple regression analyses, the ADHD-RS total score was the strongest predictor of the total score in both the WFIRS questionnaires, with internalizing disorder showing an additional small contribution. Age, gender and full-scale IQ gave no additional contribution in explaining the variance.

Conclusions: The findings support the use of the Norwegian version of the WFIRS-S and the WFIRS-P in the evaluation of functional impairment in adolescents with ADHD

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Nutrients. 2020;12:1-15.

THE IMPORTANCE OF MARINE OMEGA-3S FOR BRAIN DEVELOPMENT AND THE PREVENTION AND TREATMENT OF BEHAVIOR, MOOD, AND OTHER BRAIN DISORDERS.

Dinicolantonio JJ, OΙÇÖkeefe JH.

Most of the global population is deficient in long-chain marine omega-3s. In particular, docosahexaenoic acid (DHA), a long-chain omega-3 fatty acid, is important for brain and eye development. Additionally, DHA plays a significant role in mental health throughout early childhood and even into adulthood. In the brain, DHA is important for cellular membrane fluidity, function and neurotransmitter release. Evidence indicates that a low intake of marine omega-3s increases the risk for numerous mental health issues, including Attention Deficit Hyperactivity Disorder (ADHD), autism, bipolar disorder, depression and suicidal ideation. Studies giving supplemental marine omega-3s have shown promise for improving numerous mental health conditions. This paper will review the evidence surrounding marine omega-3s and mental health conditions

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Obesity Reviews. 2020.

GLOBAL PREVALENCE OF OBESITY, OVERWEIGHT AND UNDERWEIGHT IN CHILDREN, ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Li YJ, Xie XN, Lei X, et al.

Individuals with autism spectrum disorder (ASD) or attention-deficit hyperactivity disorder (ADHD) may have unhealthy bodyweight. This meta-analysis was performed to understand the weight status in individuals with ASD or ADHD. PubMed, Embase, Cochrane and ISI Web of Science databases were searched from inception until June 2020 to identify relevant studies. Prevalence estimates and their 95% confidence intervals (CIs) of obesity, overweight and underweight were separately pooled using random-effects models. A total of 95 studies were included in the meta-analysis. The pooled estimates of the prevalence of obesity, overweight and underweight were 21.8%, 19.8% and 6.4% in individuals with ASD and 14.7%, 20.9% and 4.0% in individuals with ADHD. In subgroup analyses, an increasing trend in the prevalence of unhealthy weight was observed from children aged 2 to 5 years to adults with ASD (obesity: from 16.7% to 31.3%, overweight: from 16.2% to 27.2%, underweight from 5.3% to 8.6%) and from children aged 6 to 12 years to adults with ADHD (obesity: from 13.5% to 19.3%, overweight: from 18.8% to 31.2%). The worrisome epidemic of obesity and overweight in individuals with ASD, ADHD highlighted the need for weight management

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Pediatr Drugs. 2020.

A PHARMACOKINETIC STUDY OF METHYLPHENIDATE HYDROCHLORIDE MULTILAYER EXTENDED-RELEASE CAPSULES (APTENSIO XR-«) IN PRESCHOOL-AGED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Adjei AL, Chaudhary I, Kollins SH, et al.

Objective: This was a single-dose, one-period, multicenter, pharmacokinetic (PK) study to evaluate the PK of methylphenidate (MPH) hydrochloride multilayer extended-release capsules (MPH-MLR) in preschool children aged 4 to < 6 years, previously diagnosed with attention-deficit/hyperactivity disorder (ADHD), and on a stable dose of MPH.

Methods: Preschool-aged children (N = 10) received a single oral dose of MPH-MLR (10, 15, or 20-ámg) sprinkled over applesauce; a dose equivalent to their pre-enrollment daily dose of MPH. Blood samples for the measurement of MPH concentrations were obtained pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24-

áh post-dose. No structural model was assumed in the derivation of PK values for analysis. Maximum plasma concentration (Cmax), area under the concentration-time curve (AUC), elimination half-life, clearance (CL), and volume of distribution (Vd) data were compared with a historical group of older children aged 6ΓÇô11-áyears (N = 11) and analyzed by bodyweight. Safety (adverse event monitoring, vital signs, electrocardiogram, clinical laboratory testing, physical examination) was assessed.
Results: Mean dose-normalized Cmax and area under the curve to the last measurable observation (AUC) values were similar across dose groups, ranging from 0.67-áng/mL/mg (MPH 15-ámg) to 0.81-áng/mL/mg (MPH 10-mg) for Cmax/dose, and from 7.80-áh +ù ng/mL/mg (MPH 20-ámg) to 8.92 ng/mL/mg (MPH 10 mg) for AUCdose. PK results were integrated into a previously described pharmacostatistical population PK model. Visual predictive check plots showed greater variability in the 6- to 11-year-old group than the 4- to < 6-year-old group, and CL increased with increasing body weight in a greater than dose-proportional manner. Mean CL, normalized for body weight, was constant for all dose groups, ranging from 4.88-L/h/kg to 5.80/h/kg. Median time to Cmax ranged from 2.00 to 3.00-áh post-dose, and overall, dose-normalized Cmax concentrations indicated greater systemic exposures of MPH-MLR in preschool children aged 4 to < 6 years compared with children aged 6-11 years. Children aged 4 to < 6 years had a lower Vd than children aged 6-11 years. There were no unexpected safety signals.
Conclusion: The PK of MPH-MLR in preschool children demonstrated the biphasic absorption profile described earlier in older children, and the PK profile in children with ADHD aged 4 to < 6 years was similar to the profile in those aged 6-11 years, apart from a lower Vd and relatively higher systemic MPH levels for children in the preschool group.
Trial registration: Clinicaltrials.gov Identifier: NCT02470234

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Pediatrics. 2020;146.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND PSYCHOTROPIC POLYPHARMACY PRESCRIBING TRENDS.
Girand HL, Litkowiec S, Sohn M.
BACKGROUND AND OBJECTIVES: Attention-deficit/hyperactivity disorder (ADHD) medication use and psychotherapeutic polypharmacy is increasing. This study was designed to assess annual rates of ADHD medication prescribing and psychotherapeutic polypharmacy among patients 2 to 24 years old in the United States, identify commonly prescribed ADHD medications and concomitant psychotropic agents, and assess if specific characteristics are associated with polypharmacy.
METHODS: In this cross-sectional study, we used publicly available ambulatory health care data sets to evaluate ADHD and psychotropic polypharmacy use in patients 2 to 24 years old from 2006 to 2015. National rates were estimated by using sampling weights, and common ADHD and psychotropic drugs prescribed were identified. Multivariate logistic regression models were developed to assess the strength of association between polypharmacy and patient or provider characteristics.
RESULTS: Between 2006 and 2015, ADHD medication prescribing increased from 4.8% to 8.4%. ADHD polypharmacy increased from 16.8% to 20.5%, whereas psychotropic polypharmacy increased from 26.0% to 40.7%. The most common ADHD combinations were stimulants and a-2 agonists (67.1%), whereas the most common concomitant psychotropic agents were selective serotonin reuptake inhibitors (14.4%) and second-generation antipsychotics (11.8%). Factors associated with polypharmacy were age, female sex (psychotropic), nonprivate insurance, northeast and south regions (ADHD), receipt of mental health counseling or psychotherapy, and calendar year.
CONCLUSIONS: ADHD and psychotropic polypharmacy use is increasing and associated with specific patient characteristics. These patterns should spark further inquiry about the appropriateness, efficacy, and safety of psychotherapeutic polypharmacy in children and young adults, particularly within subgroups in which the use is high

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Personality Neuroscience. 2019;2.

DOES BEHAVIOURAL INHIBITION SYSTEM DYSFUNCTION CONTRIBUTE TO ATTENTION DEFICIT HYPERACTIVITY DISORDER?

Sadeghi S, McIntosh J, Shadli SM, et al.

The Reinforcement Sensitivity Theory of Personality has as its main foundation a Behavioural Inhibition System (BIS), defined by anxiolytic drugs, in which high trait sensitivity should lead to internalising, anxiety, disorders. Conversely, it has been suggested that low BIS sensitivity would be a characteristic of externalising disorders. BIS output should lead to increased arousal and attention as well as behavioural inhibition. Here, therefore, we tested whether an externalising disorder, Attention Deficit Hyperactivity Disorder (ADHD), involves low BIS sensitivity. Goal-Conflict-Specific Rhythmicity (GCSR) in an auditory Stop Signal Task is a right frontal EEG biomarker of BIS function. We assessed children diagnosed with ADHD-I (inattentive) or ADHD-C (combined) and healthy control groups for GCSR in: a) an initial smaller study in Dunedin, New Zealand (population ~120,000: 15 control, 10 ADHD-I, 10 ADHD-C); and b) a main larger one in Tehran, Iran (population ~9 [city]-16 [metropolis] million: 27 control, 18 ADHD-I, 21 ADHD-C). GCSR was clear in controls (particularly at 6-7 Hz) and in ADHD-C (particularly at 8-9 Hz) but was reduced in ADHD-I. Reduced attention and arousal in ADHD-I could be due, in part, to BIS dysfunction. However, hyperactivity and impulsivity in ADHD-C are unlikely to reflect reduced BIS activity. Increased GCSR frequency in ADHD-C may be due to increased input to the BIS. BIS dysfunction may contribute to some aspects of ADHD (and potentially other externalising disorders) and to some differences between the ADHD subtypes but other prefrontal systems (and, e.g. dopamine) are also important

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Phys Occup Ther Pediatr. 2020;40:47-61.

PARENTAL OCCUPATION EXECUTIVE TRAINING (POET): AN EFFICIENT INNOVATIVE INTERVENTION FOR YOUNG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDER.

Frisch C, Tirosh E, Rosenblum S.

Background: The American Academy of Pediatrics strongly recommends first-line treatment of preschool aged children with attention deficit hyperactivity disorder (ADHD) be parent- or teacher-administered behavior therapy.Aim: To assess the efficacy of Parental Occupation Executive Training (POET), a new intervention for young children with ADHD symptomatology.

Materials and Methods: We implemented a controlled, counterbalanced design with a study and comparison group (72 children with mean age of 5.42â€‰years identified as having ADHD symptomatology. using the DSM-IV and Conners Parents and Teachers Rating Scales). Intervention included parental-training sessions focused on children's occupational goals and capitalized on the assumed relationship between daily activities and executive functions. We evaluated achievement with the Canadian Occupational Performance Measure (COPM), Behavioral Rating Inventory of Executive Functions, and a questionnaire we developed related to parental knowledge and skills.

Results: Executive functions and preselected daily functions significantly improved following the POET intervention. Parent perceptions related to their knowledge of their children's executive difficulties and appropriate management strategies changed significantly following the intervention, and significantly correlated with the COPM scores.

Conclusions: A short-term parental training program, the POET improved daily functioning of young children with ADHD symptomatology by focusing on their parents' ability to cope with the children's executive delays

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Proc Natl Acad Sci U S A. 2020 May;117:10609-13.

NEONATAL CSF VASOPRESSIN CONCENTRATION PREDICTS LATER MEDICAL RECORD DIAGNOSES OF AUTISM SPECTRUM DISORDER.

Oztan O, Garner JP, Constantino JN, et al.

Autism spectrum disorder (ASD) is a brain disorder characterized by social impairments. ASD is currently diagnosed on the basis of behavioral criteria because no robust biomarkers have been identified. However,

we recently found that cerebrospinal fluid (CSF) concentration of the "social" neuropeptide arginine vasopressin (AVP) is significantly lower in pediatric ASD cases vs. controls. As an initial step in establishing the direction of causation for this association, we capitalized upon a rare biomaterials collection of newborn CSF samples to conduct a quasi-prospective test of whether this association held before the developmental period when ASD first manifests. CSF samples had been collected in the course of medical care of 0- to 3-mo-old febrile infants (n = 913) and subsequently archived at -70 Â°C. We identified a subset of CSF samples from individuals later diagnosed with ASD, matched them 1:2 with appropriate controls (n = 33 total), and quantified their AVP and oxytocin (OXT) concentrations. Neonatal CSF AVP concentrations were significantly lower among ASD cases than controls and individually predicted case status, with highest precision when cases with comorbid attention-deficit/hyperactivity disorder were removed from the analysis. The associations were specific to AVP, as ASD cases and controls did not differ in neonatal CSF concentrations of the structurally related neuropeptide, OXT. These preliminary findings suggest that a neurochemical marker of ASD may be present very early in life, and if replicated in a larger, prospective study, this approach could transform how ASD is detected, both in behaviorally symptomatic children, and in infants at risk for developing it

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Psiquiatr Biol. 2020.

PSYCHOBIOLOGY OF GIFTEDNESS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER. DIFFERENTIAL DIAGNOSIS.

Gomez-Leon MI.

The number of children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in giftedness is higher than that of the normotypic population. This study aimed to analyze the empirical evidence that shows the coexistence, or not, of both diagnoses. The results found did not allow to affirm that ADHD is a valid construction in the context of the giftedness. When studied from a psychobiological perspective it is found that gifted children can present clinical symptoms of ADHD in the absence of specific neuronal markers to this disorder, indeed they seem to follow an different development trajectory. It suggests the need to use neuroscientific and objective approaches that help to understand giftedness and ADHD within the context of neurodevelopment and as a consequence of an integrated and multifaceted organ that is more than a simple reflection of its separate parts or the sum of specific symptoms

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Psychiatry (New York). 2020.

ADHD SYMPTOMS, ACADEMIC AND SOCIAL DIFFICULTIES IN PARENTS OF CHILDREN WITH ADHD.

Insa Pineda I, Huguet Miguel A, Chamorro Fern+índez M, et al.

Objective: To evaluate the prevalence of ADHD in a group of parents of children with ADHD compared with the general population. To compare academic level, unemployment aid rate and marital separations/divorce of this parents sample.

Methodology: The experimental group was formed by the parents of 60 children with ADHD. The control group was formed by the parents of 60 healthy children. To assess the retrospective and current ADHD symptomatology among the parents of the sample the Wender Utah Rating Scale (WURS) and the Attention Deficit Hyperactivity Disorder-rating scale (ADHD.rs) were used. Also, the Hollingshead Four-Factor Index of Socioeconomic status (SES-Child) was used.

Results: 20.33% of the mothers in the case group met criteria for a retrospective diagnosis of ADHD, while none of the control group mothers met criteria (p <-á.01). Regarding fathers, there was a retrospective ADHD diagnosis in 25% of the case group compared to 10% in the control group (p <-á.01). In terms of the current symptoms, 25.42% of the mothers and 21.43% of fathers in the case group met diagnostic criteria for probable ADHD compared to 1.67% in the control group (p .01in both genders). Parents in the case group had a lower academic level (p <.01), received more unemployment aid (p =.02) and reported a higher rate of marital separation or divorce (p =.02).

Conclusions: Parents of children with ADHD have a higher incidence of retrospective and current ADHD diagnosis and they also present worse socioeconomic factors

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Psychiatr Invest. 2020;17:596-602.

THE RELATIONSHIP BETWEEN SECOND-TO-FOURTH DIGIT RATIOS, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS, AGGRESSION, AND INTELLIGENCE LEVELS IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Isik U, et al.

Objective Observations of sex differences have led some scientists to doubt whether the neuroendocrine system is involved in attention-deficit/hyperactivity disorder (ADHD) etiology. One of the interesting study subjects in this context is prenatal steroid hormone expo-sure. The aim of the present study was to replicate and extend previous work by addressing two research questions: 1) Are second-to-fourth digit (2D:4D) ratios lower in ADHD than in controls? 2) Is there a correlation between 2D:4D ratios and symptoms of ADHD, aggression and intelligence scores in boys with ADHD?

Methods The study included 100 treatment-naive male children diagnosed with ADHD and 55 healthy male children. We measured the ratios of 2D:4D and administered a Wechsler Intelligence Scale for Children-Revised to assess IQ scores, as well as behavioral rating scales, in children with ADHD and comparison individuals.

Results We observed lower 2D:4D ratios in the right hand in ADHD in comparison to the control group. The left-hand ratios of 2D:4D, however, did not differ between ADHD and control groups. There were negative correlations between the left-hand 2D:4D ratios and the hyperactivity scores. However, no significant correlation was detected between right-hand 2D:4D ratios and the psychological questionnaire scores.

Conclusion These results provide further evidence that fetal androgen exposure may contribute to the pathophysiology of ADHD, at least in boys

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Psychiatry Res. 2020;293.

THE BALL SEARCH FIELD TASK IN THE EVALUATION OF METHYLPHENIDATE TREATMENT OF CHILDREN WITH ATTENTION DEFICIT / HYPERACTIVITY DISORDER.

Rosetti MF, Ulloa E, Mayer P, et al.

Assessing behavioral change in psychiatric contexts requires retesting patients where, however, ecologically relevant tasks are rarely used. We employed the Ball Search Field Task (BSFT) to evaluate the performance of attention deficit/hyperactivity disorder (ADHD) outpatients before and after administration of methylphenidate (MPH) and compared their performance with that of non-medicated ADHD outpatients and age-matched controls. The outpatient groups showed poorer performance at initial testing, improved performance at re-test although not to the level of the controls, and no clear effect of MPH treatment. The BSFT is thus sufficiently motivating and discriminating for the behavioral evaluation of treatments in psychiatric contexts

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Psychiatry Res. 2020;293.

DIFFICULTIES MAINTAINING PROLONGED FIXATION AND ATTENTION-DEFICIT/HYPERACTIVITY SYMPTOMS SHARE GENETIC INFLUENCES IN CHILDHOOD.

Falck-Ytter T, Pettersson E, B+Âlte S, et al.

This study investigated the association between the ability to maintain prolonged (2-minute) fixation on a visual target and ADHD traits in a sample consisting of 120 monozygotic and 120 dizygotic twin pairs, aged 9 to 14 years. More intrusive saccades during the task was associated with higher level of parent-reported ADHD traits. Both intrusive saccades and ADHD symptoms had high heritability estimates, and there was a moderate genetic correlation between number of intrusive saccades and ADHD. This study suggests that

inability to maintain ocular fixation for longer times is etiologically linked to ADHD traits in the general population

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Psychiatry Res. 2020;292.

BULLYING VICTIMIZATION, MENTAL DISORDERS, SUICIDALITY AND SELF-HARM AMONG AUSTRALIAN HIGH SCHOOLCHILDREN: EVIDENCE FROM NATIONWIDE DATA.

Islam MI, Khanam R, Kabir E.

The effects of bullying on mental health among adolescents are of major public health concern, especially following modern bullying methods that technologically victimize adolescents. However, the independent effects of different forms of bullying (traditional, cyberbullying or both) on different types of mental disorders, suicidality and self-harm are not clear. Using a cross-sectional study design, involving 2166 Australian high schoolchildren (1131 Boys and 1035 Girls) aged 12-17 years, this study examined the associations of bullying victimization (traditional, cyber and both) with mental disorders, suicidality (ideation, plan and attempt) and self-harm. Both bivariate and multivariate analyses were employed to assess the associations. Victims of traditional bullying and cyberbullying incurred a significantly higher risk of major depressive disorder, suicidality and self-harm compared to those who had not encountered such threats. Findings also indicated the need for early identification of bullying victims to prevent the risk of mental disorders, suicidality and self-harm in schoolchildren. Furthermore, this evidence can be utilized to inform decisions regarding the provision of resources to address this important health issue in the context of any developed countries like Australia

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Psychiatry Res. 2020;293.

TREATMENT USE AMONG CHILDREN WITH TOURETTE SYNDROME LIVING IN THE UNITED STATES, 2014.

Wolicki SB, Bitsko RH, Holbrook JR, et al.

Treatment of Tourette syndrome (TS) can be complicated by changes over time in tic expression, severity, and co-occurring disorders. Using the 2014 National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome, this study provides descriptive estimates of the use of behavioral interventions and medication among children living with TS. Parent-reported data on 115 children aged 5ΓÇô17 years ever diagnosed with TS were analyzed to provide descriptive, unweighted results. Overall, 77.4% of children had current or past use of any TS treatment; 59.1% ever used behavioral interventions and 56.1% had ever taken TS medication. Children with moderate or severe versus mild TS, 1 co-occurring disorders, and tics that interfered with functioning were significantly more likely to have used one or more TS treatments. Side effects were reported for 84.4% of children who took TS medication. Most parents of children with current TS (87.2%) were satisfied with the management of their child's TS. However, parents of children with moderate or severe current TS were significantly more dissatisfied compared to parents of children with mild TS. Findings from this study could be used to inform efforts to support children living with TS and their families

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Psychol Assess. 2020 Feb;32:170-81.

INTERNAL STRUCTURE AND MEASUREMENT INVARIANCE OF THE DOMINIC INTERACTIVE AMONG INDIGENOUS CHILDREN IN QUEBEC.

Garneau M, Laventure M, Temcheff CE.

This study aims to examine the reliability and validity of the French version of the Dominic Interactive screening tool (Valla, 2008) among Indigenous children in Quebec. The Dominic Interactive is a computerized screening tool, which assesses prevalent emotional and behavioral problems in children. Participants in this study were 195 Innu Nation children aged between 8 and 11 years. Statistical analyses were performed on each of the 7 scales of the Dominic Interactive to assess reliability, factor structure, and measurement invariance across boys and girls. Results show satisfactory reliability (ranging from (tet) = .83

to .94 and from = .84 to .95) for 5 out of the 7 scales scores. Separation Anxiety and Specific Phobias scales failed to show adequate reliability. Confirmatory factor analyses confirm the 1-factor structure for Opposition and Conduct Problems scales (root mean square error of approximation, RMSEA .05; comparative fit index, CFI .95). Within an exploratory framework, confirmatory factor analyses also show good fit indices of relaxed models for Inattention/Hyperactivity/Impulsivity, Depression, and Specific phobias, admitting some error correlations. Generalized anxiety had poorer model fits; factor structure is not confirmed for this scale. The Separation anxiety construct appears to be better described by a 2-factor structure than by the postulated 1-factor structure. Measurement invariance between boys and girls was sufficiently supported for most of the scales, except for Specific Phobias. Therefore, results demonstrate promising reliability and validity for scales evaluating behavioral problems and depressive symptoms, but further research is still needed to determine the generalizability of these exploratory results in Indigenous populations

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Psychol Med. 2019 Nov;49:2561-72.

ARE CHILDREN WITH UNRECOGNISED PSYCHIATRIC DISORDERS BEING EXCLUDED FROM SCHOOL? A SECONDARY ANALYSIS OF THE BRITISH CHILD AND ADOLESCENT MENTAL HEALTH SURVEYS 2004 AND 2007.

Parker C, Tejerina-Arreal M, Henley W, et al.

BACKGROUND: There is limited research that explores the association between exclusion from school and mental health, but it seems intuitively plausible that the recognition of mental difficulties by key teachers and parents would influence the likelihood of exclusion from school.

METHODS: A secondary analysis of the British Child and Adolescent Mental Health survey 2004, (n = 7997) and the 2007 follow-up (n = 5326) was conducted. Recognition of difficulty was assessed via a derived variable that combined the first item of the Impact supplement of the Strengths and Difficulties Questionnaire which asked parents and teachers if they thought that the child has difficulties with emotions, behaviour and concentration, and the presence/absence of psychiatric disorder measured by the Development and Well-being Assessment.

RESULTS: Adjusted logistic regression models demonstrated that children with recognised difficulties were more likely to be excluded [adjusted odds ratio (OR) 5.78, confidence interval 3.45-9.64, $p < 0.001$], but children with unrecognised difficulties [adjusted OR 3.58 (1.46-8.81) $p < 0.005$] or recognised subclinical difficulties [adjusted OR 3.42 (2.04-5.73) $p < 0.001$] were also more likely to be excluded than children with no difficulties. Children with conduct disorder and attention deficit hyperactivity disorder were most likely to be excluded compared with other types of disorder.

CONCLUSION: Exclusion from school may result from a failure to provide timely and effective support rather than a failure to recognise psychopathology

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Psychol Med. 2019 Oct;49:2397-404.

RISK AND COAGGREGATION OF MAJOR PSYCHIATRIC DISORDERS AMONG FIRST-DEGREE RELATIVES OF PATIENTS WITH BIPOLAR DISORDER: A NATIONWIDE POPULATION-BASED STUDY.

Chen MH, Hsu JW, Huang KL, et al.

BACKGROUND: Bipolar disorder is a highly heritable mental illness that transmits intergeneratively. Previous studies supported that first-degree relatives (FDRs), such as parents, offspring, and siblings, of patients with bipolar disorder, had a higher risk of bipolar disorder. However, whether FDRs of bipolar patients have an increased risk of schizophrenia, major depressive disorder (MDD), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) remains unclear.

METHODS: Among the entire population in Taiwan, 87 639 patients with bipolar disorder and 188 290 FDRs of patients with bipolar disorder were identified in our study. The relative risks (RRs) of major psychiatric disorders were assessed among FDRs of patients with bipolar disorder.

RESULTS: FDRs of patients with bipolar disorder were more likely to have a higher risk of major psychiatric disorders, including bipolar disorder (RR 6.12, 95% confidence interval (CI) 5.95-6.30), MDD (RR 2.89, 95% CI 2.82-2.96), schizophrenia (RR 2.64, 95% CI 2.55-2.73), ADHD (RR 2.21, 95% CI 2.13-2.30), and ASD

(RR 2.10, 95% CI 1.92-2.29), than the total population did. These increased risks for major psychiatric disorders were consistent across different familial kinships, such as parents, offspring, siblings, and twins. A dose-dependent relationship was also found between risk of each major psychiatric disorder and numbers of bipolar patients.
CONCLUSIONS: Our study was the first study to support the familial coaggregation of bipolar disorder with other major psychiatric disorders, including schizophrenia, MDD, ADHD, and ASD, in a Taiwanese (non-Caucasian) population. Given the elevated risks of major psychiatric disorders, the public health government should pay more attention to the mental health of FDRs of patients with bipolar disorder

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Psychopharmacology. 2020.
CHRONIC EXPOSURE TO COCAINE IS ASSOCIATED WITH PERSISTENT BEHAVIORAL DISTURBANCES. A CROSS-SECTIONAL DIMENSIONAL STUDY IN OUTPATIENTS WITH MULTIPLE SUBSTANCE USE DISORDERS.
Vorspan F, de Witt P, Zerdazi EH, et al.
Rationale: Behavioral disturbances (BD) are prevalent in patients with substance use disorders (SUD).
Objectives: To test the hypothesis that chronic exposure to cocaine could favor the acquisition of BD that were not present in childhood.
Methods: We used child and adult ADHD self-report screening scales (WURS-25 and ASRS-6, respectively, with their usual threshold) as assessment tools for significant BD. In a cross-sectional assessment of 382 patients with multiple SUD, we investigated BD and then de novo BD (i.e., by restricting the sample to patients below the threshold for childhood BD) (N = 214). We also tested for a gradient effect between patients lifetime DSM IV cocaine and opioid dependence status and the prevalence of BD.
Results: BD were found in 188/382 (42.9%) subjects and in 74/214 (34.6%) subjects. Three clinical factors were associated with BD in the whole sample: the number of cocaine dependence criteria (OR = 1.36 [1.14-1.64], p = 0.001), the number of opioid dependence criteria (OR = 0.69 [0.52-0.91], p = 0.010), and a personal history of using cocaine through rapid routes of administration (OR = 0.41 [0.19-0.88], p = 0.022). The same three factors were associated with de novo BD in the restricted sample: OR = 1.35 ([1.11-1.63], p = 0.002), OR = 0.83 ([0.70-0.99], p = 0.046), and OR 0.37 ([0.16-0.86], p = 0.022), respectively. There were significant gradients for BD according to the cocaine exposure categories in the whole (Mantel-Haenszel, p < 0.001) and in the restricted sample (Mantel-Haenszel, p = 0.002).
Conclusions: Cocaine exposure was positively associated with behavioral disturbances in a dose-dependent manner in this clinical sample, whilst opioid exposure showed a negative association

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Rev Colomb Psiquiatr. 2020.
PSYCHIATRIC DISORDERS IN CHILDREN AND ADOLESCENTS DURING THE COVID-19 PANDEMIC.
Palacio-Ortiz JD, et al.
Introduction: The Covid-19 pandemic has generated an unprecedented multimodal (health, occupational, economic, and social crisis, which will impact developing countries. Confinement as a preventive measure is itself a threat that produces a social impact. Pandemic and confinement have become a psychosocial adversity factor that affects families and their children. During the pandemic, children and adolescents with a psychiatric disorder may experience exacerbation of their symptoms. However, little is known about this, since studies on this population during the pandemic are scarce.
Objective: To review the data available in the current literature on the effect of the pandemic on children and adolescents with a previous psychiatric disorder.
Methods: A literature search was carried out using PubMed, Scielo and, due to the exceptional conditions of the pandemic situation, directly using internet search engines. Both English and Spanish papers were included.
Results: The information found is presented in the following sections: family and children during the pandemic, evaluation of mental disorders in children and young people during the pandemic, pre-existing psychiatric disorders during the pandemic, and telepsychiatric care. Specific information is presented on

attention deficit hyperactivity disorder, autism spectrum disorder, intellectual disability, anxiety disorder, obsessive compulsive disorder, and post-traumatic stress disorder. The current pandemic due to COVID-19 and confinement are a psychosocial adversity that threatens the stability of the family. Such a stressor can cause exacerbation of symptoms of a previous mental disorder. Children and adolescents with psychiatric disorders are a vulnerable population and require specialised care. Telepsychiatry is becoming a modality with multiple advantages

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SA Pharmaceutical Journal. 2019;86:17-27.

THE MANAGEMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN: UPDATED 2019.

Schellack N, Meyer JC, Chigome AK.

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder and involves the academic, social and family functioning of the child. It is the most commonly diagnosed behavioural disorder amongst children with a prevalence of approximately 7.2% worldwide, occurring mostly in boys. The consequences of ADHD may be substance abuse and other personality disorders, e.g. delinquency. Research has indicated that drug or behavioural interventions may decrease the rate of conduct and personality disorders. Diet therapy may include polyunsaturated fatty acids (fish oil) and iron supplements in children with low ferritin levels which may improve ADHD symptoms. Drug therapy that involves stimulants (methylphenidate) has been proven to be effective with a good safety profile. However, concerns have been raised about cardiac, psychiatric and growth side-effects. The non-stimulants (atomoxetine) have no abuse potential and reduce insomnia. They also have a better effect on growth in children. Other therapies include antidepressants and +¦2-agonists. It is important to treat each patient using individualised therapy. The role of the pharmacist is important to monitor and minimise side-effects. New treatment options comprise modified formulations of currently available medicines

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Schizophr Res. 2019 Jun;208:67-75.

ASSOCIATIONS OF SCHIZOPHRENIA RISK GENES ZNF804A AND CACNA1C WITH SCHIZOTYPY AND MODULATION OF ATTENTION IN HEALTHY SUBJECTS.

Meller T, Schmitt S, Stein F, et al.

Schizotypy is a multidimensional risk phenotype distributed in the general population, constituting of subclinical, psychotic-like symptoms. It is associated with psychosis proneness, and several risk genes for psychosis are associated with schizotypy in non-clinical populations. Schizotypy might also modulate cognitive abilities as it is associated with attentional deficits in healthy subjects. In this study, we tested the hypothesis that established genetic risk variants ZNF804A rs1344706 and CACNA1C rs1006737 are associated with psychometric schizotypy and that schizotypy mediates their effect on attention or vice versa. In 615 healthy subjects from the FOR2107 cohort study, we analysed the genetic risk variants ZNF804A rs1344706 and CACNA1C rs1006737, psychometric schizotypy (schizotypal personality questionnaire-brief SPQB), and a neuropsychological measure of sustained and selective attention (d2 test). ZNF804A rs1344706 C (non-risk) alleles were significantly associated with higher SPQ-B Cognitive-Perceptual subscores in women and with attention deficits in both sexes. This schizotypy dimension also mediated the effect of ZNF804A on attention in women, but not in men. CACNA1C rs1006737-A showed a significant sex-modulated negative association with Interpersonal schizotypy only in men, and no effect on attention. Our multivariate model demonstrates differential genetic contributions of two psychosis risk genes to dimensions of schizotypy and, partly, to attention. This supports a model of shared genetic influence between schizotypy and cognitive functions impaired in schizophrenia

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Sleep. 2020 Jun;43.

ASSOCIATIONS BETWEEN SLEEP PROBLEMS AND ADHD SYMPTOMS AMONG ADOLESCENTS: FINDINGS FROM THE SHANDONG ADOLESCENT BEHAVIOR AND HEALTH COHORT (SABHC).

Liu X, Liu ZZ, Bao-Peng L, et al.

Study Objectives Sleep problems and symptoms of attention-deficit hyperactivity disorder (ADHD) in adolescence are common. Little is known about the prospective the prospective associations between sleep and subsequent ADHD symptoms in adolescents. This study examined the prospective associations between sleep problems and subsequent ADHD symptoms in a large sample of adolescents. Methods Participants included 7072 adolescents from the Shandong Adolescent Behavior and Health Cohort (SABHC) study in Shandong, China. Participants were initially assessed in Novemberâ€"December of 2015 and were reassessed 1-year later in 2016. Sleep duration, sleep problems, and psychosocial information were collected using a structured questionnaire. ADHD symptoms were measured by the Achenbach Child Behavior Checklist-Youth Self-Report. Results At baseline, 7.6% participants had clinically relevant ADHD symptoms, which were highly comorbid with sleep problems including insomnia symptoms, poor sleep quality, symptoms of restless legs syndrome (RLS), frequent snoring, and short sleep duration. Of the 6531 participants without clinically relevant ADHD symptoms at baseline, 4.5% reported clinically relevant ADHD symptoms at 1-year follow-up. After adolescent and family covariates were adjusted for, insomnia (OR = 2.09, 95% CI = 1.45â€"3.02), RLS (OR = 1.47, 95% CI = 1.02â€"2.11), and frequent snoring (OR = 2.30, 95% CI = 1.36â€"3.90) were all significantly associated with subsequent ADHD symptoms. Conclusion ADHD symptoms and sleep problems are highly comorbid. Insomnia, RLS and frequent snoring appear to be significant predictors of subsequent ADHD symptoms. Our study highlights the importance of assessing and managing sleep problems for prevention and clinical treatment of ADHD symptoms in adolescence

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Sleep Med. 2019 Dec;64:112-15.

SLEEP-RELATED RHYTHMIC MOVEMENTS AND RHYTHMIC MOVEMENT DISORDER BEYOND EARLY CHILDHOOD.

Prihodova I, Skibova J, Nevsimalova S.

INTRODUCTION: Sleep-related rhythmic movements (SRRMs) are common in young children and become less prevalent with increasing age. When SRRMs significantly interfere with sleep and/or affect daytime functioning, potentially resulting in injury, rhythmic movement disorder (SRRMD) is diagnosed.

OBJECTIVE: The aim of our study was to assess clinical comorbidities, types of SRRMs, sleep stage/wakefulness distribution during night, and age-dependence of these parameters.

MATERIAL AND METHODS: In sum, 45 patients (age range 1-26 years, mean age 10.56Â Â±Â 6.4 years, 29 men) were clinically examined for SRRMs or SRRMD. Nocturnal polysomnography (PSG) was recorded in 38 patients. To evaluate clinical and sleep comorbidity, the cohort of 38 patients was divided according to age into four groups: (1) younger than 5 years (NÂ =Â 7), (2) 5-9 years (NÂ =Â 12), (3) 10-14 years (NÂ =Â 11), and (4)Â Â 15 years (NÂ =Â 8).

RESULTS: A clear relationship between perinatal risk factors and developmental disorders (attention deficit hyperactivity disorder - ADHD, specific learning disability) was found which extended population prevalence at least five times. A total of 62 recordings were evaluated in 38 patients; SRRMs were found in PSG in 31 of 38 patients (82%). No age-dependent correlation between type of SRRMs and sleep stage/wakefulness distribution during the night was observed. However, when all recordings were correlated together, rolling stereotypes occurred more frequently in REM sleep, and rocking stereotypes in superficial NREM sleep.

CONCLUSION: Developmental disorders and perinatal risk factors were connected with SRRMs and SRRMD in children and young adults. Rolling movements were significantly associated with REM stage and rocking stereotypes with superficial NREM sleep, independent of age

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Sleep Med. 2020;73:117-24.

RESTLESS LEGS SYNDROME IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PREVALENCE, MIMIC CONDITIONS, RISK FACTORS, AND ASSOCIATION WITH FUNCTIONAL IMPAIRMENT.

Srifuengfung M, Bussaratid S, Ratta-apha W, et al.

Objectives: To determine the prevalence of restless legs syndrome (RLS) and RLS-mimic conditions, the risk factors for RLS, and whether RLS contributes to functional impairment in children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Methods: ADHD children and adolescents were prospectively studied at the outpatient psychiatric clinic. A trained registered nurse used the 2012 Revised International Restless Legs Syndrome Study Group diagnostic criteria to diagnose RLS. Sociodemographic data and medical records were reviewed. Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) Thai version was used to identify association between RLS and 6 domains of function [family, school (learning), school (behavior), life skills, child self-concept, social activities, and risky activities].

Results: A total of 217 patients were included. Of those, 23 (11%) patients met the criteria for RLS, and 49 (23%) had RLS-mimic conditions. Those conditions included myalgia (30/49), habitual foot tapping (23/49), positional discomfort (20/49), leg ulcer/bruise (1/49), and arthralgia/arthritis (1/49). Binary logistic regression revealed first-degree relative having RLS symptom to be significantly associated with RLS in study patients (OR: 5.06, p < 0.01). Multivariate linear regression showed RLS to be independently associated with school (behavior) (+Æ = 1.18, p = 0.05) and life skills (+Æ = 2.36, p = 0.05) impairment.

Conclusions: RLS was found to be common in ADHD children and adolescents. RLS-mimic conditions were found in two-thirds of patients who previously met 4 essential RLS criteria. First-degree relative with RLS symptom was associated with RLS, and RLS was associated with functional impairment in the life skills and school (behavior) domains

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Transl Psychiatry. 2020;10.

POLYGENIC RISK SCORE ANALYSIS REVEALED SHARED GENETIC BACKGROUND IN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND NARCOLEPSY.

Takahashi N, Nishimura T, Harada T, et al.

Attention deficit hyperactive disorder (ADHD) is a highly heritable neurodevelopmental disorder, and excessive daytime sleepiness is frequently observed in ADHD patients. Excessive daytime sleepiness is also a core symptom of narcolepsy and essential hypersomnia (EHS), which are also heritable conditions. Psychostimulants are effective for the symptomatic control of ADHD (primary recommended intervention) and the two sleep disorders (frequent off-label use). However, the common biological mechanism for these disorders has not been well understood. Using a previously collected genome-wide association study of narcolepsy and EHS, we calculated polygenic risk scores (PRS) for each individual. We investigated a possible genetic association between ADHD and narcolepsy traits in the Hamamatsu Birth Cohort for mothers and children (HBC study) (n = 876). Gene-set enrichment analyses were used to identify common pathways underlying these disorders. Narcolepsy PRS were significantly associated with ADHD traits both in the hyperactivity domain (e.g., P-value threshold < 0.05, +¦ [SE], 5.815 [1.774]; P = 0.002) and inattention domain (e.g., P-value threshold < 0.05, +¦ [SE], 5.734 [1.761]; P = 0.004). However, EHS PRS was not significantly associated with either domain of ADHD traits. Gene-set enrichment analyses revealed that pathways related to dopaminergic signaling, immune systems, iron metabolism, and glial cell function involved in both ADHD and narcolepsy. Findings indicate that ADHD and narcolepsy are genetically related, and there are possible common underlying biological mechanisms for this relationship. Future studies replicating these findings would be warranted to elucidate the genetic vulnerability for daytime sleepiness in individuals with ADHD

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Vision Research. 2020;175:32-40.

ACCOMMODATION AND PUPIL DYNAMICS AS POTENTIAL OBJECTIVE PREDICTORS OF BEHAVIOURAL PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Redondo B, Vera J, Molina R, et al.

Individuals with attention deficit hyperactivity disorder (ADHD) frequently exhibit different types of visual deficits. This study investigates the dynamics of ocular accommodation and pupil size in a population of children with ADHD (6ΓÇô14 years old) and assesses the association between these ocular variables with behavioural performance during a continuous performance task. The accommodation and pupil dynamics (magnitude and variability) were objectively measured, using the WAM-5500 auto-refractor, during the execution of a ~14-min continuous performance task in a sample of twenty-three non-medicated children with ADHD and thirty-one controls of a similar age range. Our data revealed that children with ADHD present a reduced accommodative response (higher lags of accommodation) during the execution of a continuous performance task. However, no group-differences were observed for the other ocular indices. Both groups experienced changes in all ocular variables as a function of time-on-task. The variability of accommodation and pupil diameter were associated with several indicators of behavioural performance for the ADHD group. However, no bivariate correlations were found for the control group. The current outcomes suggest that the accommodation and pupil dynamics may be considered as potential predictors of behavioural performance, which could help to improve the robustness of ADHD diagnosis

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brain sciences

MDPI

Article

The Role of Executive Functions in the Development of Empathy and Its Association with Externalizing Behaviors in Children with Neurodevelopmental Disorders and Other Psychiatric Comorbidities

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Abstract: Executive functions have been previously shown to correlate with empathic attitudes and prosocial behaviors. People with higher levels of executive functions, as a whole, may better regulate their emotions and reduce perceived distress during the empathetic processes. Our goal was to explore the relationship between empathy and executive functioning in a sample of children and adolescents diagnosed with Attention Deficit and Hyperactivity Disorder alone or associated with comorbid Disruptive Behavior Disorders and/or Autism Spectrum Disorder. We also aimed to examine the role of empathic dimensions and executive skills in regulating externalizing behaviors. The 151 participants with ADHD were assigned to four groups according to their psychiatric comorbidity (either "pure" or with ASD and/or ODD/CD) and assessed by means of either parent- or self-reported questionnaires, namely the BRIEF−2, the BES, and the IRI. No questionnaire was found to discriminate between the four groups. Affective Empathy was found to positively correlate with Emotional and Behavioral Regulation competences. Furthermore, Aggressiveness and Oppositional Defiant Problems were positively associated with Executive Emotional and Behavioral Regulation competences. On the other hand, Rule-Breaking Behaviors and Conduct Problems were negatively associated with Affective Empathy and with Behavioral skills. Our study provides an additional contribution for a better understanding of the complex relationship between empathic competence and executive functions, showing that executive functioning and empathic attitudes interact with each other to regulate aggressive behaviors. This study further corroborates developmental models of empathy and their clinical implications, for which externalizing behaviors could be attenuated by enhancing executive functioning skills.

Keywords: empathy; executive functions; attention deficit and hyperactivity disorder; autism spectrum disorder; disruptive behavior disorders

1. Introduction

Feeling empathy for someone means understanding his/her emotions and/or personally experiencing the same; it means creating a customized space in one's own inner world to host the world of the other. In other words, it refers to the ability to share and comprehend another person's thoughts and moods [1]. Feeling and understanding the emotions of others are important assumptions to guide one's actions in a prosocial sense and, particularly, to avoid those behaviors that can cause harm and suffering to the other. The cognitive facet of empathy implies the ability to understand the inner situation of the other and to take his/her own perspective [2]. On the other hand, the affective component of empathy is defined as the ability to share the emotional state of others [3]. The latter implies the involvement of limbic and paralimbic structures and develops earlier than the cognitive one, which assumes a fine-tuned maturation of prefrontal and temporal networks [4].

In light of the close association of empathy with contextual factors, early childhood experiences and social behaviors, it is direct to assume that psychopathological conditions are often convoyed by empathy deficits [5,6]. Empathy deficits have been implicated in several neurodevelopmental disorders, among which autism spectrum disorder (ASD) is the most studied [7–9]. ASD have been primarily associated with cognitive empathy deficits [9,10] but the potential role of affective empathy in this framework has been questioned [11].

The reduction or absence of empathy represents the cornerstone of Conduct Disorders (CD) characterized by disruptive and antisocial behaviors [12]. Adults with psychopathic traits show a selective deficit of the affective component of empathy related to impaired emotional responses to facial expressions of feelings of sadness and fear [13–15], which is likely due to dysfunctional neuronal circuits underlying the amygdala [16]. A recent study by our group [17] confirmed these findings in a cohort of young boys with CD, corroborating the association between callous-unemotional (CU) traits and affective empathic attitudes. Interestingly, studies aimed at outlining the differences between children with CD and CU traits and ASD [18] show that, while psychopathy seems to be best characterized by a preserved understanding of what the other thinks, with a deficient capacity to share compassionate feelings towards the others, ASD specifically lacks the ability to take others' perspective. Conversely, a study conducted by Mazza et al., 2014 [11] on a group of adolescents with ASD reported a difficulty in cognitive empathy and a deficit in affective empathy specific for the negative emotional valence, assuming, also for these subjects, the existence of an atypical function and structure of the amygdala [19].

Some evidence has also shown that empathy is compromised in a proportion of children with Attention Deficit and Hyperactivity Disorder (ADHD); in particular, lower levels of social perspective taking are observed [20–22]. Indeed, young people with ADHD may have low cognitive empathic attitudes, as demonstrated for instance by the frequently observed unawareness of other children playing the same game [23]. Further corroborating evidence appeared in a recent study by Maoz et al., 2019 [24], who confirmed the existence of a global deficit in both components of empathy by using the Interpersonal Reactivity Index [25] in its self-report form. In another study conducted by the same research group [26], differences in the empathic profile are identified between the Combined and the Inattentive subtypes of ADHD, identifying a greater impairment in the former for all scales of the IRI questionnaire. According to Uekermann et al., 2010 [27], these deficits might be explained at least in part by the impulsive response modalities typically found in ADHD patients, and thus may be linked to dysfunctions of the fronto-striatal brain networks, functionally related to empathic processing and executive functioning. Interestingly, Barkley, 2006 [28], argues that behavioral inhibition deficits, the core symptoms of ADHD children, might impair social cognition skills, but how much they could affect empathic abilities still remains an unsolved question.

Despite the identification of selective or global impairments of empathy in clinical settings, functional studies, aimed at assessing brain correlates of the experience of feeling the emotions of others, found that empathic attitudes are activated through an emotional processing which is regulated both by bottom-up and top-down circuitry within the prefrontal and limbic cortex [29]. An early influential theory, the Perception-Action Model by Preston and de Waal, 2002 [30], based on an evolutionary perspective, proposed that empathy is considered an uncontrolled response that

operates automatically and develops early in life. More recently, the Russian Doll Model by the same authors [31] questioned this simplistic view and posited that bottom-up routes of empathic processing and top-down executive modulators are two interrelated systems that develop sequentially. This model has included executive functions as a regulating factor and considered it as a fundamental ground for the development of cognitive empathy [31–33].

According to the Russian Doll Model, several components of the empathic response, which have been added layer by layer during evolution, remain functionally integrated [34]. At its core is the perception-action mechanism, which induces a similar emotional state in the observer as in the target. Indeed, its basic expressions are motor mimicry and emotional contagion, representing the functional reactions of newborns and infants according to Hoffman's developmental theory of empathy [35]. On the other hand, the external layers of the doll, such as empathic concern and perspective taking, are grounded on the previously described socio-affective basis but require a fine-tuned regulation of emotional responses and a distinct perception between self and cognition. Although the outer layers of the doll depend on prefrontal circuitry, they remain functionally connected to the basic perception-action mechanism [31]. Therefore, cognitive empathic attitudes are supported by the neural regions that underlie working memory, executive functioning, emotional regulation and visuo-spatial processing, overpowering the affective representations of the other in a top-to-bottom fashion [31,36]. In other words, the effective control of empathic responses is thus obtained through the executive functioning regulation system, which allows a fine adaptation and modulation of the sharing experience.

A stepwise transition from immature forms of emotional contagion to more sophisticated expressions of prosocial attitudes, as brilliantly theorized by Hoffman's developmental theory of empathy [37], may be indeed paralleled by the progressive maturation of prefrontal circuitry and executive functions (EF) required to perform a fine-tuned control of such responses. Interestingly, a discrete amount of studies, conducted in community and clinical samples, has repeatedly shown that EF as a whole can modulate empathic attitudes, or in other words people with higher EF competences may better regulate their emotions and reduce perceived distress during the empathic processes [38–46]. Moreover, Gökçen et al. [43,44] found positive correlations between EF and empathic attitudes in individuals with ASD traits, suggesting the role of EF in regulating empathic competences in neurodevelopmental disorders. Similarly, a recent study in ADHD patients versus healthy controls by Abdel-Hamid et al., 2019 [47], found significant positive correlations between theory of mind (ToM) and empathy competences and EF performances in the ADHD group but not in the control group. In a recent review, which analyzed fifteen studies conducted on ADHD samples, with or without comorbidities and included mostly male children, Pineda-Alhucema et al., 2018 [48], found the EF most correlated with ToM were inhibitory control, working memory, cognitive flexibility and attention (for further updated details on the relationship between EF and ToM please refer to Andreou et al. 2020 [49]).

It should be noted, however, that in these studies, EF were variably measured through different neuropsychological tasks, such as the Go/No-Go test and the Wisconsin Card Sorting Test, which assess specific EF such as Cognitive Flexibility and Working Memory in laboratory settings. No study, however, used caregiver-reported measures of behavioral patterns for children and adolescents to evaluate EF in everyday life environments. Given the centrality of EFs in controlling behaviors in everyday life, relying only on laboratory measures of EF performances, detected with clinical tests, may limit the confidence and completeness of the clinical evaluation. The measures based on performances, in fact, depict only limited aspects of the EF system in a narrow time frame and do not fully capture the integrated multidimensional decision-making process based on an analysis of the priority which is often that of real life situations [50].

A recent meta-analysis [29] summarized these results, corroborating the evidence that empathy is strongly related to EF, and interestingly its cognitive facet is more closely related to executive skills than the affective one. Particularly, strong relationships were found between cognitive empathy and specific subcomponents of EF, including Inhibitory Control, Working Memory and Cognitive Flexibility, while affective empathy would only correlate to Inhibitory Control. Despite this, it should

be observed that this meta-analysis did not consider further subdivisions of EF in their subgroup analyses, such as emotional regulation abilities and several other metacognitive skills. Moreover, no significant effect of age was demonstrated, though a considerable heterogeneity in the age range of samples of included studies is noticeable. Another potential source of bias was the inclusion of the results of three unpublished dissertations. Finally, many of these studies are made up of heterogeneous samples, while the meta-analysis does not take into account psychiatric comorbidities. The authors emphasized indeed that this field of research is still under open investigation, since the results of single studies are somewhat inconsistent and inadequate to draw definite conclusions.

The present study aims to explore possible relationships between the different facets of empathy and the specific subcomponents of EF in a clinical sample of children and adolescents primarily diagnosed with ADHD, compared to children with comorbid ASD or ODD/CD or both. EF profiles have been evaluated through the Behavior Rating Inventory of Executive Function (BRIEF) [51] questionnaire, which provides a structured assessment of EF behaviors in everyday life environments. Since the EF deficits can strongly affect the cognitive and behavioral manifestations of ADHD and ASD [52,53], our aim was indeed to investigate if and how EF are associated with the dimensions of empathy within these neurodevelopmental disorders.

Moreover, the current study examined the role of empathic dimensions and executive skills in regulating the externalizing behaviors typical of some clinical manifestations of ADHD and ODD/CD, such as for instance aggression, oppositional behaviors and rule transgression. It is believed, in fact, that emotional regulation plays an important role in inhibiting aggressive behaviors by implementing perspective-taking abilities and empathic concern towards the others [54].

2. Methods

2.1. Participants and Diagnostic Procedures

Our study included 151 drug-naïve participants (137 boys, age range 6–18 years old, mean age 9.51 ± 2.64 years) recruited in our third-level Department of Child and Adolescent Psychiatry from March 2019 to December 2019. Subjects underwent a multi-dimensional assessment, through individual clinical evaluations and observations of social interactions within a group of peers, in order to thoroughly investigate ASD symptomatology. The diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders–Fifth edition (DSM−5) [55], based on medical history, clinical observations, a structured interview, the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL) [56], and clinical questionnaires, namely the Child Behavior Checklist and the Social Communication Questionnaire, commonly used to assist the diagnostic process.

The Child Behavior Checklist for ages 6 to 18 years (CBCL–6/18) [57,58] is a 118-item scale, completed by parents, with 8 different syndromes scales, a Total Problem Score and two broad-band scores designated as Internalizing Problems and Externalizing Problems. The reliability coefficients (Cronbach's alpha) of the original validation study were 0.82, 0.81 and 0.82, respectively. The Social Communication Questionnaire (SCQ) [59] is a widely used screening measure for ASD. It was designed as a questionnaire version of the Autism Diagnostic Interview–Revised (ADI-R) [60], the gold standard developmental history measure that is widely used in research and often in clinical practice. Caregivers can rate the individual's lifetime and/or current characteristics. Compared to other rating scales, the development research was significantly more robust, including good diagnostic validation on participants, and it has been widely adopted by both the research and clinical community worldwide.

Patients were included if they received a diagnosis of ADHD, with or without comorbid psychiatric conditions, including ODD/CD and ASD. The latter was suspected based on either medical history and clinical observations or a total SCQ score above the cut-off value and later confirmed through the administration of the Autism Diagnostic Observation Schedule–Second Edition (ADOS-2) [61]. The exclusion criteria were as follows: presence of comorbid intellectual disability, as detected through formal psychometric assessment by means of the WISC-IV, i.e., when

either the Full-Scale Intelligence Quotient or the General Ability Index were below than 70 points; younger than 6 years old or older than 18 years old; current or previous use of psychoactive medications; neurologic impairments or neurodegenerative conditions.

We identified four clinical groups in our samples: "pure" ADHD group (namely, without comorbid ASD and/or ODD/CD, here-in-after referred as the ADHD alone group), including 64 subjects (12.5% girls, mean age 10.02 ± 2.49 years); comorbid ADHD + ODD/CD group (here-in-after referred as the ADHD+ODD/CD group), including 43 subjects (9.3% girls, mean age 9.37 ± 2.95 years); comorbid ADHD + ASD group (here-in-after referred as the ADHD+ASD group), including 19 subjects (5.26% girls, mean age 9.58 ± 2.69 years); comorbid ADHD + ASD + ODD/CD group (here-in-after referred as the ADHD+ODD/CD+ASD group), including 25 subjects (4% girls, mean age 8.40 ± 2.24 years). All participants and parents were informed about assessment instruments and participated voluntarily in the study after written informed consent was obtained for assessment procedures from parents of all children. The study conformed to the Declaration of Helsinki and the Regional Ethics Committee for Clinical Trials of Tuscany, Pediatric Ethics Committee section, approved the study (ethical approval code: GENCU/03/2019).

2.2. Clinical Assessment

Patients' clinical profiles were also assessed by means of several questionnaires, either through self or parental reports. Particularly, the Italian versions of the following measures were used: the Behavior Rating Inventory of Executive Functions–Second version (BRIEF-2) [51] administered to parents of all included children for the assessment of EF profiles; the Antisocial Process Screening Device (APSD) [62] administered to parents of all included children for the evaluation of CU traits; the Basic Empathy Scale (BES) [12], administered to parents of all children aged 11 years old or less, and the Interpersonal Reactivity Index (IRI) [25], administered in its self-report version to adolescents aged 12 years old or more, for the assessment of empathic competences.

The Behavior Rating Inventory of Executive Function–Second version (BRIEF-2) [51] is the updated version of the BRIEF questionnaire which provides a structured assessment of executive function behaviors in everyday life environments, allowing the identification of helpful clinical manifestations in different contexts, i.e., home and school. In its parent-report version that was used in the present study, this tool has been validated for 5- to 18-year-old children and adolescents. BRIEF-2 is a multi-dimensional measure and items are nearly equally distributed across nine factors, each referring to specific executive functions: Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task Monitor, Organization of Materials. Three composite scales are also identifiable, each including at least two factors: Behavioral Regulation Index (BRI) (including Inhibit and Self-Monitor), Emotional Regulation Index (ERI) (Shift and Emotional Control) and Cognitive Regulation Index (CRI) (Initiate, Working Memory, Plan/Organize, Task Monitor, Organization of Materials). A Global Executive Composite (GEC) score is also computed as sum of the three aforementioned composite indexes.

The Antisocial Process Screening Device (APSD) [62] is a 20-item clinician-administered rating scale normed on a community sample of pre-adolescent children. The available version of the APSD was designed to be completed by parents and teachers; the former was used in the present study. Items are rated on a three-point Likert scale and the scale consists of three main dimensions, based on factor analysis: Narcissism, Impulsivity and Callous-Unemotional. There is substantial support for the validity of the APSD for distinguishing sub-groups of antisocial youths with more severe and aggressive behavior, with characteristics similar to adults with psychopathy [63] (Cronbach's α = 0.86).

The Basic Empathy Scale (BES) [12] is a self- or parent-reported questionnaire, the latter being used in this study, for children and/or adolescents composed of 20 items distributed across two subscales, respectively, referring to the affective and cognitive components of empathy. Both exploratory and confirmatory analyses of the original validation established good internal consistency for each subscale with Cronbach's α ranging from 0.79 to 0.85. The Interpersonal Reactivity Index (IRI) was originally developed by Davis, 1980 [25], as a self-reported questionnaire

for adults and subsequently adapted for adolescents by Litvack-Miller and colleagues [64]; it is composed of 28 items distributed across four subscales, respectively referring to Fantasy and Perspective-Taking (combined into the Cognitive Empathy subscale), Empathic Concern and Personal Distress (combined into the Affective Empathy subscale).

2.3. Data Analysis

Statistical analyses were performed by means of MatLab® (MathWorks, Natick, MA, USA) and RStudio® (RStudio Inc., Boston, MA, USA) software. For each clinical variable with continuous distribution, outliers were defined as observations lying outside the range between [first quartile–1.5 * interquartile range] and [third quartile + 1.5 * interquartile range] and removed. For each BRIEF-2 subscale-related variable, observations were removed whether the corresponding values at either the Infrequency or the Inconsistency scale was higher than 99° percentile of normalized data. As for the BES and the IRI questionnaires, z-scores were computed for each subscales, i.e., the Cognitive and the Affective Empathy scales; thus, z-scores of the two questionnaires were merged together so that a single pair of variables assessing cognitive and affective empathy was available for all subjects irrespectively of the age.

Analyses of Variance (ANOVA) were used to assess significant differences (p-value < 0.05) between clinical variables with continuous distribution. A Tukey post-hoc test was used whenever the ANOVA led to a statistically significant result in order to identify significant comparisons between variables. Spearman's ranks correlation coefficients were estimated to detect significant relationships between rank values of questionnaire variables. Benjamini and Hochberg's False Discovery Rate (FDR) correction method [65] for multiple comparisons was applied after assessing significant differences at a traditional significance level of 5%.

Finally, four linear regression models were applied to identify statistically significant relationships between selected subscales of the administered questionnaires. Namely, four subscales of the CBCL (Aggressive Behavior [AB], Rule-Breaking Behavior [RBB], Oppositional Defiant Problems [ODP], Conduct Problems [CP]) were included as dependent variables of the models, whilst the three main indexes of the BRIEF (Behavioral, Emotional and Cognitive Regulation Indexes), the z-scores of the two subscales of the merged Empathy Questionnaire (Affective and Cognitive Empathy) and the SCQ total scores were used as independent variables of the models.

3. Results

3.1. Questionnaires

Scores obtained by the four clinical groups in the aforementioned questionnaires are reported in Figure 1A–C. No significant differences could be detected in the APSD (Figure 1A) and in the SCQ questionnaires (Figure 1B). Finally, no significant difference emerged neither in the Affective nor in the Cognitive Empathy subscales, neither of the two Empathy questionnaires considered individually (BES and IRI–data not shown) nor in the merged one (Figure 1C).

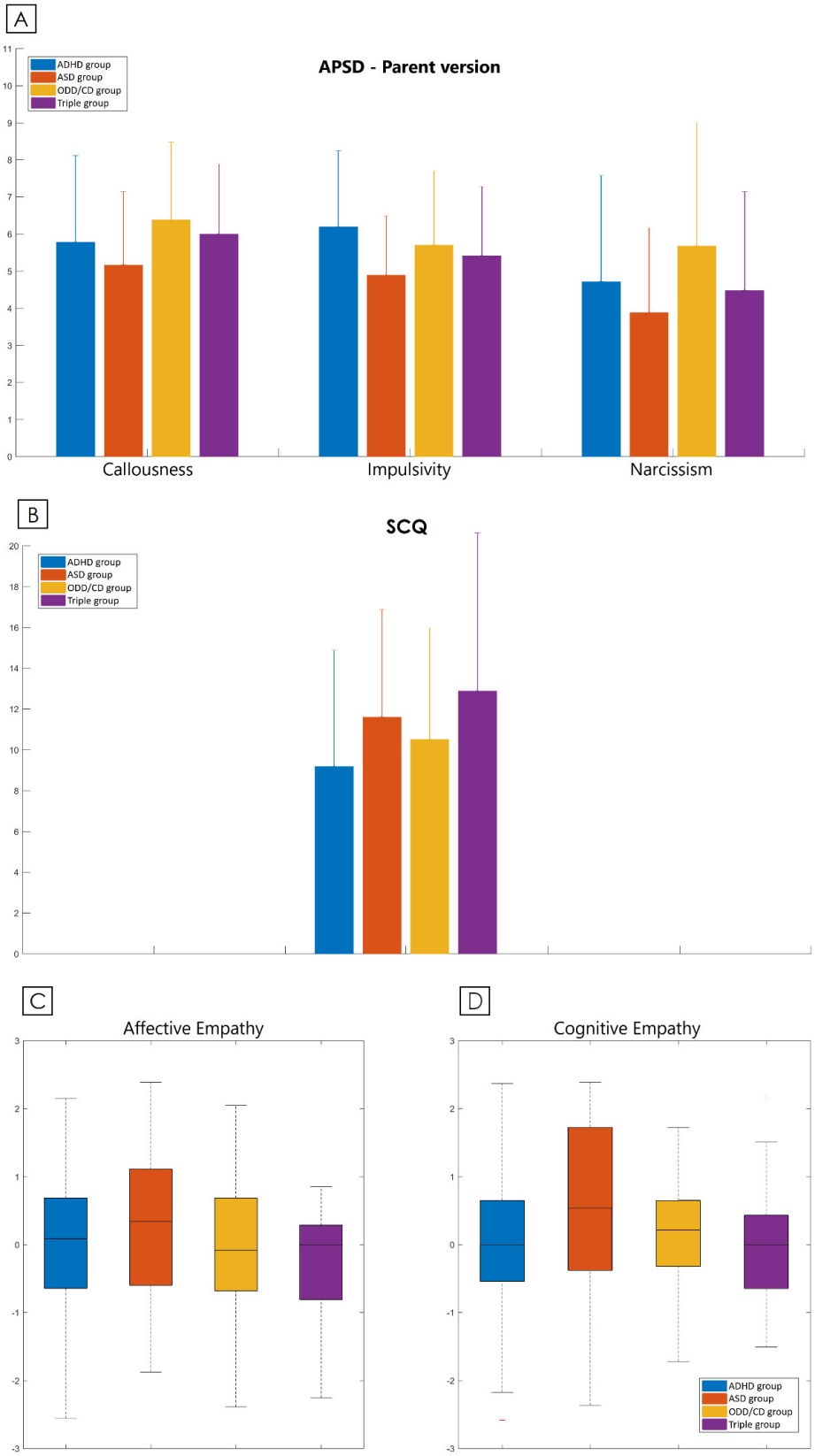

Figure 1. Questionnaires. Scores obtained by the four clinical groups in the Antisocial Process Screening Device (APSD, (**A**)), the Social Communication Questionnaire (SCQ, (**B**)) and the merged Empathy Questionnaire (**C**) are here illustrated. Scores are compared between ADHD group (blue bars), ASD group (red bars), ODD/CD group (yellow bars) and Triple group (purple bars). Graphs represent means with standard deviation bars, except for (**D**) where boxplots represent medians and first and third quartiles with minimum/maximum bars. * p-values < 0.05, ** p-values < 0.01, *** p-values < 0.001.

3.2. Correlations

Significant correlations between BRIEF-2-related subscales and APSD, SCQ and Empathy questionnaires are illustrated in Figure 2. Briefly, the Callousness subscale of the APSD was positively associated with the Inhibit and Self-Monitor scales of the BRIEF-2, while the Impulsivity subscale was positively correlated with all scales of the questionnaire. Similar findings were reported for the Narcissism subscale of the APSD, which was positively associated to most subscales of the BRIEF-2 across its three dimensions. The SCQ total score was positively associated to the Emotional and Behavioral Regulation related subscales of the BRIEF-2 and with the Initiate and Plan/Organize subscales. Finally, no significant correlations emerged for the Cognitive Empathy scale, while the Affective Empathy scale was negatively correlated with the Inhibit, the Self-Monitor and the Emotional Control subscales of the BRIEF-2.

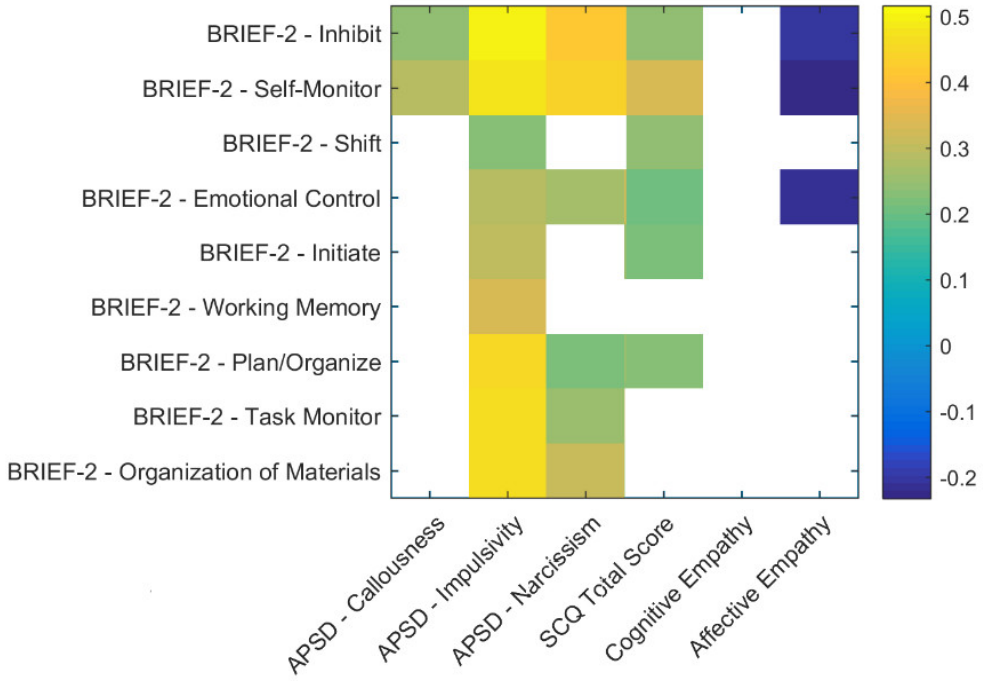

Figure 2. Correlations.

Pearson's linear correlation coefficients were here represented as colored boxes to show only significant relationships between continuous variables of selected questionnaires. The traditional significance level of 5% was corrected by means of Bonferroni's correction method for multiple comparisons. A color legend bar is displayed on the right.

3.3. Regression Models

Finally, a linear regression model was applied to identify statistical relationships between four aggressive/disruptive behavior-related CBCL subscales (AB, RBB, ODP, CP), as dependent variables, and several subscales from the other questionnaires, as independent variables, namely: the three main indexes of the BRIEF-2 (Behavioral, Emotional and Cognitive Regulation Indexes), the two Empathy subscales (Affective and Cognitive Empathy scales) and the SCQ total score.

As displayed in Table 1A–D, a significant positive association was found between both AB (Table 1A) and ODP (Table 1B) subscales of the CBCL, and the Behavioral and Emotional Regulation Indexes of the BRIEF-2. A significant positive relationship emerged, instead, between the RBB (Table 1C) and the CP (Table 1D) subscales of the CBCL, and the Behavioral—but not the Emotional—Regulation Index of the BRIEF-2, while a significant negative relationship was found for the Affective—but not the Cognitive—Empathy subscale.

Table 1. Linear Regression Models.

A. CBCL – AB	**Estimates**	**β – Coefficients**	**Standard Errors**	***p*–values**
Intercept	26.3134	0.0000	4.9028	4.21e-07 ***
BRIEF-2 – BRI	0.7645	0.3891	0.1843	6.49e-05 ***
BRIEF-2 – CRI	0.0667	0.2932	0.0715	0.3525
BRIEF-2 – ERI	0.4610	0.0753	0.1481	0.0023 **
Affective Empathy	-1.2782	-0.1137	0.9909	0.1996
Cognitive Empathy	0.6295	0.0580	0.9616	0.5139
SCQ Score	-0.0541	-0.0306	0.1317	0.6816
B. CBCL – ODP	**Estimates**	**β – Coefficients**	**Standard Errors**	***p*–values**
Intercept	35.6661	0.0000	3.8429	1.23e-15 ***
BRIEF-2 – BRI	0.5471	0.3891	0.1445	0.0002 ***
BRIEF-2 – CRI	0.0535	0.2932	0.0560	0.3420
BRIEF-2 – ERI	0.3042	0.0753	0.1161	0.0099 **
Affective Empathy	-0.9299	-0.1137	0.7767	0.2336
Cognitive Empathy	0.1635	0.0580	0.7537	0.8285
SCQ Score	0.0105	-0.0306	0.1032	0.9186
C. CBCL – RBB	**Estimates**	**β – Coefficients**	**Standard Errors**	***p*–values**
Intercept	38.4738	0.0000	3.6169	< 2e-16 ***
BRIEF-2 – BRI	0.6978	0.3891	0.1355	1.11e-06 ***
BRIEF-2 – CRI	0.0355	0.2932	0.0526	0.5008
BRIEF-2 – ERI	0.0637	0.0753	0.1091	0.5606
Affective Empathy	-1.5698	-0.1137	0.7326	0.0343 *
Cognitive Empathy	-0.0574	0.0580	0.7121	0.9359
SCQ Score	-0.0296	-0.0306	0.0968	0.7599
D. CBCL – CP	**Estimates**	**β – Coefficients**	**Standard Errors**	***p*–values**
Intercept	37.5833	0.0000	3.7916	< 2e-16 ***
BRIEF-2 – BRI	0.7870	0.3891	0.1424	2.12e-07 ***
BRIEF-2 – CRI	-0.0062	0.2932	0.0547	0.9096
BRIEF-2 – ERI	0.1749	0.0753	0.1165	0.1359
Affective Empathy	-1.7449	-0.1137	0.7665	0.0247 *
Cognitive Empathy	-0.3663	0.0580	0.7409	0.6220
SCQ Score	-0.1235	-0.0306	0.1008	0.2229

Estimates, standard errors and *p*-values are here presented for four linear regression models between selected subscales of the administered questionnaires. Four subscales of the Child Behavior Checklist questionnaire, namely Aggressive Behaviors (**A**), Oppositional-Defiant Problems (**B**), Rule-Breaking Behaviors (**C**), and Conduct Problems (**D**), were included as dependent variables of the models. The three main indexes of the Behavior Rating Inventory of Executive Functions–Second version (Behavioral, Emotional and Cognitive Regulation Indexes), the two subscales of the Empathy questionnaire (Affective and Cognitive Empathy), and the Social Communication Questionnaire total scores were used as independent variables of the model. * *p*-values < 0.05, ** *p*-values < 0.01, *** *p*-values < 0.001.

4. Discussion

The first aim of the present study was to explore possible relationships between the different aspects of empathy and specific subcomponents of EF in children and adolescents with ADHD alone, ADHD and ODD/CD and/or ASD. To this aim, our effort was to achieve at least three major objectives: (1) to assess empathic attitudes, CU traits, antisocial behaviors and socio-relational skills in our four groups of patients; (2) to identify potential relationships between these variables and the EF profiles; (3) to explore the interrelated role of the cognitive and affective dimensions of empathy and the EF in regulating antisocial behaviors and aggressiveness. To the best of our knowledge, this is the first study of the kind performed in such a multi-structured sample of children and adolescents.

First, none of the questionnaires used in our study was individually able to discriminate between the four clinical groups. The SCQ is a clinical checklist, based on parents or caregivers report, aimed at identifying the presence of abnormal social and communicative behaviors. Although the SCQ is used as a screening tool for ASD symptoms, the lack of significant differences in our sample between ADHD patients with or without ASD suggests that the social functioning deficits reported in ADHD patients [21], at least in their parents' judgement, were severe enough to mitigate the difference among groups. It is also likely, however, that, since parents of ADHD children, with or without ASD, are usually more aware of, and worried about, the behavioral consequences of the disorder, socio-communication difficulties could go unnoticed even in patients with a confirmed diagnosis of ASD. A complementary but not alternative explanation may be that our high-functioning ASD patients did not exhibit such a great severity of social and communicative symptoms [66,67], so that caregivers could not be fully aware of their functional consequences.

Similarly, no significant differences emerged between groups in the two questionnaires assessing CU traits. Our finding may suggest that these traits may be trans-nosographic and thus be present not exclusively in ODD/CD, but also in ADHD [68] and in ASD patients [69]. As for the Empathy questionnaires, neither the BES and IRI nor the merged version of the two, did show any significant differences between the four clinical groups. Unfortunately, few data are available in the literature on the empathic attitudes of ADHD children with comorbid psychiatric conditions [70]. One would expect, based on previous findings on non-comorbid conditions, a greater impairment of the affective component for subjects with ADHD in comorbidity with behavioral disorders [17], while a greater impairment of the cognitive component in subjects with ADHD+ASD [10,18]. Our results could be interpreted in light of the subtle complexity of empathy deficits in these neurodevelopmental disorders, which limited the likelihood to find significant differences among comorbid conditions. It should be also taken into account that all our subjects were diagnosed with ADHD and this shared clinical condition may have obscured possible differences among groups. However, this finding further supports the notion that comorbid conditions are not the simple summation of two different disorders. In light of this, ADHD + ASD patients are not simply ASD patients with an additional ADHD, but a specific phenotype, possibly with a lesser cognitive empathic deficit or greater affective empathic impairment. Similarly, ADHD + ODD/CD patients may present a lesser affective empathic deficit or greater cognitive empathic impairment. This hypothesis should be tested by comparing "pure" ASD and ODD/CD with patients with ADHD and comorbidity conditions. Interestingly, recent studies shed some light on future research about specific empathy impairments in ASD and ODD/CD individuals, suggesting that different mechanisms and factors may be involved in empathic problems in such conditions [71,72].

The principal goal of the present study was to assess the reciprocal relationship between empathic attitudes and EF in ADHD patients. A recent meta-analysis [29], mainly including studies performed on healthy subjects, found positive correlations between empathic competences and EF. Gökçen et al. [43,44] reported similar findings in individuals with ASD traits, suggesting the role of EF in regulating empathic competences in neurodevelopmental disorders. Similarly, a more recent study by Abdel-Hamid et al., 2019 [47], identified in ADHD patients, but not in healthy controls, overlapping significant correlations between theory of mind and empathy measures and EF performances at the Trail Making Test, which specifically assesses Cognitive Flexibility and Working Memory skills. As for the so-called "hot" EF, that is the process underlying the affective modulation of behavioral responses [73,74], Miranda et al., 2017 [75], observed significant correlations between social cognition deficits, assessed by means of a specific subscale of the NEPSY–II test [76], and the BRIEF inhibition and emotional control scales in an ADHD sample, while the former are linked to metacognitive deficits in high functioning ASD patients.

In our sample, affective empathic competences, assessed through the BES and the IRI questionnaires, are negatively correlated with Emotional and Behavioral Regulation impairments, identified through the BRIEF-2 questionnaire. The greater the difficulties in "hot" EF, the lower the empathic attitudes, or, in other words, individuals with severe deficits in the EF profile exhibited

lower scores on Empathy questionnaires. Nonetheless, no significant correlations were found neither for EF metacognitive domains nor with the cognitive empathy subscale.

Our results suggest that inhibitory and emotional control play an important role in regulating externalizing behavior, even controlling for empathic competences. As stated above, empathic attitudes are activated through an emotional processing which is regulated both by bottom-up and top-down circuitry within the prefrontal and limbic cortex [29,77]. This effective control is achieved through EF modulation, allowing for a fine adjustment of the sharing experience [33]. It should be noted that bottom-up and top-down processes are hardly separable when examined on a behavioral level. Nonetheless, the Russian Doll Model by Preston and de Waal [31] recently posited that top-down executive regulation of empathic processing develops later than bottom-up routes, which are responsible for uncontrolled empathic responses that operates automatically. This model is in line with the Hoffman's developmental theory of empathy [37], according to which Emotional Contagion would develop earlier than more regulated forms of empathic attitude towards the others.

Our results indicate that EF are more strongly related to the affective empathy than to the cognitive one, which is in disagreement with the results of the aforementioned meta-analysis [29]. Nonetheless, it should be emphasized that the studies of this meta-analysis did not include ADHD patients, who could exhibit such a severe impairment in their EF and a deficit in their cognitive empathic competences, that reciprocal associations would not result in statistical significance. In other words, we posit that ADHD patients are somewhat constrained by their executive dysfunction in an underdevelopment of their empathic attitude, which would be limited to the expression of an emotional contagion from the other.

Furthermore, significant positive relationships were found between several variables of the APSD questionnaire and the BRIEF-2 subscales related to the Emotional and Behavioral Regulation domains. Namely, the higher the scores in CU traits-related questionnaires, the higher the impairment in the Emotional-Behavioral Regulation competences. This finding is in line with a recent study assessing the relationship between CU traits and parent ratings of EF [78]. In particular, this study [78] highlights how CU traits are related to emotional self-regulation, but not to the EF performance scales. Since parental ratings are believed to capture EF behavioral representations, these clinical ratings may be more closely associated with behavioral representations of CU traits, which are also identified by the parents' report [78].

Finally, in our research, we tried to investigate, in a clinical sample of ADHD patients with psychiatric comorbidities, the relationships between two of the fundamental psychological grounds in the neuropsychologic developmental milestones of children and adolescents, namely EF and empathic attitudes, and how they reciprocally interact to regulate behavioral self-regulation and aggressiveness. Our results confirm a strong and finely structured relationship between these variables, being aggressive behaviors and related disturbances significantly influenced by these underlying processes. Our work highlights two different interactions between EF and empathy to regulate social behaviors in ADHD, where a dysfunction of these elements is essential for aggressive and antisocial behaviors to be carried out towards the others.

A first model identifies aggressiveness and oppositional problems, as indexed through the CBCL questionnaire, mainly associated with difficulties in executive emotional-behavioral regulation processes (such as impulse control and the ability to appropriately regulate one's behavior according to the context), but not with dimensions of empathy. Interestingly, reactive aggressiveness usually emerges as an impulsive response to hostile-perceived environmental events, often precipitated by irritability and tantrums [79]. This type of aggressiveness has been related to an orbito-frontal cortical dysfunction, for its primary role in adapting system reactivity to stress events [9,17,80].

On the other hand, rule-breaking behaviors and conduct disorders, as indexed through the CBCL questionnaire, likely relate to a proactive type of aggressiveness, which is associated to the activation of self-oriented behaviors to take advantage for personal purposes to the achievement of benefits at the emotional expense of the others' perspective [79]. Our study confirms that these aspects possibly relate to low levels of affective, but not cognitive, empathy and to impaired behavioral, but not emotional, regulation functioning. It has been hypothesized that proactive aggressiveness might

be caused by dysfunctional mechanisms of violence inhibition, which are usually activated by others' discomfort signs, such as fear and sadness [15]. A deficient activation of this self-control mechanism is usually attributed to abnormal responses of the limbic system, particularly of the amygdala, which have been linked to antisocial behaviors in psychopathy [14,15].

Our results are thus in line with previous studies and further elucidate the complex and intriguing relationships between empathic attitudes and EF. In other words, it seems that both impaired behavioral self-regulation and difficulties in the emotional sharing of others' internal state may lead to a down-regulation of proactive aggressiveness inhibition systems, while emotional and behavioral regulation functioning systems are essential in preventing more reactive forms of aggressiveness towards the others. Thus, the multifaceted interactions of both "hot" EF and empathic attitudes have a central role in regulating prosocial behaviors.

Our study displays, however, a number of limitations that might undermine the robustness of our conclusions; notably, a marked discrepancy in group size, particularly between the "pure" ADHD and ADHD+ODD/CD+ASD groups, and the absence of a control group of healthy children. The purpose of this preliminary study was, indeed, to explore the issues addressed above; therefore, further studies on larger samples, possibly including heathy controls, a greater number of girls and ASD patients, and children with limited prosocial emotions, will be performed to confirm the results.

5. Conclusions

In conclusion, our study provides a further contribution for a better understanding of the complex and intriguing relationship between empathic competence and executive skills. These evidences could be beneficial for the definition of treatment strategies aimed at attenuating externalizing behaviors. Aggressive behaviors would, indeed, be modified by an empathic attitude-oriented approach, which should focus on the underlying executive dysfunction. To sum up, we showed that executive functioning and empathic attitudes interact with each other to regulate aggressive behaviors, being the former more related to reactive aggressiveness and the latter to proactive aggressiveness.

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REVIEW

Early motor signs of attention-deficit hyperactivity disorder: a systematic review

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Abstract

ADHD is a common neurodevelopmental disorder with onset of symptoms typically in early childhood. First signs of the disorder, including language delay, motor delay and temperament characteristics, may be evident as early as infancy. The present review describes published evidence about early motor signs of either children with later symptoms of ADHD or a later diagnosis of the disorder. Nine published cohort studies were included after a systematic search of related terms in PubMed and PsycInfo databases. Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participants' assessment by/at 12 months of age; (3) report of a later presence of ADHD symptoms. The limited number of reports included suggests an association between mild early neurological markers and later developmental coordination disorder and motor overflow movements. Unfortunately, due to their small sample sizes and focus on group reports rather than individuals, they have limited power to find strong associations. Early motor indicators of ADHD, if present, appear to be non-specific, and therefore not yet useful in clinical screening. Spontaneous motility seems to be a promising measure for early ADHD detection, although further studies with large cohorts are recommended to determine its clinical role in children at risk for ADHD.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Early motor signs · Infancy · General movements (GMs)

Introduction

ADHD is a common neurodevelopmental disorder with symptoms typically emerging during early school years and a worldwide prevalence estimated between 5 and 7% [1, 2].

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity–impulsivity which hinders adaptive functioning or compromises development [3]. To be diagnosed with ADHD, symptoms of the disorder must be observed in two or more settings and have negative effects on fundamental aspects of the child's daily activities. Co-occurring psychiatric conditions are frequently observed, including oppositional defiant disorder (ODD), conduct disorder, anxiety disorders, depression, autism spectrum disorder (ASD) and learning disabilities [4–9]. Children with ADHD also often face difficulties in everyday life, including in their social relationships, academic performance and achievements, and low self-esteem [10]. In addition, they may experience deficits in visuospatial and verbal working memory, vigilance, inhibitory control and planning, problems with coordination of gross and fine motor functions, sequencing of movements [11], difficulties with working memory and self-regulation of emotions, language and speech deficits, arousal and activation and temporal information processing and timing [11–17].

Investigating early motor signs during the first year of life could be of high importance for the study of early

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biomarkers of common neurodevelopmental disorders, such as ADHD and ASD, which may share neurobiological underpinnings [18–21]. There is evidence that children with ADHD have worse gross motor and fine motor skills than their typically developing peers [22]. Two hypotheses on the source of the motor disadvantages in individuals with ADHD have been put forward. The first hypothesis attributes these motor abnormalities to the core triad of ADHD symptoms: hyperactivity, impulsivity and inattention. According to this theory, inattention [22] and vigilance problems [23] affect motor skill development. The second hypothesis attributes the motor delays to a likely presence of a comorbid disorder such as developmental coordination disorder (DCD) or ASD [23, 24]. Overall, research indicates that attention and impulse control are strongly predictive of gross and fine motor skill development in children with ADHD [24].

The neurobiological basis for the primary theory is that delays in brain maturation are associated with delays in motor development and specific motor skills [25] in the ADHD population. More specifically, motor control and executive function rely on the integrity of the thalamus, known to be affected in individuals with ADHD [26]. In addition, cortical thickness structure abnormalities and hypoactivation in the right globus pallidus, the right frontal cerebellum and frontal region, reported to be present in ADHD, are responsible, among other functions, for precise motor control.

The second theory—of the comorbidity between ADHD and DCD as the potential cause of motor delays—is also supported by neurological findings. Although the comorbidity of ADHD and DCD is not often taken into account, a high percentage of children with ADHD (30–50%) experiences co-occurring DCD with a familial correlation of 0.38 [27–31]. Almost half of individuals with ADHD (34% out of 63%) have been reported to show motor difficulties within the DCD range, particularly in manual dexterity. These difficulties result in low self-esteem and reduced popularity in children [29, 30]. At present, there is evidence that a dopamine-induced imbalance of basal ganglia neuro circuits could also be involved in the underlying neurobiological mechanisms [32, 33]. Thus, health care professionals should be aware of the high prevalence of this co-occurring motor condition.

Cerebellar abnormalities in children with DCD could also explain postural control and balance problems. Children with ADHD without co-occurring DCD have shown fine motor fluency and flexibility, but when a co-occurring DCD condition is present, fine motor difficulties are observed [34]. However, few studies have focused on brain region atypicalities in ADHD children with co-occurring DCD. McLeod et al [35]. found that these children have increased functional connectivity between the primary motor cortex and brain regions involved in motor control, and claimed this is fundamental for their ability to organize and successfully execute movement [36]. However, motor abnormalities in ADHD cannot be attributed only to the co-occurence with DCD, since children with ADHD without DCD do also have motor difficulties, although these are less prominent [37].

Since ADHD symptoms usually emerge during the early school years, both clinical and neurobiological research have focused on school-aged children, adolescents and adults. Interest in early signs of ADHD is, however, rapidly growing. Recent studies report initial evidence of some indicators appearing prior to school-age, including difficult temperament, and language and motor delay [38, 39]. Still, a little is known about whether early signs of ADHD can be reliably observed during the first year of life. This may be partly due to the relative immaturity of cognitive functions related to sustained attention and focused activity during the first months of life, and to the consequent difficulty in reliably assessing them. Increasing evidence suggests that specific motor behaviors observed during the first months of life may be a marker of neurodevelopmental disorders, which show clinical and genetic overlap with ADHD [40]. Some authors suggest that increased activity in infancy could be considered an early sign of ADHD [38, 41–45]. However, other researchers argue that the quality of movements in infancy per se does not predict the disorder [46–48].

To shed light on early motor signs in ADHD and their emergence, we systematically reviewed the publications investigating motor behavior during the first year of life in infants who later develop subclinical ADHD symptoms or are diagnosed with the disorder.

Methods

A systematic literature search was performed in PubMed and PsycInfo databases including the following keywords: (1) “ADHD” OR “Attention deficit hyperactivity disorder” OR “Attention deficit-hyperactivity disorder”; (2) AND “infant*” OR “infancy” OR “neonatal” OR “newborn” OR “baby”; AND “movement*” OR “motor” OR “sensory-motor” OR “sensori-motor” OR “motion”. A systematic review of the references of the included papers was also performed to ensure a thorough search. The first search was performed in July 2016, and once more in January 2017, which yielded one additional relevant article.

Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participants’ assessment by/at 12 months of age; (3) report of a later presence of ADHD symptoms. The first selection was based on the study titles, as identified by one of the authors (AA). Second, abstracts were independently screened for eligibility by two authors (AA and OC). Two authors (AA and OC) independently performed the data

extraction and discussed their findings to reach a consensus. Full texts of potentially relevant papers were read to ascertain whether the study met all selection criteria.

The following data were extracted from the included articles: type of study (e.g., longitudinal, cross-sectional, or case control, both retrospective and prospective), source population (e.g., population-based or hospital referrals), participants' age range, type and timing of early motor signs, type and timing of ADHD diagnosis (based on the DSM-5) [3], or ADHD-specific symptoms (based on interviews/questionnaires), and the study outcome assessment.

Quality ratings were conducted using a modified Methodological Quality Checklist [49] developed for assessing the methodological quality of both randomized and non-randomized studies. Two of the authors (AA and OC) performed the quality ratings independently, and when necessary, reached a decision by consensus. Thirteen out of the 27 items of the scale were used in the present study, after removing those that applied only to randomized trials and intervention studies. This modified scale yielded a final rating from 0 to 14 points (see Table 1). The same approach was previously used in a systematic review on ADHD [50].

Results

In total, 417 articles were identified via the database search on both PubMed and PsycInfo; 30 studies were selected for review. Nine articles were included after completing the selection process (see flow diagram in Fig. 1). All included publications were cohort studies. The findings of all reviewed articles are reported in Table 2. Design and outcome measures differed substantially among the studies, which made a formal meta-analysis not feasible. The quality ratings of the included studies ranged between 11 and 14 out of 14 (see Table 1). Overall, the reports were of good quality.

Spontaneous movements during the first 3 months of age

Three prospective studies [42–44] explored very early motor signs of ADHD. They focused on the quality of spontaneous motility, as assessed by the General Movements (GMs) approach with infants at risk for neurodevelopmental delays. General movements are distinct spontaneous movement patterns that infants exhibit without external stimulation [53]. Investigations of early motor indicators of ADHD through the evaluation of GMs have included both healthy infants and those with increased risk for neurodevelopmental delays. Consistent with the GM method, the investigators evaluated infants several times in the first months of life and then followed up with standardized behavioral assessments at school-age. One study [42] reported that infants with definitely abnormal GMs including extremely reduced complexity, variability and fluency were at significantly increased risk to develop cerebral palsy. Furthermore, a significant association was found between milder GM abnormalities and attention problems at 4–9-year follow-up (odds ratio 6.88, 95% CI 1.39–33.97) assessed by the DSM-IV ADHD questionnaire. In particular, unlike infants with normal fidgety movements at 3–4 months, children with mildly abnormal GMs were significantly more distractible, inattentive and hyperactive as assessed by the Groningen Perinatal Project Questionnaire (GPPQ) and the DSM-IV ADHD Questionnaire for Attention-Deficit/Hyperactivity Disorder. Another study [40] indicated that abnormal GMs at both writhing and fidgety age were significantly associated with the presence of ADHD only when it was co-occurrent with another psychiatric diagnosis, but not when it was present in isolation. Furthermore, abnormal GMs at fidgety age were related to a higher total score on the DSM-IV ADHD questionnaire, and in particular, to higher subscores for hyperactivity and impulsivity, and lower subscores for inattention. Another report of GMs with preterm born infants, however, showed no significant association between GMs and attention problems at 7–11 years, as assessed by a separate subscale of the Child Behavior Checklist (CBCL) [55]. This dissociation was even stronger when children with cerebral palsy were excluded from the analysis [44].

Motor signs during the first year

Of the included reports, four were large longitudinal cohort studies exploring early neurodevelopment in the general population [38, 46, 48] or in families with lower socioeconomic status [45]. Neurodevelopmental characteristics of children with ADHD symptoms or an ADHD diagnosis were compared to the same characteristics of control children.

A retrospective chart review study of 58 children diagnosed with ADHD at school-age and 58 controls that participated in a population-based developmental program at a 'Well-Baby' clinic evaluated longitudinal data from birth, 1-, 3-, 9- and 18-month visits [38]. Higher incidence of emergency caesarian sections, smaller head circumference at 3 months and feeding or sleeping difficulties before 6 months were all identified as early signs significantly correlated with ADHD. However, the only motor-related early sign identified was a delay in gross motor development, as assessed by the Denver Developmental Screening Test (DDST) [54]. A delay in gross motor movements was identified at 9 months of age in 34.5% of the ADHD group compared to 13.8% of the controls. The most reported deviation from typical gross motor development was the refusal to maintain supine position, which led to difficulties in head control, and thus, to general motor development difficulties. The delay was reported to be relatively mild, and attributed

Table 1 Quality ratings of studies

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
Reporting									
1. Is the hypothesis/aim/objective of the study clearly described?	I	I	I	I	I	I	I	I?	I
2. Are the main outcomes to be measured clearly described in the "Introduction" or "Method" section?	I	I	I	I	I	I	0?	I	I
3. Are the characteristics of the patients included in the study clearly described?	I	I	I	I	I	I	I	I	I
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2	2	2	2	0?	1?	1	1	2
6. Are the main findings of the study clearly described?	I	I	I	I	I	I	I	I	I

Table 1 (continued)

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
7. Does the study provide estimates of the random variability in the data for the main outcomes?	I	I	I	I	0	I	I (CI)	I	I
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	I	I	I	I	I	I	I (≤ 0.01)	I	I ($p<0.09$)
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	I	I	I	I	I	I	I	0 Unable to determine	I

Table 1 (continued)

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	I	I	I	I	I	I	I	0 Unable to determine	I
13. If any of the results of the study were based on "Data dredging", was this made clear?	I	I	I	I	I	I	I	I	I
14. Were the statistical tests used to assess the main outcomes appropriate?	I	I	I	I	I	I	I	I	I
15. Were the main outcome measures used accurate (valid and reliable)?	I	0 ADHD outcome was based only on the DSM-IV scale (7 items)	0 Possible follow-up bias	I	I	I	I	I	I
16. Did the study have sufficient power to detect a clinically important effect?	I (80%)	0 No calculation of the sample size	0 Small sample size	0 No calculation of the sample size	0 Small sample size	0 Small sample size	I?	I	0 Small sample size. Not calculated
Quality rating score									

Yes = I, No = 0, Unable to determine = 0

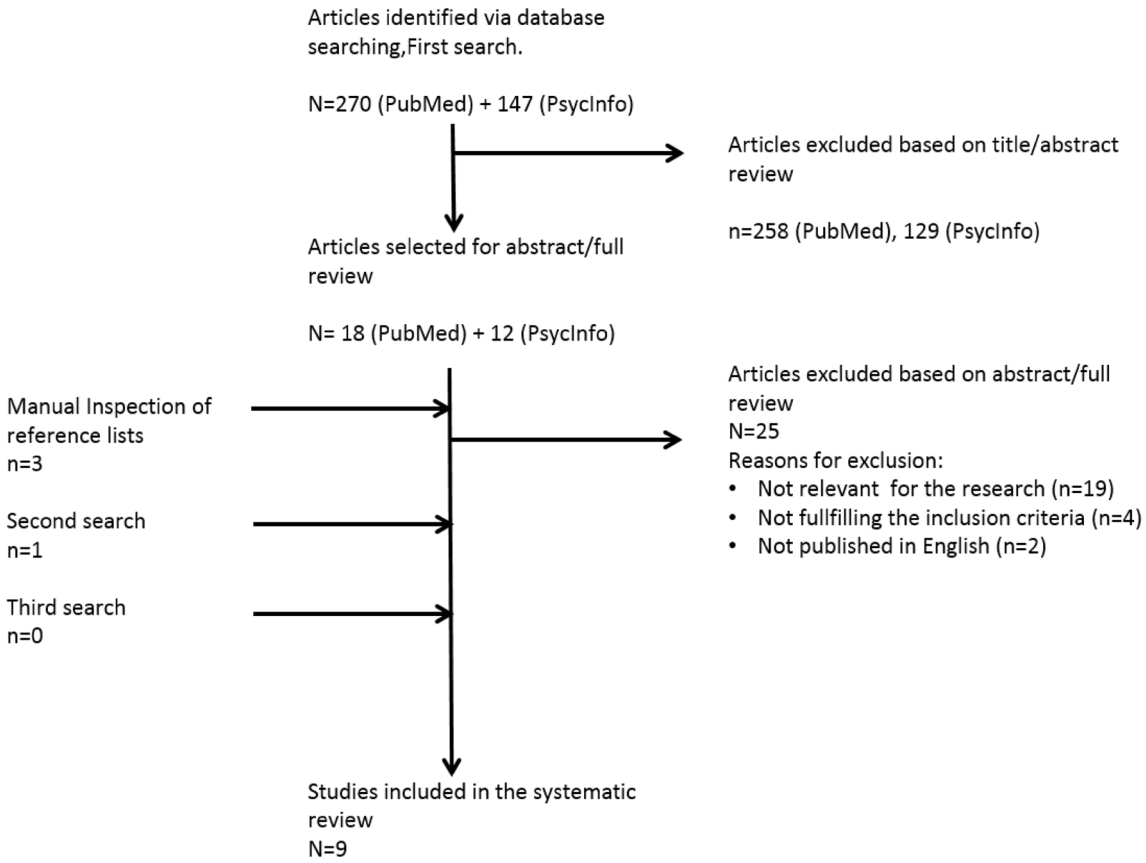

Fig. 1 Selection process

to physical characteristics including lax ligaments and hypotonia. Importantly, some children in the ADHD group were early achievers and some were late achievers, with both subgroups reported by the authors as showing "extreme" motor behavior.

A prospective study exploring early development in 267 infants from families with lower socioeconomic status [45] also included a smaller retrospective evaluation of 34 hyperactive children and 34 age-matched controls. The presence of hyperactivity was determined at around 6 years of age from subscores of the teacher-administered CBCL [55]. Thirty-eight child behavior variables were obtained during the first 2.5 years of life including neonatal behavioral assessments, mother-administered Carey questionnaire evaluating temperament, activity and attention, and other ratings of activity at 3 and 6 months of age [56]. Children who were hyperactive in kindergarten had been motorically less mature at 7 days old as assessed by the motor maturity Brazelton factor [57]. However, this was the only variable, out of the 38, which differentiated hyperactive children from typical children.

Another large study by Lemcke et al. [48] included 2034 children with a diagnosis of ADHD, who came from a large population-based cohort from the Danish National Birth Cohort (DNBC). As part of the DNBC, 76,286 mothers were interviewed about their child's development at 6 and 18 months. Children were followed up between 8 and 14 years of age, when they were assessed for the presence of ADHD based on International Classification of Diseases, 10th Revision (ICD-10) criteria. The interview at 6 months of age explored specific aspects of motor development, such as the infant holding their head straight while being picked up, sitting up while on an adult's lap, rolling over from back to stomach, crawling on the stomach. When comparing the ADHD group with the total study cohort, the only significant finding in the ADHD group was a higher number of infants who could not sit up straight when put on lap at 6 months ($p \leq 0.001$).

Similarly, Jaspers et al. [46] studied early indicators of ADHD (and ASD) in a population of 1816 subjects who took part in a prospective cohort study among (pre-)adolescents in the general population. Early indicators were obtained by identifying correlations between routine data from the community pediatric services during the first year of life and ADHD-risk as measured by parent-administered CBCL between 11 and 17 years old. Early motor indicators

Table 2 Studies included in the current systematic review

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Johnson et al. [47]	Community-based, within ALSPAC	16 ADHD, 120 controls	Retrospective longitudinal	Body movements (14)	12 months	ADHD diagnosis based on DSM-IV	7 years	No correlation between motion variables at 12 months and ADHD diagnosis at 7 years
Jaspers et al. [46]	Dutch pre-adolescents	348 adolescents with ASD, 419 adolescents with ADHD	Prospective cohort (TRAILS) based on PCH setting	Gross motor skills (16), fine motor skills and adaptation (11), communication and social behavior (10)	Birth, 18 months	CSBQ, CBCL, DSM-IV, oriented attention-hyperactivity problem scale, PCH	10–12 years	Good gross motor skills within the first year significantly correlated with development of ADHD
Jeyaseelan et al. [41]	Neonatal patients	45 extremely low birth weight (< 1000 g) and/or very preterm (< 27 weeks GA) infants	Retrospective longitudinal	NSMDA, neurological status, infant movement patterns, postural development and motor responses to sensory input	12, 24 months	CRSR, ADHD-RS	7–9 years	Motor development of ELBW 24 month infants correlated with specific clinical measures of attention at school-age, independent of biological and social factors
Hadders-Algra and Groothuis [42]	Children from the study of Hadders-Algra et al. [51, 52] (cohort of a larger study)	52 children: 28 healthy term infants, 24 at high-risk for neurodevelopmental disorders	Longitudinal	GM complexity, GM variation, GM fluency	2–4 weeks (low-risk group), 1–6 weeks (high-risk group)	Neurological examination and evaluation of behavior by parental questionnaires GPPQ, DSM-IV based questionnaire adapted for ADHD	4–9 years	Mildly abnormal GMs were associated with the development of MND, ADHD and aggression
Hadders-Algra et al. [43]	Neonatal patients, cohort from a larger study (1988–1993)	41 infants:25 low-risk full-term infants, 16 infants at high-risk for neurodevelopmental disorder	Follow-up prospective	Two forms of normal GMs (normal–optimal, normal–suboptimal) and two forms of abnormal (mildly and definitely abnormal)	Multiple ages during the first postnatal months	ADHD diagnosis, TRF questionnaire based on DSM-IV, CBCL	4–9 years, 9–12 parents completed CBCL and DSMq	Abnormal GMs at 'writhing' and 'fidgety' age are linked to ADHD along with a psychiatric comorbidity, but no isolated ADHD

Table 2 (continued)

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Butcher et al. [44]	Neonatal intensive care unit patients (1993–1998)	65 infants born at ≤ 33 gestational weeks	Follow-up	Spontaneous movement (GMs) quality as an indicator of intelligence and behavior at school-age	4–6 week intervals between birth, and at 6 months post-term	Neurological status assessed with Touwen's test, CBCL with a separate subscale for attention problems	7–11 years (intelligence and behavior)	Spontaneous movements at 11–16 weeks seem to predict both motor development and intelligence. FM quality is strongly associated with later neurological dysfunction. No significant correlation with attention problems
Lemcke et al. [48]	Large population-based birth cohort from a network database	2034 singletons from Danish health registers with a clinical diagnosis of ADHD	Retrospective	Activity and motor development, mothers interviewed about child's development and temperament	Birth, at 6 and 18 months	ADHD diagnosis based on DSM-IV	8–14 years old	Mothers of children later diagnosed with ADHD reported more or less activity along with a limited cautiousness and a delay in language development. Majority of the children did not show deviations in motor development. There were early and late achievers of independent walking

Table 2 (continued)

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Gurevitz et al. [38]	Children followed up in well-baby-care clinics	58 children diagnosed with ADHD, 58 typical children	Retrospective	Gross and fine motor (general tone, head and neck control, hyperlaxity of ligaments, physical/neurological abnormalities), language and speech, and cognition and communication	0–1, 3, 9 and 18 months	ADHD diagnosis, family, perinatal and postnatal history, biometric parameters of the infant/toddler, DDST, common difficulties during the first 3 months, sleep and feeding problems, child temperament description by parents and pediatricians, behavior characteristics, abnormal findings on physical examination	Early childhood	Motor (hypotonia and lax ligaments) and language development delay, along with difficult temperament
Jacobvitz and Sroufe [45]	cohort from a larger study of 267 families	34 hyperactive (24 males, 10 females), 34 control children (24 males, 10 females)	Longitudinal	Neonatal status (orientation, arousal, motor maturity, physical ability/body tonus and quieting/consolability), newborn ratings, Carey Infant Temperament Questionnaire, EASI Temperament Survey, home and laboratory observations	Day 7, day 10, 6 months	Teachers completed the Achenbach "Child Behavior Checklst" at the end of kindergarten	5 or 6 years	Hyperactive kindergarteners were less motorically mature on the 7/10 day (isolated finding). Only one out of 38 variables differentiated hyperactive children from controls

ADHD attention-deficit hyperactivity disorder, *ASD* autism spectrum disorder, *TRAILS* tracking adolescents' individual lives survey, *PCH* preventive child healthcare, *CSBQ* children's social behavior questionnaire, *CBCL* child behavior checklist, *ESSENCE* syndromes eliciting neurodevelopmental clinical examinations, *IDD* intellectual developmental disorder, *DCD* developmental coordination disorder, *NTR* Netherlands twin register, *SES*: socioeconomical status, *ELBW* extremely low birthweight, *NSMDA* neurosensory motor developmental assessment, *GMs* general movements, *MND* minor neurological dysfunction, *DBNC* Danish national birth cohort

as assessed by the Van Wiechen scheme [58] explored the scores of gross and fine motor skills and social behavior. This study reports that good gross motor skills within the first year were significantly correlated with the development of ADHD problems.

Motor signs at 1 year

Two studies explored motor signs at 12 months of age. Johnson et al. [46] studied 16 children with ADHD (based on DSM-IV criteria), and 120 control children. Both groups were extracted from a focus study group within a larger community-based cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). As part of the ALSPAC focus study group, 1240 infants at 1 year took part in a video-recorded parent–infant interaction in a naturalistic environment [59]. Software was used to track 8 body markers [(nose (N), right (RH) and left hand (LH), right (RE) and left elbow (LE), right (RS) and left shoulder (LS) and pelvis (P)]. Thirteen motion summaries were used to determine robust indexes of motor activity including speed, acceleration along with their variability, acceleration, periodicity and agitation. Finally, 14 out of 104 variables were chosen for further investigation, including the speed and variability of 5 markers (N, RH, LH, LE, LS), the agitation of 3 (N, LH, LE) and rhythmic movement of one marker (RH). No significant association was found between the motion variables examined and the diagnosis of ADHD at 7 years. A correlation between motor activity and scores on the inattentiveness subscale of the ADHD diagnostic interview was found in male participants, but considered questionable by the authors due to the small size of the subsample ($n = 14$).

Lastly, motor signs of extremely low birth weight and very preterm infants were evaluated at 12 months with the Neurosensory Motor Developmental Assessment (NSMDA) and these scores were examined together with clinical and psychometric measures of attention at 7–9 years of age [41]. At 12 months, NSMDA evaluated gross and fine motor function, motor patterns, neurological status, postural development, and the reaction to sensory input. Measures of attention in childhood included the Conner's Rating Scale Revised-Long Form (CRSR) and Du Paul ADHD Rating Scale IV (ADHD-RS).

Discussion

ADHD is a neurodevelopmental disorder characterized by a pattern of inattention and/or impulsivity and hyperactivity across different contexts. Since early identification of ADHD is essential to optimize the quality of life, there is growing research interest in the investigation of early clinical and behavioral features of children later diagnosed with ADHD. To further investigate this topic, we reviewed the literature summarizing the full spectrum of motor impairments which might be potential early indicators of ADHD. In particular, we included studies which report motor skills of infants during the first year of life who subsequently (1) received a formal psychiatric diagnosis of ADHD based on DSM-IV or the ICD-10, or (2) whose behaviors were related to high levels of ADHD symptoms, as identified by questionnaires.

Diagnosis of ADHD and early motor signs

Four of nine studies presented included a formal diagnosis of ADHD through a psychiatric assessment [36, 42, 47, 48]. The clinical diagnosis of ADHD was either based on the criteria of the DSM-IV or the ICD-10. In these studies, children with ADHD showed atypical motor development detectable in the first 9 months [47], but not as late as 12 months, when compared to typically developing infants.

The first detectable abnormalities of motor development, GMs, in children later diagnosed with ADHD seem to be associated more strongly with ADHD when it is co-occurring with other psychiatric disorders than with ADHD alone. This is consistent with previous reports suggesting that ADHD with a co-occurring disorder is a probably more severe form of ADHD [60, 61]. Indeed, although children diagnosed with cerebral palsy were excluded from Hadders-Algra's [42] study, to avoid bias related to the known association between cerebral palsy and behavioral problems, their study population was at high risk for neurodevelopmental problems [43]. Therefore, the relationship found in this study between abnormal GMs and ADHD still suggests that the vulnerability of periventricular white matter, typical of preterm subjects and associated to abnormal GMs, may contribute to the development of ADHD with co-occurring conditions [62, 63]. In any case, the results of Hadders-Algra [42] should be considered as preliminary, since its sample size was insufficient to reach definite conclusions [43].

During the time of spontaneous motility (0–5 months) and beyond, at least up to 9 months, a delay in gross motor function was significantly more common in infants who later developed ADHD. At 3 and 9 months, Gurevitz et al. [38] reported a delay in gross motor development as assessed by the Denver Developmental Screening Test, while at 6 months Lemcke et al. [48] found a significantly higher number of infants who could not sit up straight when put on lap in the ADHD group. Motor delay seems to be no longer present at 12 months, according to the findings by Johnson et al. [46], who found no significant association between a series of motor variables at 12 months with the clinical diagnosis of ADHD at 7 years of age. As the authors hypothesized, their inconclusive outcome could be due to the small sample size of the study.

Auerbach et al. [64], examining 7-month-old infants at risk of ADHD based on mother reports and observational measures, found that children with later ADHD were significantly different from the control group in respect of behavioral states, interest and activity level.

Overall, these results support the hypothesis of a link between mild neurological markers and developmental coordination disorder, and motor overflow movements, all of which are more common in children with ADHD [64]. Nevertheless, non-specific factors related to physical characteristics, such as lax ligaments and hypotonia, are also likely to have contributed to the described gross motor delay.

Symptoms of ADHD and early motor signs

Results are more inconsistent when it comes to the relationship between early motor signs and later subclinical ADHD symptoms. Some reports state that early spontaneous motility is correlated with attention problems, including less motoric maturity at 7 days of life in children who are later hyperactive in kindergarten. Similarly, Jeyaseelan et al. [41] found a correlation between decreased motor and sensory assessment scale scores (NSMDA) and psychometric measures of verbal attention span at 12 months. However, Jaspers et al. [46] found that ADHD problems were significantly correlated with good gross motor skills, as defined by the authors, within the first year of life.

There are multiple possible reasons for these inconsistent findings. The populations that were studied are extremely heterogeneous and have different degrees of risk for ADHD, from infants with clinical signs of early hyperactivity to those who are born preterm or were small for gestational age. The assessments used to test the presence and characteristics of early motor signs were also heterogeneous, including parental questionnaires, qualitative and quantitative assessments of motor behavior, and early attentional measures. Finally, the diagnostic instruments that were used to evaluate later presence of ADHD symptoms differed among studies, making comparisons very challenging.

The limitation of our review is that the studies which are included have small sample sizes and focus on group reports rather than individuals, so they have limited power to find strong associations. Although the studies are of high quality according to the rating scheme, the outcome measures have questionable accuracy (see Table 1).

Concluding remarks

In summary, there are a limited number of reports investigating gross motor function in the first year of life in children who later have ADHD symptoms or are diagnosed with ADHD. Early detection of ADHD-related motor abnormalities would be important to provide a timely diagnosis, and most importantly, early intervention, especially in case of a very strong association between ADHD and early motor signs. This would assist clinicians in the continuous development and implementation of interventions at a very critical period of child development, when the brain is rapidly developing and neuroplasticity is highest. Unfortunately, data emerging from this review show that early motor signs, if present, seem to be non-specific, and therefore not yet worth implementing in clinical screening protocols. Some qualities of spontaneous motility seem promising as an early detection tool for risk of ADHD, although further studies based on the individual, with larger cohorts and more specific and semi-quantitative scoring systems, are necessary to determine their clinical role in populations at risk for ADHD.

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Conflict of interest None.

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Sleep and Prospective Memory: A Retrospective Study in Different Clinical Populations

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Abstract: Prospective memory (PM) is essential in everyday life because it concerns the ability to remember to perform an intended action in the future. This ability could be influenced by poor sleep quality, the role of which, however, is still being debated. To examine the role of sleep quality in PM in depth, we decided to perform a retrospective naturalistic study examining different clinical populations with a primary sleep disorder or comorbid low sleep quality. If sleep is important for PM function, we could expect poor sleep to affect PM performance tasks both directly and indirectly. We examined a total of 3600 nights, recorded using actigraphy in participants belonging to the following groups: primary insomnia (731 nights); narcolepsy type 1 (1069 nights); attention deficit hyperactivity disorder (152 nights in children and 239 in adults); severe obesity (232 nights); essential hypertension (226 nights); menopause (143 nights); healthy controls (808 nights). In a naturalistic activity-based PM task, each participant originally wore an actigraph around the non-dominant wrist and was requested to push the event-marker button at two specific times of day: bedtime (activity 1) and get-up time (activity 2). Each clinical group showed significantly lower sleep quality in comparison to the control group. However, only narcolepsy type 1 patients presented a significantly impaired PM performance at get-up time, remembering to push the event-marker button around half the time compared not only to healthy controls but also to the other clinical groups. Overall, the present results seem to point to sleep quality having no effect on the efficiency of a naturalistic activity-based PM task. Moreover, the data indicated that narcolepsy type 1 patients may show a disease-specific cognitive deficit of PM.

Keywords: prospective memory; actigraphy; sleep; narcolepsy; primary insomnia; attention deficit hyperactivity disorder; obesity; essential hypertension; menopause

1. Introduction

Prospective memory (PM) refers to the ability to remember to perform an action in the future [1]. An optimal functioning of PM is essential in everyday life [2], for example, in a patient who is required to take a drug every day at specified intervals. This example refers to the so-called habitual PM [3], a PM subdomain alongside vigilance (e.g., preventing a kettle from boiling over, as suggested by [3]) and PM proper (e.g., buying groceries on the way home, as proposed by [3]). Habitual PM can be assessed through a PM task that has to be executed repeatedly, while vigilance and PM proper can be assessed through tasks with the absence or the presence of a time delay (or intervening task) between PM task instructions and the beginning of the ongoing task, respectively [3].

It has been suggested [4,5] that two processes are involved in prospective remembering (remembering to perform a delayed intention in the future): (1) a top-down mechanism implicated in the strategic monitoring, i.e., maintaining the intention in memory while monitoring the environment in order to detect potential stimuli related to the intention; (2) a bottom-up mechanism involved in the spontaneous retrieval, which is spontaneously activated when an intention-related stimulus is detected.

The interaction of the two processes depends on the executive functions which regulate the distribution of cognitive load between ongoing activity and prospective intention. This sharing of resources is therefore considered to be primarily responsible for the interference effects underlying the prospective failure in everyday memory performance [6].

It has been hypothesized that these two processes are part of the Multiprocess Framework Model, originally proposed by McDaniel and Einstein in the early 2000s [4,5]. In 2013, Scullin and colleagues [7] proposed the Dynamic Multiprocess Framework; according to this framework, in the same prospective task, both strategic monitoring and spontaneous retrieval could be used, but with different timing and in separate contexts.

Three types of PM task have been described. (1) Time-based tasks [8], i.e., intentions to be performed at a specific time of day. Self-generated retrieval processes [9] are crucial in time-based tasks, which rely on top-down mechanisms due to the lack of external cues, with time monitoring representing a self-initiated mental process. (2) Event-based tasks [8], i.e., an external cue is necessary in order to spontaneously activate the intention to be performed [10]. Bottom-up mechanisms are involved in this specific PM task. (3) Activity-based tasks [11], i.e., an intention to be performed prior to or after an activity. Because activity-based PM tasks occur at the end of a task, they do not require the interruption of the ongoing cognitive load and thus are likely to be easier. A top-down and bottom-up mixed activation is required by this specific PM task. In particular, it is necessary that the external cue (bottom-up mechanism) is integrated with temporal monitoring (top-down process), requiring a mechanism of both internal and self-generated remembering.

The relationship between sleep quality and PM performance has attracted the interest of both sleep and cognitive scientists. The sleep literature has widely documented the relationship between sleep and executive function efficiency, demonstrating how sleep deprivation significantly compromises PM [12,13]. A recent systematic review and meta-analysis has been published on the effects of sleep on prospective memory [14]. In their work, Leong and colleagues [14] examined 20 studies overall, published between 2002 and 2019; some works investigated strategic monitoring while others explored spontaneous retrieval. The main finding of this systematic review and meta-analysis was, in general, a small-to-medium positive effect of sleep on PM. However, when strategic and spontaneous retrieval were considered separately, no effects of sleep were detected on strategic monitoring, but were, on the contrary, observed on the spontaneous retrieval process. Furthermore, when time- and event-based

tasks were examined separately, a medium-sized effect of sleep was observed for time-based tasks, while a small effect was apparent for event-based tasks. Although not discussed by Leong and colleagues [14], a further potential source of inconsistency between the results of different studies in the association between sleep and PM could be the different focus on the three pillars of sleep, i.e., quality, quantity, and timing. Moreover, it is still not currently known which of the three sleep pillars could be more strongly associated with PM. Overall, this pattern of results highlights the fact that the role of low sleep quality in the impairment of PM performance is still a matter of debate, as also shown by a recent study [15] that failed to find a significant association between sleep and PM and which is not included in the above-mentioned systematic review and meta-analysis [14]. Confirming that the role of low sleep quality in the impairment of PM should still be clarified, a recent study of our research group [16] showed, in a large healthy lifespan sample, that sleep quality, quantity, and timing do not play a predictive role in PM performance contrary to aging that was per se associated with its worsening.

With the aim of objectively clarifying the role of sleep quality in habitual PM, we decided to perform a retrospective naturalistic study examining different clinical populations, with a primary sleep disorder or comorbid low sleep quality, alongside a sample of healthy controls. We chose to focus on habitual PM because its optimal functioning is of extreme relevance in everyday life, to the point of being considered a relevant component of medication adherence [17]. We used a naturalistic activity-based PM task: remembering to press the event-marker button on the top of the actigraph at bedtime (activity 1) and at get-up time (activity 2). This naturalistic activity-based PM task was firstly introduced by our research group [18,19], showing no differences in PM performance between primary insomnia patients and healthy controls. Later, the same task was adopted by the research group coordinated by Kinsella [20,21], showing the lack of a strong association between sleep and PM performance in a sample of community-dwelling older adults. This task is interesting for several reasons; it is simple but of great importance for the participants and also allows for an objective evaluation of the executive component of prospective memory. If sleep per se has an effect on PM, we should be able to observe this effect regardless of the different clinical features of the populations examined, in other words, we should expect a worsening in PM performance proportional to the sleep impairment. More specifically, if low sleep quality, a characteristic of each clinical population, plays a major role in the deterioration of PM, we could expect: (1) an impaired PM performance at get-up time in each clinical group in comparison to healthy controls; (2) a highly impaired PM performance at get-up time compared to bedtime within each clinical population; (3) a correlation between poor sleep and impaired PM performance at get-up time within each clinical sample.

2. Materials and Methods

2.1. Participants

Three hundred and sixty participants (206 females and 154 males), actigraphically monitored for a total of 3600 nights, were examined in this retrospective study.

They belonged to the following groups: (1) childhood attention deficit hyperactivity disorder (C-ADHD) [22]: 22 patients, four females and 18 males, mean age ± SD = 8.77 ± 1.77, 152 actigraphy-recorded nights; (2) healthy controls (HC) [23–25]: 95 participants, 57 females and 38 males, mean age ± SD = 27.93 ± 14.35, 808 actigraphy-recorded nights; (3) adult ADHD (A-ADHD) [26]: 35 patients, 14 females and 21 males, mean age ± SD = 37.29 ± 12.23, 239 actigraphy-recorded nights; (4) narcolepsy type 1 (NT1) [27]: 40 patients, 28 females and 12 males, mean age ± SD = 39.7 ± 10.96, 1069 actigraphy-recorded nights; (5) severe obesity (SO) [28]: 34 patients, 18 females and 16 males, mean age ± SD = 45.79 ± 9.43, 232 actigraphy-recorded nights; (6) primary insomnia (PI) [23]: 82 patients, 49 females and 33 males, mean age ± SD = 49.69 ± 21.44, 731 actigraphy-recorded nights; (7) menopause (MP) (unpublished data): 21 women, mean age ± SD

= 54.55 ± 5.19, 143 actigraphy-recorded nights; (8) essential hypertension (HP) [28]: 31 patients, 15 females and 16 males, mean age ± SD = 63 ± 8.54, 226 actigraphy-recorded nights.

In order to clarify the role of sleep quality in PM, we chose to retrospectively examine these clinical populations because they presented a primary sleep disorder (i.e., NT1 and PI) or comorbid low sleep quality (i.e., the remaining clinical groups).

2.2. Actigraphy

All participants used the same model of actigraph, the Actiwatch AW-64 (Cambridge Neurotechnology Ltd., Cambridge, UK). This device is equipped with an accelerometer which is sensitive to movement. Motor activity data are then transformed into sleep/wake information using a validated algorithm [29]. This device has been successfully validated against polysomnography (e.g., [30]), the gold standard for sleep assessment.

The hardware of this device is composed of a piezoelectric accelerometer presenting a sensitivity of ≥0.05 g. Filters were set to 3–11 Hz, with sampling frequency equal to 32 Hz. Actiwatch Activity and Sleep Analysis software (version 5.32, Cambridge Neurotechnology Ltd., Cambridge, UK) was used in order to initialize actigraphs to collect data in 1-min epochs.

Actigraphy is particularly useful in the case of long-term home monitoring, when information on sleep stage is not of primary importance [31].

2.3. Procedure of the Original Studies

Each participant was originally requested to wear the actigraph around the non-dominant wrist for at least seven consecutive days. Due to logistic reasons, some participants wore the actigraph for a period lower or higher than the standard of 7 days, resulting in a mean length of actigraphy recording equal to 10 (standard deviation = 6.91) consecutive days. For each participant, the whole recording period, regardless of its composition in terms of weekdays and/or weekend days, was examined. They were required to push the event-marker button on the actigraph in order to signal: (1) the time of day they went to bed in order to attempt to sleep, bedtime (BT); (2) the time of day they got out of bed at the end of a night's sleep, get-up time (GUT). Within 30 min of morning awakening, participants had to fill in a daily sleep log, which also included questions on BT and GUT.

Using the low wake sensitivity threshold [23,30] implemented within the Actiwatch Activity and Sleep Analysis software (version 5.32, Cambridge Neurotechnology Ltd., Cambridge, UK), an expert scorer analyzed the actigraphic recordings using the information on BT and GUT provided by the participants' pressing of the event-marker button of the actigraph. If participants failed to press the event-marker button, the scorer referred to their replies to the questions on BT and GUT reported in the sleep log.

Adult participants gave written informed consent prior to inclusion in the original studies; if underage, written informed consent was provided by parents. Original studies were approved by the Ethics Committee in charge.

2.4. Actigraphic Measures

Through actigraphic recording, we were able to objectively monitor sleep timing, quantity, and quality. A description of the actigraphic parameters used to assess these three different aspects of sleep is reported below.

Sleep timing was assessed by the midpoint of sleep (MS), i.e., the clock time that splits the interval between BT and GUT, i.e., the time in bed (TIB), in half. Sleep quantity was investigated by the total sleep time (TST), i.e., the sum in minutes of sleep epochs between sleep onset (SO) and GUT. Sleep quality was examined through the wake after sleep onset (WASO; the sum in minutes of wake epochs between SO and GUT), sleep onset latency (SOL; the interval in minutes between BT and SO), sleep efficiency (SE; the ratio between TST and TIB multiplied by 100), mean activity score (MAS;

mean value of activity counts per epoch over the assumed sleep period), and fragmentation index (FI, the percentage of immobility phases of 1 min as a proportion of the total number of immobility phases).

2.5. Activity-Based Prospective Memory Task

We considered the request received by all participants to remember to push the event-marker button at bedtime and get-up time as the activity-based prospective memory task. In particular, the pushing of the event-marker button at bedtime and get-up time corresponded to activity 1 and 2, respectively.

2.6. Procedure of the Current Study

With reference to the activity-based prospective memory performance, in the current study, each actigraphic recording was visually inspected night by night in order to verify whether participants remembered to press the event-marker button at BT—activity 1—and GUT—activity 2. In order to validate the PM performance for activity 2, we implemented a limit of 15 min between the GUT and the time activity 2 was performed.

2.7. Statistical Analyses

First, with the aim of exploring differences between groups in sleep timing, quality, and quantity, we carried out some pair comparisons between HC and each clinical sample, through a set of independent sample *t*-tests with group as the independent variable (two levels: HC and clinical group) and actigraphic sleep parameter as the dependent variable.

In order to explore the potential effects of a night's sleep on prospective memory performance, firstly, we carried out an ANOVA with group as the independent variable (eight levels, each one corresponding to the group examined) and the percentage of successful event-marker button pressing at GUT subjected to arcsine transformation as the dependent variable. In the case of a significant effect, Tukey's honestly significant difference (HSD) post hoc test for unequal samples was performed. Arcsine transformation was applied to correct the non-normal distribution of percentage values. Secondly, we compared, separately for each group, the prospective memory performance at BT (activity 1) with that at GUT (activity 2) through dependent sample *t*-tests. Thirdly, we performed a set of point-biserial correlation analyses, separately for each group, between each actigraphic sleep parameter and PM performance at GUT (activity 2).

Since multiple comparisons were performed, the Bonferroni correction was applied, considering *p*-values less than 0.001 as significant.

3. Results

3.1. Actigraphic Sleep Parameters

Table 1 shows the means and standard deviations of actigraphic sleep parameters in each group, while Table 2 illustrates the statistics for each pair comparison between HC and clinical samples. As shown in Table 2, all clinical groups significantly differed from HC by a minimum of four to a maximum of six parameters.

Table 1. Means and standard deviations of actigraphy-measured sleep parameters of different groups of patients and healthy controls, listed in increasing order of average age.

Actigraphy-Measured Sleep Parameter	C-ADHD	HC	A-ADHD	NT1	SO	PI	MP	HP
MS	03:12 ± 0:33	04:17 ± 01:23	03:58 ± 1:19	04:37 ± 1:49	03:55 ± 0:58	03:58 ± 1:06	03:07 ± 0:50	03:31 ± 1:18
TST	468.33 ± 36.03	405.52 ± 44.44	420.02 ± 61.31	411.48 ± 61.95	362.04 ± 69.04	435.75 ± 55.67	401.74 ± 54.97	390.84 ± 44.03
WASO	82.22 ± 27.55	27.98 ± 9.96	44.03 ± 18.95	45.82 ± 28.48	39.45 ± 25	47.71 ± 19.77	39.14 ± 14.27	37.38 ± 19.99
SOL	18.04 ± 9.26	6.48 ± 3.90	15.17 ± 12.42	10.80 ± 8.82	25.20 ± 27.88	13.88 ± 11	7.71 ± 7.07	14.53 ± 11.49
SE	81.40 ± 5.05	91.45 ± 2.64	86.96 ± 4.31	86.89 ± 7.47	83.43 ± 10.75	86.67 ± 5.11	88.73 ± 3.97	87.23 ± 5.12
MAS	22.50 ± 16.27	11.92 ± 3.50	20.42 ± 9.74	20.06 ± 11.86	21.82 ± 15.82	21 ± 10.17	18.97 ± 7.27	19.62 ± 11.93
FI	34.03 ± 7.32	21.91 ± 4.94	33 ± 8.07	42.17 ± 15.56	41.85 ± 26.05	31.33 ± 8.65	30.03 ± 8.75	33.51 ± 10.40

Legend. MS = midpoint of sleep (h:min); TST = total sleep time (min); WASO = wake after sleep onset (min); SOL = sleep onset latency (min); SE = sleep efficiency (%); MAS = mean activity counts (activity counts); FI = fragmentation index (sum of percentages). Groups included: C-ADHD = childhood attention deficit hyperactivity disorder; HC = healthy controls; A-ADHD = adult attention deficit hyperactivity disorder; NT1 = narcolepsy type 1; SO = severe obesity; PI = primary insomnia; MP = menopause; HP = essential hypertension.

Table 2. Pair comparisons between healthy controls (HC) and patients from several clinical samples.

Actigraphy-Measured Sleep Parameter	C-ADHD vs. HC (t_{115})	A-ADHD vs. HC (t_{128})	NT1 vs. HC (t_{133})	SO vs. HC (t_{127})	PI vs. HC (t_{175})	MP vs. HC (t_{114})	HP vs. HC (t_{124})
MS	3.55; $p = 0.001$	1.18; $p = 0.239$	−1.18; $p = 0.241$	1.43; $p = 0.154$	1.63; $p = 0.105$	**3.71; $p = 0.000$**	2.69; $p = 0.008$
TST	**−6.17; $p = 0.000$**	−1.48; $p = 0.141$	−0.63; $p = 0.530$	**4.19; $p = 0.000$**	**−4.01; $p = 0.000$**	0.34; $p = 0.736$	1.60; $p = 0.112$
WASO	**−15.47; $p = 0.000$**	**−6.26; $p = 0.000$**	**−5.40; $p = 0.000$**	**−3.74; $p = 0.000$**	**−8.55; $p = 0.000$**	**−4.27; $p = 0.000$**	−3.47; $p = 0.001$
SOL	**−9.22; $p = 0.000$**	**−6.09; $p = 0.000$**	**−3.96; $p = 0.000$**	**−6.42; $p = 0.000$**	**−6.13; $p = 0.000$**	−1.11; $p = 0.271$	**−5.91; $p = 0.000$**
SE	**13.19; $p = 0.000$**	**7.16; $p = 0.000$**	**5.24; $p = 0.000$**	**6.76; $p = 0.000$**	**7.96; $p = 0.000$**	**3.87; $p = 0.000$**	**5.98; $p = 0.000$**
MAS	**−5.85; $p = 0.000$**	**−7.35; $p = 0.000$**	**−6.11; $p = 0.000$**	**−5.76; $p = 0.000$**	**−8.17; $p = 0.000$**	**−6.64; $p = 0.000$**	**−5.63; $p = 0.000$**
FI	**−9.40; $p = 0.000$**	**−9.45; $p = 0.000$**	**−11.45; $p = 0.000$**	**−7.16; $p = 0.000$**	**−9.05; $p = 0.000$**	**−5.82; $p = 0.000$**	**−8.39; $p = 0.000$**

Legend. MS = midpoint of sleep; TST = total sleep time; WASO = wake after sleep onset; SOL = sleep onset latency; SE = sleep efficiency; MAS = mean activity counts; FI = fragmentation index. Groups included: C-ADHD = childhood attention deficit hyperactivity disorder; HC = healthy controls; A-ADHD = adult attention deficit hyperactivity disorder; NT1 = narcolepsy type 1; SO = severe obesity; PI = primary insomnia; MP = menopause; HP = essential hypertension. The *t*- and *p*-values, referring to each pair, are reported, with significant effects highlighted in bold.

3.2. Sleep Effect on Prospective Memory Performance

Prospective memory performance at get-up time was significantly different between groups ($F_{7352} = 12.65$; $p = 0.000$) (Figure 1). When post hoc comparisons were performed, NT1 patients significantly differed from all the remaining groups ($p = 0.000$ for each comparison). No other post hoc comparisons reached significance.

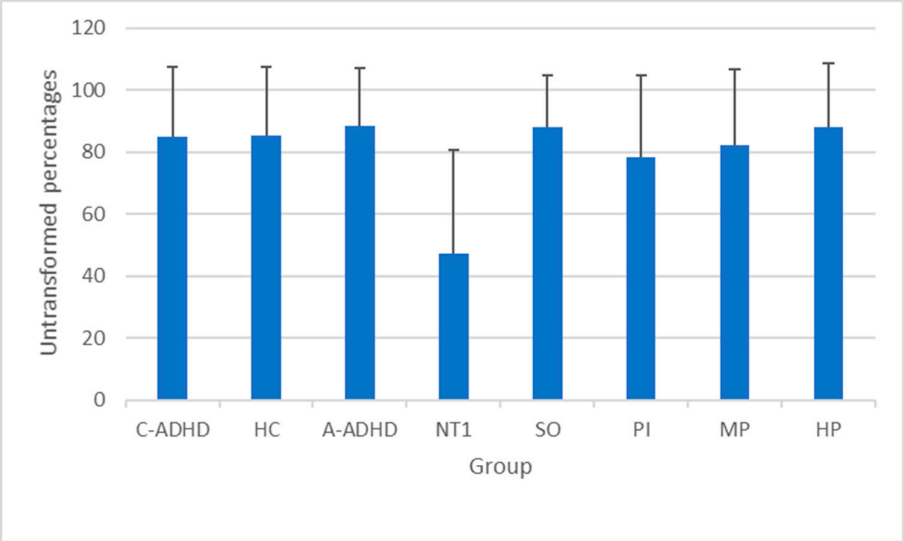

Figure 1. Means and standard deviations of prospective memory performance at get-up time in each group. In order to present the results more clearly, we have chosen to report the untransformed percentages in the figure, even though the statistical analyses were performed on the percentages subjected to arcsine transformation. C-ADHD = childhood attention deficit hyperactivity disorder; HC = healthy controls; A-ADHD = adult attention deficit hyperactivity disorder; NT1 = narcolepsy type 1; SO = severe obesity; PI = primary insomnia; MP = menopause; HP = essential hypertension.

No significant differences were observed when we performed a within-group comparison between prospective memory performance at bedtime (activity 1) and get-up time (activity 2) (see Table 3).

Table 3. Means and standard deviations of prospective memory performance at bedtime (activity 1) and get-up time (activity 2). Although statistical analyses were performed on arcsine-transformed percentages, we chose to report the untransformed percentage values in the table. Statistics are also reported.

Group	BT	GUT	Statistics
C-ADHD	79.61 ± 25.16	85.06 ± 22.25	$t_{21} = 0.90$; $p = 0.381$
HC	83.92 ± 24.16	85.31 ± 22.28	$t_{94} = 0.52$; $p = 0.606$
A-ADHD	83.82 ± 20.20	88.45 ± 18.63	$t_{34} = 1.27$; $p = 0.213$
NT1	50.90 ± 30.83	47.14 ± 33.34	$t_{39} = 0.91$; $p = 0.367$
SO	82.63 ± 22.87	87.89 ± 16.97	$t_{33} = 1.21$; $p = 0.233$
PI	81.19 ± 19.21	78.50 ± 26.11	$t_{81} = 0.78$; $p = 0.440$
MP	75.62 ± 32.58	82.09 ± 24.42	$t_{20} = -0.80$; $p = 0.433$
HP	86.94 ± 20	88.15 ± 20.29	$t_{30} = -0.53$; $p = 0.603$

Legend. BT = bedtime; GUT = get-up time; C-ADHD = childhood attention deficit hyperactivity disorder; HC = healthy controls; A-ADHD = adult attention deficit hyperactivity disorder; NT1 = narcolepsy type 1; SO = severe obesity; PI = primary insomnia; MP = menopause; HP = essential hypertension.

When we performed a set of within-group point-biserial correlation analyses between each actigraphic sleep parameter and PM performance at get-up time (activity 2), we observed the following significant correlations in the NT1 sample (see Table 4): negative correlations between WASO, MAS, FI, and MS and PM performance; a positive correlation between SE and PM performance.

Table 4. Point-biserial correlations, within each group, between each actigraphic sleep parameter and PM performance at get-up time (activity 2).

Actigraphy-Measured Sleep Parameter	C-ADHD	HC	A-ADHD	NT1	SO	PI	MP	HP
MS	−0.100; $p = 0.220$	0.026; $p = 0.462$	−0.201; $p = 0.002$	**−0.183; $p = 0.000$**	−0.053; $p = 0.420$	−0.099; $p = 0.007$	0.005; $p = 0.956$	0.005; $p = 0.935$
TST	0.055; $p = 0.501$	−0.001; $p = 0.985$	−0.099; $p = 0.126$	0.059; $p = 0.055$	0.104; $p = 0.113$	−0.028; $p = 0.452$	0.045; $p = 0.592$	−0.092; $p = 0.169$
WASO	−0.045; $p = 0.580$	−0.021; $p = 0.559$	−0.023; $p = 0.718$	**−0.329; $p = 0.000$**	0.061; $p = 0.357$	−0.036; $p = 0.325$	−0.127; $p = 0.130$	0.033; $p = 0.622$
SOL	0.003; $p = 0.971$	−0.034; $p = 0.330$	−0.079; $p = 0.226$	−0.047; $p = 0.124$	−0.183; $p = 0.005$	−0.051; $p = 0.165$	−0.226; $p = 0.007$	−0.083; $p = 0.214$
SE	0.002; $p = 0.977$	0.034; $p = 0.331$	0.014; $p = 0.827$	**0.265; $p = 0.000$**	0.113; $p = 0.087$	0.037; $p = 0.320$	0.144; $p = 0.087$	0.030; $p = 0.649$
MAS	0.003; $p = 0.973$	−0.085; $p = 0.016$	0.019; $p = 0.768$	**−0.327; $p = 0.000$**	−0.009; $p = 0.893$	0.005; $p = 0.888$	−0.122; $p = 0.148$	0.053; $p = 0.430$
FI	−0.031; $p = 0.708$	0.027; $p = 0.449$	−0.034; $p = 0.599$	**−0.273; $p = 0.000$**	−0.046; $p = 0.484$	0.028; $p = 0.456$	−0.105; $p = 0.213$	−0.006; $p = 0.933$

Legend. MS = midpoint of sleep; TST = total sleep time; WASO = wake after sleep onset; SOL = sleep onset latency; SE = sleep efficiency; MAS = mean activity counts; FI = fragmentation index. Groups included: C-ADHD = childhood attention deficit hyperactivity disorder; HC = healthy controls; A-ADHD = adult attention deficit hyperactivity disorder; NT1 = narcolepsy type 1; SO = severe obesity; PI = primary insomnia; MP = menopause; HP = essential hypertension. R and *p*-values are shown, with significant correlations highlighted in bold.

4. Discussion

The main aim of the present study was to explore the potential role of sleep quality and amount in PM, which is currently still a matter of debate [14–16]. To this end, we carried out a retrospective naturalistic study in which we examined different clinical populations with a primary sleep disorder or comorbid low sleep quality. In more detail, we compared the PM performance of these groups in a naturalistic activity-based PM task [18–21]. If sleep played a primary role in the modulation of PM, we expected to find an impaired PM performance at get-up time in each clinical group compared to healthy controls. Furthermore, such a sleep effect (if any) should translate, within each clinical population, into a worse PM performance at get-up time compared to bedtime, as well as into significant correlations between poor sleep and PM performance at get-up time.

With regard to actigraphy-measured sleep, as shown in Table 2, we observed three homogeneous patterns of results between different clinical populations, i.e., lower sleep efficiency, as well as higher mean activity score and fragmentation index (all markers of sleep quality), compared to healthy controls.

These data seem to point out that each clinical population significantly differed from healthy controls in terms of their impaired sleep quality. This pattern of results is in line with the currently available knowledge on sleep quality in these clinical populations [32–38], confirming the representativeness of our sample.

In spite of these significant differences between clinical groups and healthy controls in actigraphy-measured sleep, when we examined the prospective memory performance at get-up time (Figure 1), we observed a significantly impaired PM performance only in narcolepsy type 1 patients compared to each of the remaining groups. Moreover, as reported in Table 3, we tried to carry out a more thorough investigation into a potential sleep effect on PM by comparing performance in the activity-based PM task at bedtime with that at get-up time, separately for each group; however, we did not observe any significant differences. Finally, as shown in Table 4, only in narcolepsy type 1 patients did we observe significant associations between impaired sleep quality and delayed sleep timing on one hand, and a weakened PM performance at get-up time on the other. These three patterns of results are completely in disagreement with the expectations we put forward, based on the supposition that low sleep quality, that characterizes each clinical population, could play a major role in the deterioration of PM.

Therefore, bearing in mind the differences between groups in actigraphy-measured sleep (Table 2), the pattern of results reported in Figure 1 and Tables 3 and 4 seems to smooth the potential modulating role of sleep quality on PM, at least in this specific type of PM task carried out in a naturalistic setting. A possible explanation for the impaired PM performance in narcolepsy type 1 patients at get-up time is more likely related to a sort of disease-specific cognitive deficit of PM in these patients, regardless of sleep quality. An additional explanation could be that in narcolepsy the functional importance of the sleep architecture is lacking, and this aspect may have important effects on memory processes [39]. To the best of our knowledge, only Ohayon and colleagues [40] have examined the self-referred PM deficits in narcolepsy patients, asking them to fill in the Cognitive Difficulties Scale [41] which also included a dimension on PM cognitive difficulty. The authors found that, when controlling for some potential confounding factors (age, ongoing psychotropic medication treatment, sleep apnea, physical disease, and sleepiness), narcolepsy remained significantly related to attention–concentration and PM deficits. This pattern of results would seem to suggest that PM deficits in narcolepsy patients cannot be explained by factors other than narcolepsy itself. A review by Cipolli and colleagues [42] highlighted a sleep-dependent consolidation impairment in narcolepsy–cataplexy only for visual and procedural skills, the latter being pertinent to PM. In fact, prospective memory involves both the episodic memory system (content of the intention) and executive processes (acting upon the intention). Mazzetti and colleagues [43] observed difficulties in the consolidation of both visual discrimination and motor skills (procedural memory system) in narcoleptic patients. Another specificity of narcolepsy is represented by the abnormalities in rapid eye movement sleep [44]; the decrease in rapid eye movement sleep length with aging has been suggested to mediate the age-related PM decline in healthy adults [45].

However, a recent review highlights how data on the specific components of memory in relation to sleep are still controversial, and further and more precise research is needed in this regard [46]. As Stickgold [47] points out, "At the very least, one has to address the question of how five stages of sleep interact with at least six types of memories and six stages of post-encoding memory processing, for a combined total of 144 distinct sub-questions" (page 305).

We acknowledge some limitations of the present study. First, we examined just one type of PM task, i.e., the activity-based PM task, so our conclusions cannot be generalized to the other two types of PM task (time- and event-based). Second, since we retrospectively examined clinical groups, their sizes could not be defined a priori, thus resulting in samples that were unbalanced in size. Third, not all clinical groups were drug free, and therefore potential side effects on sleep and PM may have been present. Fourth, polysomnographic recording was lacking; this technique would have allowed us to analyze the sleep architecture and examine in more depth the potential association between slow wave [48] and rapid eye movement [45] sleep on one hand and prospective memory on the other. Fifth, due to the naturalistic setting of our study, we were not able to check the use of external aids to remember to perform the activity-based PM task.

This study also presents some strengths, such as the impressively large number of actigraphically recorded nights (3600), the naturalistic setting in which participants performed the activity-based PM task, and the objective assessment of sleep quality, quantity, and timing through actigraphy.

Future studies should try to examine the PM performance in time, as well as event-based PM tasks in a naturalistic setting, by prospectively enrolling a balanced number of drug-free patients belonging to different clinical populations with a primary sleep disorder or comorbid low sleep quality.

5. Conclusions

The present study contributes to the still open research question about the potential role of sleep quality in the modulation of PM. The main finding is that, despite impaired sleep quality in each clinical group compared to healthy controls, only narcolepsy type 1 patients presented a weakened PM performance at get-up time in comparison to the remaining groups. This pattern of results allows us to conclude that, at least for an activity-based PM task carried out in a naturalistic setting, the role of sleep quality does not seem to be crucial. On the contrary, the results observed seem to point to a disease-specific cognitive deficit of PM in narcolepsy type 1.

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Methylphenidate in Autism Spectrum Disorder: A Long-Term Follow Up Naturalistic Study

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Abstract: Autism spectrum disorder (ASD) often co-occurs with attention deficit/hyperactivity disorder (ADHD). Although methylphenidate (MPH) efficacy and safety are well-demonstrated for ADHD, evidences are scant in the context of ASD. This naturalistic study aimed to analyze long-term MPH efficacy and safety in 40 ADHD children and adolescents with comorbid ASD, comparing them with 40 ones affected by ADHD without ASD. Treatment lasted from 6 to 156 months (longer than 24 months in more than three quarters of patients). Efficacy and safety were measured by clinical global impression and children global assessment scales; influence of intellectual functioning was examined. Comparisons between groups were made by Wilcoxon or Friedmann tests; relationships between functioning scores and other characteristics were analyzed by ordinal logistic and linear regression. Results demonstrated that MPH in patients with ASD was associated with significative reduction of illness severity, clinical improvement and amelioration of global functioning, without significant differences with patients having ADHD without ASD. The trend of reduction of illness severity and increase of global functioning were favorably related with intellectual functioning. No serious adverse events were reported. The findings showed that long-term MPH was effective and well-tolerated in ADHD children and adolescents with comorbid high functioning ASD.

Keywords: methylphenidate; MPH; autism spectrum disorder; ASD; attention deficit/hyperactivity disorder; ADHD; high-functioning ASD

1. Introduction

1.1. ASD and ADHD

Until 2013, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) have been both included in the category of neurodevelopmental disorders [1]. 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% [2–4]; whereas ADHD is characterized by inattention and hyperactivity/impulsivity, having a prevalence between 2% and 7% in the pediatric population [5].

Until the fourth revised version of the Diagnostic and statistical manual of mental disorders [6], this one included, diagnosis of ASD in subjects with ADHD has not been allowed, causing clinical and research implications. Instead, in the last version of DSM, ASD and ADHD can be diagnosed as comorbidities, thus they can be studied together. Indeed, also before DSM change, a great amount

of studies was performed in order to analyze the potential relation between the two disorders. The co-existence of ASD and ADHD has been reported to be between 25% and 85% [7–11]. This wide range could be justified by both the different nosographic approach used before DSM-5 as well as the clinical difficulties to clearly distinguish the boundaries of each disturbance. Atypical attention patterns, deficit in motor speed, impairment in behavioral inhibition, and social difficulties could be central symptoms of both disorders [12–15]. Moreover, ASD and ADHD share some common risk factors such as genetics, as found by studies from family, twin and molecular data [16–20]. The shared genetic factors are believed to affect the structure and function of molecular networks in the brain, possibly implicated in the etiology of ASD and ADHD, such as circuits involving executive functions (EF): EF impairment, manifested as deficit in cognitive flexibility, planning, working memory, response inhibition, selective, sustained and shifting attention, has been considered as central etiological deficits in ADHD and recent studies found EF alterations in ASD as well [21–23]. Moreover, in the context of co-occurring ASD and ADHD, the functional impairment may be more severe than in the context of ASD alone, since ADHD symptoms may cause obstacles to educational achievement and behavioral management, and since higher risk for psychopathologies such as anxiety and depression may be found [24–28]. As a result, recognizing the comorbidity between ASD and ADHD or the symptoms overlap is crucial for treatment implications.

1.2. Psychotropic Drugs in ASD

Epidemiological studies suggested that at least 50% of subjects with ASD receives psychotropic medication during their whole lifespan, and, in pediatric population, the range varies from about 10% to 30% [29–32].

Indeed, no psychotropic medications have been currently approved by any regulatory agencies for the treatment of ASD core symptom, even if thousands of clinical trials are ongoing [33,34]. For the treatment of associated symptoms, a psychopharmacological approach (antipsychotics, serotonergic agents, stimulants, melatonin) may be beneficial, but data on this topic are not conclusive [10,29,35–41]. Among second generation antipsychotics (SGA), risperidone and aripiprazole are approved by the Food and Drug Administration for the treatment of irritability associated with ASD, and risperidone has been approved for the same purpose by the European medicines agency. Both have shown modest efficacy for the management of repetitive behaviors, although their use is limited by the risk of adverse effects, especially extrapyramidal and metabolic. Serotonergic agents (SSRIs) are used to treat depression and obsessive-compulsive disorder comorbid with ASD and have shown some benefit for the management of repetitive behaviors and anxiety. Melatonin has demonstrated to be an effective and well-tolerated drug in specifically treating sleeping problems in children with ASD.

Among ADHD targeting drugs in ASD (stimulants, norepinephrine reuptake inhibitors and alpha-agonist agents), the main evidences support the use of MPH; atomoxetine and α2A receptor agonists (clonidine and guanfacine) should be considered as alternatives among those who are not responsive or intolerant to MPH, even if both showed lower efficacy [42–45].

Despite the common clinical use of psychotropic medications, several reasons underscore the need for caution and additional evidences; in particular, concerning stimulants' efficacy and safety in ADHD children and adolescents with comorbid ASD, mixed and not conclusive results have been reported from previous studies.

1.3. MPH in ADHD with Comorbid ASD

Early studies reported that methylphenidate (MPH) in ASD had modest efficacy, poor tolerability and worsening of behavioral and social problems: Campbell in 1975 noted increased irritability, aggressiveness and stereotypical movements [46]; case reports in 1980s confirmed the worsening of behavioral problems, describing agitation, stereotypes and induction of psychotic symptoms [47–50]. Following literature, in 1990s and 2000s, has provided additional, but divergent insights both about adverse events and favorable effects, since studies did not find increased irritability nor aggressive

behaviors and stereotypes, but rather an improvement in impulsivity and hyperactivity as well as in joint attention, social communication and self-regulation [51–59].

These findings were confirmed and enriched by review studies [40,60] comparing MPH-derivatives to placebo in children with ASD. Reichow reviewed four double-blinded, randomized, placebo-controlled trials, involving 94 participants [51,52,56,61]; the Cochrane database included four crossover studies, involving 113 children aged 5 to 13 years [51,52,58,61]. Globally, reviews show that MPH was superior to the placebo for the treatment of hyperactivity and mildly superior for inattention, irritability and stereotypes. There was no evidence that MPH worsened or improved the core symptoms of ASD. In both reviews, the main adverse event reported was decreased appetite. No trials reported serious adverse events, even if authors concluded that the evidence for adverse events had a poor quality, since trials were short and with small sample size.

In 2017, Kim [62] reported significant decrease of irritability and hyperactivity, substantial clinical global improvement, reassuring safety data and low discontinuation rate thanks to extended-release liquid formulation of MPH; nevertheless, the number of subjects was 27 and the treatment duration was 6 weeks.

Considering the common co-occurrence of ASD and ADHD, the current lack of ASD-targeted medications, the misuse of antipsychotics being weighted by adverse events, as well as the well-demonstrated efficacy and safety of MPH (both short and long-term treatment) in ADHD [63–65], it could be reasonable to question if a routine use of stimulants for the treatment of ADHD symptoms in the context of ASD is enough supported by evidences.

We aimed to assess, in a naturalistic setting, long-term efficacy and safety of MPH, as monotherapy or associated with other psychotropic drugs, in ADHD children and adolescents with comorbid ASD, comparing them with an ADHD control group, homogeneous for age and intellectual functioning.

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 21 years, consecutively referred to Child Neuropsychiatric Unit of the University of Bari during a three years period (March 2017–March 2020). The inclusion criteria were ADHD diagnosis according to DSM-5, pharmacological treatment with immediate release MPH (IR-MPH) or extended release MPH (ER-MPH) and therapy lasting at least six months. The exclusion criteria were syndromic autism and age under 6 years. Given the naturalistic design of the 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 by child and adolescent neuropsychiatrists and psychologists, specialists in neurodevelopmental disorders. Diagnosis was also supported by standardized diagnostic tools, specific for ADHD and ASD: Revised Conners' Parent Rating Scale (CPRS-R) [66], Autism Diagnostic Observational Schedule, Second Edition (ADOS-2) [67,68], Autism Diagnostic Interview-Revised (ADI-R) [69] and Autism spectrum Diagnostic Interview (ASDI) [70]. Moreover, all the subjects had their intellectual quotient assessed with Wechsler scales: Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) [71] and Wechsler Intelligence Scales for Children- Fourth Edition (WISC-IV) [72] or Leiter International Performance Scale-Revised (Leiter-R) [73] in patients with communication impairment and were screened for other psychiatric disorders using medical history. Clinical observation and children behavioral checklist (CBCL) [74]. Among 89 patients who started MPH, 9 were excluded because of syndromic autism or being under 6 years of age. The enrolled sample consisted of 80 patients of which 40 had a diagnosis of ADHD comorbid with ASD (henceforth named ASD + ADHD group) and 40 had a diagnosis of ADHD without comorbidity with ASD (henceforth named ADHD group).

Demographic and clinical characteristic of the two groups, comorbidities and pharmacological treatments beside MPH are described in Table 1.

Table 1. Demographic and clinical characteristics of the sample, comorbidities and other psychotropic medications beside methylphenidate (MPH).

	ASD + ADHD Group (n = 40)		ADHD Group (n = 40)		p-Value
	n	%	n	%	
Sex					
M	32	80	28	70	
F	8	20	12	30	0.3047
	Median	**95% CI**	**Median**	**95% CI**	
Age (years)	15.5	14–17	15	14–17	0.7502
	n	%	n	%	
ASD level					
1	34	85			
2	4	10			
3	2	5			
ADHD severity level					
Severe	12	30	14	35	0.6352
Moderate	28	70	26	65	
ADHD specifiers					
Inattentive	8	20	6	15	0.5587
Combined	32	80	34	85	
	Median	**95% CI**	**Median**	**95% CI**	
Intelligence Quotient (IQ)	89.5	84.33–101.66	98.5	86.33–104.32	0.4558
	n	%	n	%	
Comorbidities					
Learning disorder	31	77.5	32	80	
Motor coordination disorder	11	27.5	2	5	
Sleep–wake disorder	10	25	11	27.5	
Anxiety disorder	9	22.5	6	15	
Oppositional defiant disorder	6	15	32	80	
Disruptive mood dysregulation disorder	5	12.5	8	20	
Other psychotropic medications					
Antipsychotics (FGA and SGA)	11	27.5	7	17.5	
Mood stabilizer	4	10	5	12.5	
Antidepressants	2	5	1	2.5	
Anxiolytics	1	2.5	0	0	
Melatonin	8	20	9	22.5	

ASD—autism spectrum disorder; ADHD—attention deficit hyperactivity disorder; CI—confidence interval; FGA—first generation antipsychotics; SGA—second generation antipsychotics.

All the diagnostic and 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 the assessment measures and different treatment options and gave their written informed consent to the treatment with MPH. Medication was prescribed according to clinical indications, along with routine community care (including psychoeducational interventions), as part of a management protocol.

The Ethic Committee of the Azienda Ospedaliera-Universitaria Consorziale Policlinico di Bari approved the study (5009/29-07-2016).

The research team reviewed medical records of all the patients for the purpose of the study; in particular, the team extrapolated data concerning efficacy and safety measures, such as scores at clinical global impression scale (CGI) [75] and children's global assessment scale (C-GAS) [76], as well as anthropometric measures (height and weight), vital parameters (blood pressure, heart rate), blood test reports (blood cell count, blood chemistry, electrolytes, thyroid function) and cardiac assessment (ECG including QTc interval).

CGI is a brief clinician-rated instrument that consists of three different global measures: severity of illness (CGI-S), global improvement (CGI-I) and efficacy index (CGI-E). CGI-S is rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). CGI-I is a 7 points scale that requires the clinician to assess how much the patient's illness has improved or worsened with respect to a baseline state at the beginning of the intervention and is rated from 1 (really improved) to 7 (really worsened). CGI-E is a 4×4 rating scale assessing the therapeutic effect of treatment with psychiatric medication and associated side effects. The patient's response to treatment is combined with any salient side effect on a grid to give an CGI-E. A child with a good response to treatment and no reported side effects would have an CGI-E of 4.00. A patient with no response to treatment or who got worse during treatment, having significant side effects thus requiring a change in treatment, would have an CGI-E of 0.25.

C-GAS is a numeric scale used by mental health clinicians to rate the general functioning of child and youths under the age of 18. Scores range from 1 to 100, with higher scores indicating better functioning. Patients with a C-GAS ranging from 70 to 61 struggle in a single area, albeit functioning generally well; patients with a C-GAS ranging from 60 to 51 have variable functioning with sporadic difficulties or symptoms in several, but not all social areas; patients with a C-GAS ranging from 50 to 41 have moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area; patients with a C-GAS ranging from 40 to 31 have major impairment of functioning in several areas; patients with a C-GAS ranging from 30 to 21 are unable to function in almost all areas.

Primary outcomes were efficacy and safety data, measured by CGI-S, assessed at the baseline (T0), after 1 month (T1), after 6 months (T6), after 24 months (T24); CGI-I, assessed after 1 month (T1), after 6 months (T6), after 24 months (T24); CGI-E, assessed at the last follow-up and C-GAS—assessed at the baseline (T0) and at the last follow-up. Safety data were analyzed at baseline and at each follow-up. Discontinuation rate was recorded and described.

Secondary outcome was the influence of different variables (intellectual functioning, age of therapy onset and length of therapy, dose of drugs, sex and age) on efficacy (measured by CGI-S and CGI-I) and global functioning (measured by C-GAS).

All data obtained from ASD + ADHD group and ADHD group were compared to each other, henceforth analyzed.

2.2. Statistical Analysis

Quantitative data, as CGI-S, CGI-I, CGI-E, C-GAS, were not normally distributed, therefore the comparison between disease group was performed with Wilcoxon for independent groups. A test for repeated measures, i.e., Friedman test, was performed separately in each disease group, in order to compare results among follow-ups. Given the multiple test approach of the analysis, p-values were adjusted according to Bonferroni. Quantitative variables were summarized as median, range and interquartile range or 95% confidence interval for the median.

Qualitative variables are summarized as count and percentage, comparisons between independent groups were performed by χ^2 test or Fisher's exact test when appropriate. In order to compare the percentages of side effects, a multiple comparison strategy was applied: the statistical Fisher's exact test was used, and *p*-values were adjusted according to a permutation method for the purpose of controlling family wise error rate.

An ordinal logistic model was performed to evaluate predictors of changes in CGI-I and CGI-S.

The model for CGI-S had ΔCGI-S as dependent variable, defined as the difference obtained subtracting the CGI-S score at T24 from the CGI-S score at T0, classified as neutral (0) and classes of increasing improvement (from −1 to −3).

The model for CGI-I had a dependent variable classified as improved if the score decreased, neutral if there was no difference between CGI-I score at T1 and CGI-I score at T24, and not improved if the score increased.

The predictors in both models were: age, sex (as dummy: M = 1, F = 0), length of therapy (in months), age of therapy onset, dose of drug, disease group (as dummy: ADHD = 1, ASD + ADHD = 0). A backward selection procedure was used for the multivariable model, but, in order for variables to have an effect independently from the disease group, a new model was fitted including this variable; R-square was used as measure of fitting.

A *p*-value < 0.05 was used to assess statistical significance.

A multiple linear regression was used to evaluate if changes in C-GAS depend on IQ and other possible predictors (disease group, age, sex, age of therapy onset, dose of drugs, length of therapy). A backward selection method was applied with a *p*-value < 0.1 as threshold to enter the model, in order to choose best predictors.

The software used for the analysis was SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. MPH Treatment

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 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 range of therapy duration was from 6 to 156 months. A total of 18/80 participants (22.5%) of the total sample had a follow-up treatment lower than 24 months, 22/80 participants (27.5%) had a follow-up treatment ranging from 24 months and 36 months, 40/80 participants (50%) had a follow-up treatment higher than 36 months. At the last follow-up, 73/80 participants (91.25%) were treated with ER-MPH (37/40 ASD + ADHD subjects and 36/40 ADHD subjects); 7/80 participants (8.75%) were treated with IR-MPH (3/40 ASD + ADHD subjects and 4/40 ADHD subjects). Characteristics of MPH treatment were described in Table 2.

Table 2. MPH treatment.

	ADHD + ASD		**ADHD**		***p*-Value**
Age of therapy onset (Years)	**Median (IQR)**	**95% CI**	**Median (IQR)**	**95% CI**	0.2309
	9 (7–13)	7–10	10 (8.5–13)	9–11.6	
MPH dose (mg/kg/day)	0.6 (0.46–0.7)	0.5–0.7	0.6 (0.46–0.825)	0.52–0.7	0.6026
Therapy duration (months)	36 (24–78)	24–78	48 (36–57.97)	24–72	0.5679

ASD—autism spectrum disorder; ADHD—attention deficit hyperactivity disorder; MPH—methylphenidate; IQR—Inter-quantile Range; CI—confidence interval.

3.2. Primary Outcomes

3.2.1. CGI Measures

In ASD + ADHD group the difference in CGI-S from T0 to T24 was statistically different ($p < 0.0001$) Comparing the ASD + ADHD group with the ADHD group, the difference in CGI-S improvement was not statistically significant in none of the follow-up points. Moreover, 62,2% (23/36) in ASD + ADHD group and 79.5% (31/39) in ADHD group has shown a ΔCGI-S (from T0 to T24) lower or equal to −2, which is a fairly good amelioration, in both groups, without statistically significant difference ($p = 0.3255$).

In ASD + ADHD group the difference in CGI-I from T0 to T24 was statistically different ($p = 0.0001$). Comparing the ASD + ADHD group with the ADHD group, the difference in CGI-I was not statistically significant in none of the follow-up points. The percentage of responders (patients with a CGI-I T24 score 1, "very much improved" and score 2, "much improved") was 70.3% (26/37) in ASD + ADHD and 64.1% (25/39) in ADHD patients, but the difference was not statistically significant ($p = 0.5699$).

In ASD + ADHD group the median (95% CI) CGI-E was 2 (1.5–2). Comparing the ASD + ADHD group with the ADHD group, the difference in CGI-E was not statistically significant. CGI measures are described in Table 3.

Table 3. Clinical global impression scale (CGI) measures.

CGI-S	**ASD + ADHD Group**	**ADHD Group**	***p*-Value**
T0	$n = 40$	$n = 40$	
Median Range (95% CI)	5 4–7 (5–6)	5 4–7 (5–6)	0.5609
T1	$n = 40$	$n = 40$	
Median Range (95% CI)	5 3–7 (4.5–5)	5 3–6 (4–5)	0.1138
T6	$n = 39$	$n = 40$	
Median Range (95% CI)	4 2–7 (4–5)	4 2–6 (3–4)	0.0501
T24	$n = 37$	$n = 39$	
Median Range (95% CI)	4 2–5 (3.4–4)	3 2–6 (3–4)	0.1104
***p*-value** (T0–T24)	<0.0001	<0.0001	
CGI-I	**ASD + ADHD group**	**ADHD group**	***p*-value**
T1	$n = 40$	$n = 40$	
Median Range (95% CI)	3 2–5 (3–3)	3 2–4 (3–3)	0.9715
T6	$n = 39$	$n = 40$	
Median Range (95% CI)	3 2–6 (2–3)	2 2–4 (2–3)	0.594
T24	$n = 37$	$n = 39$	
Median Range (95% CI)	2 1–4 (2–3)	2 1–4 (2–3)	0.8116
***p*-value** (T1–T24)	0.00001	<0.00001	
CGI-E	**ASD + ADHD group**	**ADHD group**	***p*-value**
Median Range (95% CI)	2 0.25–3 (1.5–2)	2 0.5–4 (1.5–2)	0.7986

ADHD—attention deficit hyperactivity disorder; ASD—autism spectrum disorder; CGI-S—clinical global impression-severity scale; CGI-I—clinical global impression-improvement scale; CGI-E—Efficacy Index; CI—confidence interval; T0—baseline; T1—after 1 month; T6—after 6 months; T24—after 24 months.

3.2.2. C-GAS Measures

In ASD + ADHD group the difference in C-GAS from T0 to the last follow-up was statistically different ($p < 0.0001$) Comparing the ASD + ADHD group with the ADHD group, the difference in C-GAS was not statistically significant at either T0 or last follow-up. C-GAS measures are described in Table 4.

Table 4. C–GAS measures.

	ASD + ADHD Group	ADHD Group	*p*-Value
T0			
Median	43	45	
Range (95% CI)	25–50 (40–45)	30–55 (45–47.66)	0.0632
Last follow-up			
Median	55	60	
Range (95% CI)	25–70 (50–58.32)	40–70 (55–64.32)	0.0907
***p*-value** (T0–T24)	<0.0001	<0.0001	

ADHD—attention deficit hyperactivity disorder; ASD—autism spectrum disorder; C-GAS—children's global assessment scale; CI—confidence interval; T0—baseline.

3.2.3. Other Psychotropic Medications at the Last Follow-Up

At the last follow-up, in ASD + ADHD group, 7.5% of patients assumed antipsychotics (second generation; 27.5% at baseline), 7.5% mood stabilizers (10% at baseline), 2.5% antidepressants (5% at baseline), 2.5% anxiolytics and 20% melatonin (both equal to baseline); in ADHD group, 12.5% of patients assumed antipsychotics (second generation; 17.5% at baseline), 10% mood stabilizers (12.5% at baseline), 2.5% antidepressants and 22.5% melatonin (both equal to baseline).

3.2.4. Safety

No severe adverse events were reported; indeed, among these, no cardiovascular events neither suicidal ideations nor behaviors were seen.

Comparing ASD + ADHD group with ADHD group, the prevalence of the lack of side effects was not statistically significant (respectively 29/40, 72.5%; 27/40, 67.5%; $p = 0.6256$)

The most frequent side effects in ASD + ADHD group were loss of appetite, abdominal discomfort and headache (respectively 47.5%, 45% and 25%), each temporary, in the first days or weeks of treatment; the same side effects were seen in ADHD group (respectively in 57.7%, 35% and 15%).

Two ADHD patients with comorbid ASD (5%), both affected by level 3 ASD associated with intellectual disability, after partially responding to the treatment for few weeks, presented worsening of behavior with restlessness and increased stereotypes, that completely resolved after treatment discontinuation. In the ADHD group, one patient (2.5%), affected by anxiety disorder, had to stop the drug, despite it worked on attention, due to the onset of restlessness and a state of "inner tension", that resolved once stopping the medication. Side effects are described in Table 5.

Table 5. Side effects.

	ASD + ADHD Group *n* (%)	ADHD Group *n* (%)	*p*-Value
Loss of appetite	19 (47.5)	23 (57.5)	0.9865
Abdominal discomfort	18 (45)	14 (35)	0.9792
Headache	10 (25)	6 (15)	0.8147
Irritability	4 (10)	3 (7.5)	1
Palpitation	3 (7.5)	1 (2.5)	0.9974
Restlessness	3 (7.5)	1 (2.5)	0.9974

Table 5. *Cont.*

	ASD + ADHD Group *n* (%)	ADHD Group *n* (%)	*p*-Value
Anxiety	2 (5)	0	0.97
Insomnia	1 (2.5)	2 (5)	1
Dizziness	1 (2.5)	1 (2.5)	1
Drowsiness	0	0	1
Tic disorder	0	0	1
Hallucinations	0	0	1

ASD—autism spectrum disorder; ADHD—attention deficit hyperactivity disorder.

3.2.5. Discontinuation Rate

In ASD + ADHD group, eight patients interrupted MPH treatment (20%) for the following reasons: four patients because of clinical improvement (10%); two patients (both of level 3 of severity and intellectual disability) because of clinical worsening (5%); one patient because of low compliance to the treatment (2.5%); one patient was lost at follow-up (2.5%).

In ADHD group, nine patients interrupted MPH treatment (22.5%) for the following reasons: clinical improvement for six patients (15%); clinical worsening for one patient (2.5%); low compliance to the treatment for one patient (2.5%); one patient was lost at follow-up (2.5%).

The discontinuation rate did not result significantly different ($\chi^2 = 0.075$, $p = 0.7846$).

3.3. Secondary Outcomes

3.3.1. Evaluation of Factors to Predict Amelioration in Severity of the Illness

The model for ΔCGI-S has shown that IQ was the only statistically significant variable related to changes in severity of illness; other variables (sex and age; disease groups; age of therapy onset; length of therapy; dose of drug) were removed from the model by the selection procedure. The regression for ΔCGI-S was fitted with IQ (b = 0.031, Se(b) = 0.01, $p = 0.0094$), the model resulted statistically significant (likelihood 10.74, $p = 0.0046$) and the R-square of the model was 13.2%. The model allows to estimate the probability of each class of improvement as function of IQ (Figures 1 and 2): the probability of no improvement or of low-class improvement decreases with the increase of IQ; the probability of higher class of improvement, on the contrary, increases with IQ.

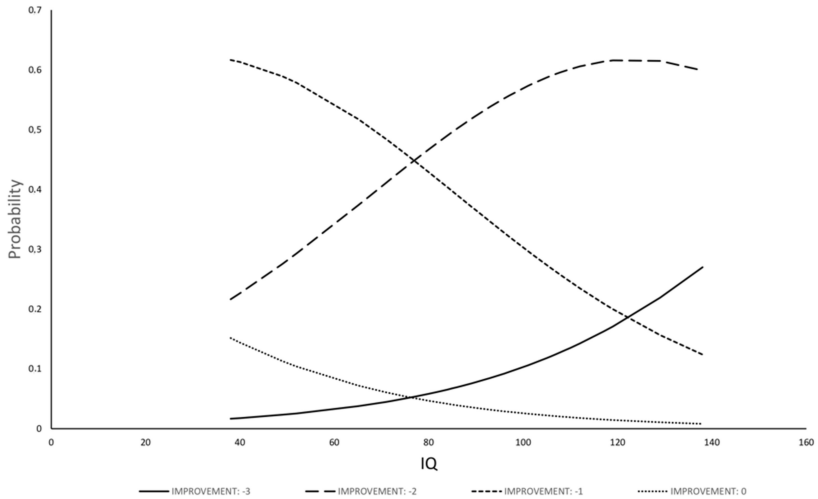

Figure 1. Relationship between probability to have a certain class of ΔCGI-S amelioration and IQ in ASD + ADHD group.

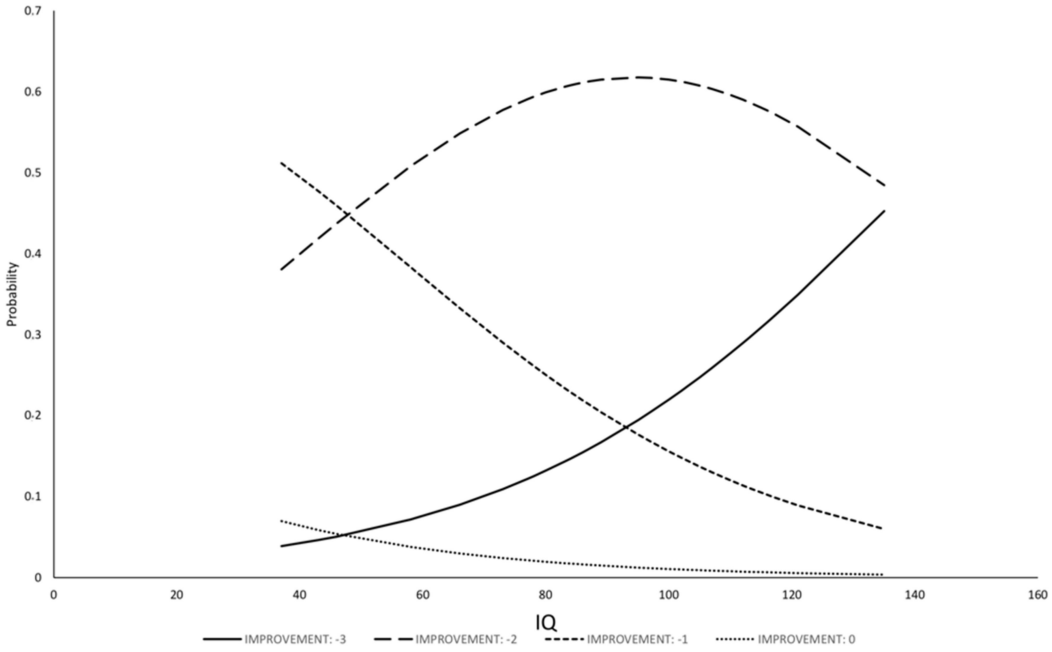

Figure 2. Relationship between probability to have a certain class of ΔCGI-S amelioration and IQ in ADHD group.

3.3.2. Evaluation of Factors to Predict Clinical Improvement

The model for CGI-I has shown that statistically significant variables related to changes in clinical improvement were age (b = −0.23, Se(b) = 0.09, p = 0.0094) and age of therapy onset (b = 0.21, Se(b) = 0.09, p = 0.021). Coefficients suggest that the elder the patient the lower the probability of the improvement and the earlier starting treatment the higher the probability of improvement. The disease group was not statistically significant (b = −0.05, Se(b) = 0.23, p = 0.8356) and also the other variables were removed from the model because not being statistically significant and having a false increase in R-square measure, which was 9.6% in the final model.

3.3.3. Evaluation of Factors to Predict Amelioration in Global Functioning

A statistically significant effect on amelioration of C-GAS by IQ (b = 0.1, p = 0.0003), dose of drug (b = 6.3, p = 0.0065), sex (dummy 1 = male, 0 = female; b = −2.8, p = 0.0446) and age (b = 0.38, p = 0.0231) was found. The results of the regression, having an R-square = 32%, suggested that C-GAS increased in higher IQ and for higher dose, but it decreased in male subjects. The disease group was not statistically significant (b = −0.29, p = 0.8030) and also the other variables (length of therapy, age of starting treatment) did not result statistically significant. The effect of IQ could be described by a line with the slope obtained by the model that shows how improvement of C-GAS increases when IQ is higher (Figure 3). It should be noticed that IQ gives a partial prediction, because the predicted value depends upon all factors entered in the model.

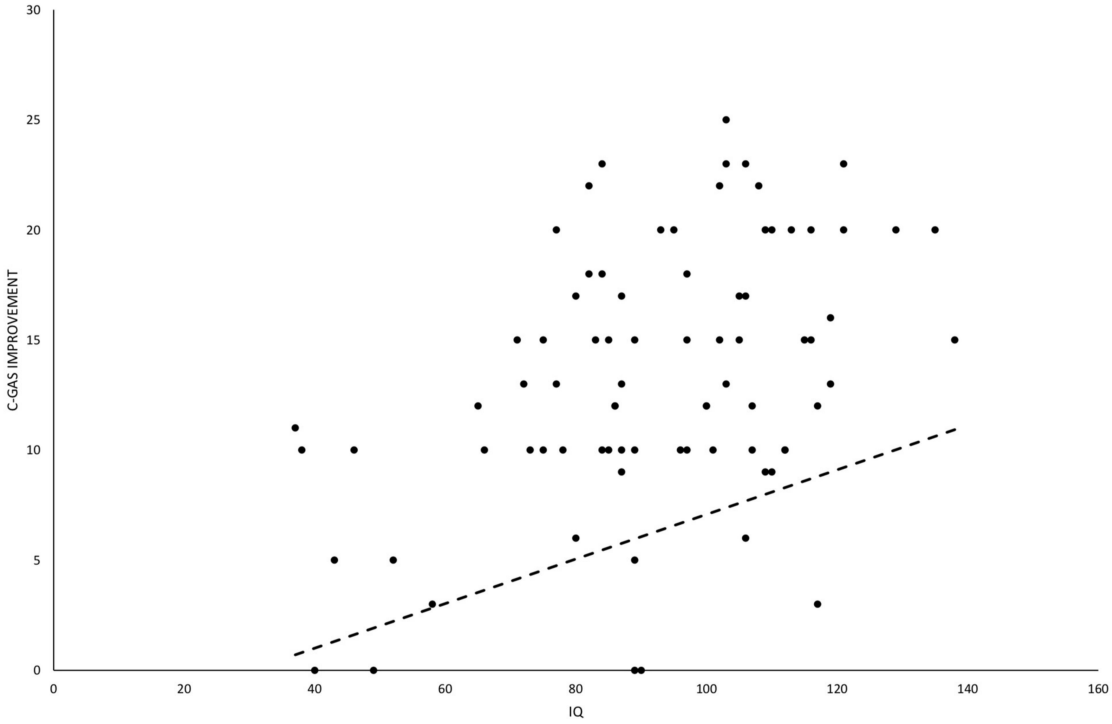

Figure 3. Scatter plot to evaluate relationship between C-GAS improvement and IQ. This factor resulted statistically significant in the multivariable model. The line is drawn with the slope (b = 0.1, p = 0.0003) estimated in the multivariable model and other variables set at their mean level.

4. Discussion

To date, no medications have been approved for the clinical use specifically for ASD, but, in clinical settings, psychotropic drugs were largely prescribed for comorbid symptoms. Stimulants were among the most prescribed medications: a large study of 2800 children recruited from the Autism Treatment network in North America displayed that stimulants were often prescribed in ASD (13%), followed by SSRIs (8%) and SGA (8%) [30]; data from a study in the United Kingdom, using a representative primary care database, revealed that psychotropic drugs are prescribed to about a third of children and adolescents with ASD and found sleep medications (9.7%), stimulants (7.9%) and antipsychotics (7.3%) to be the most commonly prescribed categories of drugs for ASD [32]; a recent study, based on the Danish national database registry, described psychotropic drugs prescription trends from 2010 to 2017 in 23,935 ASD children and adolescents, born between 1992 and 2011, confirming that 30% of the sample used psychotropics, most commonly ADHD medications (17%) and melatonin (13%), followed by antipsychotics (5%) and antidepressants (5%) [29].

As a matter of fact, the history concerning the co-presence of ASD and ADHD, as well as the consequent application of stimulants also for autistic subjects, has been marked by limits and ambivalences that delayed diagnostic and therapeutic progress. Nowadays, in scientific community, the comorbidity between ASD and ADHD is judged as a common feature and stimulants application emerges as a prolific research field. Considering the clinical traits and neurobiological deficits shared by ASD and ADHD, it has been possible to speculate that subjects with ASD may benefit from the same evidence-based pharmacological treatment, successfully used in subjects with ADHD without ASD.

The first findings have shown that methylphenidate (MPH) was less efficacious and tolerated in people with ASD, compared to ADHD alone [46–50]. Following research found different results, better for efficacy and safety than previous ones [51–59]. Nevertheless, both case report and following reviews [40,60] were not conclusive and poorly significant, due to the small number of studies which all had small sample size, poor clinical characterization and short-term follow-up.

The present study analyzed long-term MPH efficacy and safety in a naturalistic setting of 40 ADHD patients with comorbid ASD, compared to 40 patients with ADHD. All the participants had a follow-up lasting from 6 to 156 months (median of therapy duration: 36 months in ASD and ADHD; 48 months in ADHD) of treatment, strictly clinically characterized and monitored.

Results suggested that MPH in ADHD children and adolescents with comorbid ASD was associated with significative reduction of illness severity, clinical improvement in the first two years of treatment and amelioration of global functioning until the last follow-up, without significant differences with children and adolescents with ADHD without ASD at one, six and twenty-four months follow-up.

The present study also found a higher probability of clinical improvement in subjects from both groups who start an earlier MPH treatment. Furthermore, by analyzing the influence of intellectual functioning, results demonstrated a favorable trend of reduction of severity of illness and amelioration of global functioning associated with higher IQ. These findings are in accordance with previous studies [58], in which high functioning ASD were more likely to have a favorable response to MPH treatment than low functioning ones. As for MPH efficacy in ADHD without ASD, considering the robust literature, the influence of intellectual functioning seems controversial. The study from Grizenko et al. (2012) [77], about 502 children with ADHD treated with MPH, showed that there was no statistically significant difference in the response of MPH for children in the border-line, average and superior IQ levels. Tarrant et al. (2018) [78] reviewed studies including 315 participants in order to compare the effectiveness of MPH in typically growing children and adolescents with an intellectual disability (ID). This review showed that the ES of MPH in ID children was lower than that in the non-ID children (0.5 vs 0.8–1.3); type and rate of adverse effects among the two groups seem similar [78].

As for safety data, treatment with MPH in ASD patients was well-tolerated. There were no serious adverse events. The main adverse events were temporary loss of appetite, abdominal discomfort and headache, without significant differences with ADHD group. Only two ADHD patients with comorbid ASD (5%) presented major adverse events consisting in worsening of behavior with restlessness and increased stereotypes that caused the interruption of treatment and both resolved completely after treatment discontinuation; interestingly, both patients were affected by level 3 ASD associated with intellectual disability.

The mean of efficacy index, measured by dividing therapeutic effect score by side effect score, was indicative of a marked therapeutic effect with no significant interference of side effects, or, alternatively, of a minimal therapeutic effect without side effects and there were not significant differences among the two groups. Concerning treatment persistence, previous studies revealed that MPH in ASD patients, compared to other classes of psychotropic drugs, showed a lower rate of treatment discontinuation, with a higher adherence rate in children than in adolescents, that may be explained by children's greater parent involvement in controlling treatment [29,79]. In the present study, the adherence rate was preserved both in children and adolescents by a strictly monitored follow-up, with informative and motivational support to parents and adolescents. Discontinuation rate did not result significantly different in the two groups and it was prevalently motivated by clinical improvement.

Although not being a focus of this study, our results revealed that co-therapy (e.g., stimulants and risperidone or mood stabilizers or antidepressants or melatonin) did not interfere with response rate to MPH or increased side effects, according with other reports [58,62], and, in addition, a decreased trend in the assumption of other psychotropic medications was found. The intake of melatonin did not change in both groups from the baseline to the last follow-up, proving that MPH treatment did not significantly interfere with sleep/wake rhythm.

These reassuring findings about MPH efficacy, safety and treatment persistence were in accordance with literature from 2000s [52,55,58,62,80] and in discord with early studies that found more MPH adverse events in ASD patients than in ADHD patients [46–50]. We hypothesize that these discordant data could be caused by clinical heterogeneity of the recruited samples or by the assumption of other psychotropic drugs. Both Birmaher (1988) [80] and Quintana (1995) [51] have suggested that the

increase in stereotypies seen in children reported by Campbell and colleagues may be more related with withdrawal dyskinesia associated with antipsychotic discontinuation rather than with stimulant induced stereotypies. We assume that low functioning ASD could have an increased risk of worsening behaviors and stereotypes, since in our experience we found worsening of these adverse events only in two patients with ASD associated with intellectual disability.

The present study had different strengths: first of all, the sample was phenotypically characterized, throughout intellectual profile, severity specifiers, diagnostic subtypes and comorbidities; patients were strictly monitored and followed at least every six months, the follow-up period being longer than 2 years in over three-quarters, higher than most the other studies; it described both effectiveness of Immediate Release and Extended Release formulation of MPH. Finally, being it a naturalistic study, clinicians could feel confident in titrating medication and adjusting doses as needed, therefore collected data are closer to real-life setting.

The limitations concerned the utilization of global efficacy measures, rather than specific ASD and ADHD measures for core symptoms. These aspects, not deeply investigated in this study, could represent a future direction of research about MPH effect in ASD + ADHD patients.

Compared with previous studies, the present one showed higher response rate and tolerability of MPH treatment in ASD patients. We hypothesized that this improved stimulants' profile in ASD may be explained, besides the above-mentioned features associated with naturalistic setting, by the high percentage of subjects with average intellectual functioning in the sample.

In conclusion, our study shows that long-term MPH treatment, lasting 24 months on average, is effective and well-tolerated in ADHD children and adolescents with comorbid high-functioning ASD, even in association with other psychotropic drugs. Although long term studies are necessary to confirm these results, we recommend a routine use of MPH in ADHD with comorbid high-functioning ASD.

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JAMA Network Clinical Guideline Synopsis

Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder

Irene M. Loe, MD; Pooja A. Kakar, MD; Lee M. Sanders, MD, MPH

Guideline title: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents

Developer: American Academy of Pediatrics ADHD expert panel

Release date: October 1, 2019

Prior release: 2011, 2001, and 2000

Funding source: American Academy of Pediatrics

Target populations: Children aged 4 to 18 years

Major recommendations and quality of evidence ratings:

(1) The primary care clinician (PCC) should initiate ADHD evaluation for children who present with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity (grade B).

(2) Diagnosis requires meeting *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria, including symptoms and impairment in more than 1 setting per multiple informants (grade B).

(3) Evaluation should include screening for comorbid emotional, behavioral, developmental, and physical conditions (eg, tics, sleep apnea) (grade B).

(4) Each case should be managed by the principles of the chronic care model in the medical home (grade B).

(5) Age-specific guidelines:

(a) 4 to 6 Years: the PCC should prescribe evidence-based parent training in behavior management (PTBM) and/or behavioral classroom interventions (grade A). Methylphenidate may be considered if behavioral interventions are ineffective or unavailable (grade B; strong recommendation for methylphenidate).

(b) 6 to 12 Years: the PCC should prescribe US Food and Drug Administration–approved medications, plus PTBM and/or behavioral classroom intervention (grade A). Educational interventions and individualized instructional supports are necessary and often include an individualized education program or 504 plan.

(c) 12 to 18 Years: the PCC should prescribe medications with adolescent assent (grade A). Evidence-based training and/or behavioral interventions are encouraged (grade A), plus educational interventions and individualized instructional support.

(6) The PCC should titrate doses of medication to achieve maximum benefits with tolerable adverse effects (grade B).

(7) The PCC may initiate treatment of comorbid conditions or make appropriate referrals (grade C).

Summary of the Clinical Problem

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that affects nearly 1 in 10 children and significantly affects academic achievement, well-being, and social interactions.[1] Although ADHD is usually diagnosed in childhood and continues through adolescence and adulthood,[2] many children remain untreated or undertreated.[3] Comorbid conditions, such as learning and language disorders, anxiety, depression, oppositional defiant disorder, and conduct disorder, are commonly associated with ADHD and often missed.

Characteristics of the Guideline Source

This guideline is an update of the American Academy of Pediatrics (AAP) 2011 guideline, incorporating changes in a recent revision to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) and interval research findings. The guideline supplement[4] includes an updated process of care algorithm and implementation aids. The guideline authors represent a range of disciplines (primary and subspecialty pediatrics, family medicine, psychiatry, and psychology) and professional organizations, with input from a patient advocacy group. These authors' potential conflicts of interest were identified and taken into consideration in the group's deliberations; no conflicts prevented author participation. Further information is in the **Table**.

Evidence Base

An expert panel developed 7 research questions addressing ADHD diagnosis and treatment to direct a review by the Evidence-Based Practice Center of the US Agency for Healthcare Research and Quality. The review was informed by a systematic literature review of empirical research from 2011 to 2016.[5] Additional information on psychosocial treatments[6] and prevalence was considered. Seven key action statements (KASs), 4 diagnostic and 3 therapeutic, were developed after reaching consensus on the evidence. Grading of each KAS was based on University of Oxford Centre for Evidence-Based Medicine guidelines, as adapted by the AAP.[7] Six KASs received a strong recommendation (grade A or B), and 1 (treatment of comorbid conditions) received a recommendation (grade C).

A diagnosis of ADHD should be based on *DSM-5* criteria, with multiple adult informants from more than 1 setting (eg, parent, teacher) providing symptom and impairment ratings of the child. Alternative causes of ADHD symptoms should be ruled out. Because *DSM-5* criteria differ minimally from *DSM-IV* criteria,

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline: systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of the recommendations	Good
External review	Good/fair
Updating	Fair/poor
Implementation issues	Fair

existing diagnostic survey tools can continue to be used. The *DSM-5* criteria can appropriately identify ADHD in preschool-aged children. The review found that neuropsychological testing, electroencephalography, or neuroimaging confer no improvements in diagnostic accuracy. Treatment of ADHD should be guided by the child's age group, in a medical home that includes the primary care clinician (PCC), families, teachers, and mental health consultants following principles of the chronic care model. For preschool-aged children, the PCC should recommend evidence-based parent training in behavior management and school supports; methylphenidate therapy should be considered if there is lack of improvement and continued functional impairment or parent training in behavior management is unavailable. For school-aged children, the PCC should prescribe US Food and Drug Administration–approved medication alongside parent training in behavior management and school supports. For adolescents, the PCC should assess for substance abuse and comorbid conditions before prescribing medication and school supports; evidence-based training and/or behavioral interventions should be encouraged.

Benefits and Harms

With appropriate diagnosis and treatment, most children with ADHD should experience clinically significantly reduced symptoms and improved functioning. Potential harms associated with the diagnostic process include an inappropriate diagnosis of ADHD (eg, a missed diagnosis of trauma or abuse), unrecognized comorbid conditions leading to inappropriate treatment, or a missed diagnosis. Risks associated with behavioral treatment include an increased time burden for the family and school personnel, as well as possible resultant conflicts among the child, family members, and school personnel. Risks associated with medication include appetite loss, abdominal pain, headache, sleep disturbance, decreased growth, and increases in heart rate and blood pressure. An additional burden of both medication and behavioral treatment, depending on the family's insurance provider and individual school resources, may be out-of-pocket costs. No studies assessed the potential psychosocial harm or stigma associated with an ADHD diagnosis.

Discussion

The 2019 ADHD guidelines used a comprehensive expert review with an extensive evidence-based literature review. The resulting age-based action statements achieved strong evidence to guide primary-care-based diagnosis and treatment. To aid PCC implementation, the guidelines include an updated process of care algorithm and new recommendations on diagnosis and treatment of comorbid conditions. Other tools for PCCs include the Society for Developmental-Behavioral Pediatrics Clinical Practice Guideline for Assessment and Treatment of Children and Adolescents with Complex ADHD[8] and the AAP's Mental Health Initiatives and Primary Care Tools.[9]

Areas in Need of Future Study or Ongoing Research

Future studies should aim to improve or develop tools for primary care settings, including screening and diagnostic tools for ADHD and comorbid conditions, tools to monitor functional improvement, and tools to aid child population health management. Experimental studies should evaluate, across the age spectrum, the safety, efficacy, and long-term outcomes of non–FDA-approved medications; medication combinations; and novel psychosocial, school-based, and other nonpharmacologic therapies. Behavioral studies should examine effective mechanisms to improve treatment adherence; address barriers to care; and reduce literacy, language, and cultural disparities.

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Considerations for Young Children and Those With Special Needs as COVID-19 Continues

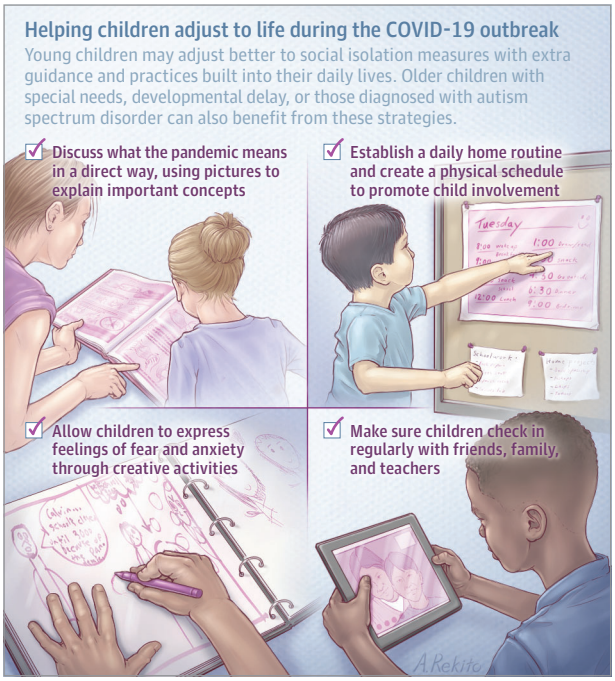
The coronavirus disease 2019 (COVID-19) pandemic continues to affect children and their families.

While the country navigates reopening of the economy, many child-friendly places such as schools, libraries, parks, museums, and zoos remain closed. Social distancing continues to be one of the primary methods used to slow the spread and transmission of the infection. All of these important measures affect young children and children with special needs immensely.

Adjusting to the new reality caused by the COVID-19 outbreak is difficult for children, particularly those who are younger or have additional challenges related to developmental delay or medical diagnoses such as autism spectrum disorder. For many, it can be difficult to fully understand the changes that are happening in the world, even in their homes. Disruptions in their schedule conflict with the stability of routines and, when coupled with any communication difficulty, can lead to anxiety, frustration, and negative behaviors. Even attending to a familiar task in an unfamiliar setting can be challenging, and with time, these children are at risk for losing these skills.

It is important that parents use clear, simple, and concrete language when explaining the COVID-19 pandemic. For instance, phrases such as "they caught the bug causing COVID-19" or "they are under the weather" can be confusing to children. Using direct and concrete language such as "they are sick" can be easier to understand. Parents can also use story boards to explain the situation. In these short stories or narratives, parents can describe new situations or activities using literal language and pictures. This can be a useful tool to teach important concepts such as hand washing, putting on a mask, or social distancing.

Parents need to establish a home routine for their children. Keeping a similar daily schedule can be comforting as the child becomes familiar with a new routine. Parents should set the same wake and sleep time, as well as specific times for meals, schoolwork, play time, and exercise. A visual of the daily schedule can be particularly helpful. Children can preview the calendar the day before so that they can anticipate events before they happen. Furthermore, these visual cues can also help note the passing of time. Otherwise, without the typical school and weekend schedule, days and weeks merge together, which can be disorienting. Having a child mark the calendar can be a concrete way to track time and to feel in control. Transition periods can also cause a lot of anxiety for these children. Use of visual timers allow the child to see how much time is remaining for a particular activity before transitioning to the next activity compared with using phrases like "in just a second."



FOR MORE INFORMATION

Autism spectrum disorder:
https://www.healthychildren.org/English/health-issues/conditions/Autism/Pages/default.aspx

Young children and children with special needs may have difficulty expressing their emotions, whether it is fear, anxiety, or frustration with the unknown. It is important for parents to recognize that difficult behaviors may be an expression of these feelings and for them to be proactive in providing alternate expressive opportunities via music, art, or by using augmentative devices such as a tablet. Finally, it is essential that children stay connected with their social support system, including other family members, teachers, therapist, and friends via scheduling of regular check-ins.

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