NEWSLETTER

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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD MARZO 2022

Am J Psychiatry. 2021;179:142-51.

VARIABLE PATTERNS OF REMISSION FROM ADHD IN THE MULTIMODAL TREATMENT STUDY OF ADHD.

Sibley MH, Eugene Arnold L, Swanson JM, et al.

Objective: It is estimated that childhood attention deficit hyperactivity disorder (ADHD) remits by adulthood in approximately 50% of cases; however, this conclusion is typically based on single endpoints, failing to consider longitudinal patterns of ADHD expression. The authors investigated the extent to which children with ADHD experience recovery and variable patterns of remission by adulthood.

Methods: Children with ADHD (N5558) in the Multimodal Treatment Study of ADHD (MTA) underwent eight assessments over follow-ups ranging from 2 years (mean age, 10.44 years) to 16 years (mean age, 25.12 years) after baseline. The authors identified participants with fully remitted, partially remitted, and persistent ADHD at each time point on the basis of parent, teacher, and self-reports of ADHD symptoms and impairment, treatment utilization, and substance use and mental disorders. Longitudinal patterns of remission and persistence were identified that considered context and timing.

Results: Approximately 30% of children with ADHD experienced full remission at some point during the follow-up period; however, a majority of them (60%) experienced recurrence of ADHD after the initial period of remission. Only 9.1% of the sample demonstrated recovery (sustained remission) by study endpoint, and only 10.8% demonstrated stable ADHD persistence across study time points. Most participants with ADHD (63.8%) had fluctuating periods of remission and recurrence over time.

Conclusions: The MTA findings challenge the notion that approximately 50% of children with ADHD outgrow the disorder by adulthood. Most cases demonstrated fluctuating symptoms between childhood and young adulthood. Although intermittent periods of remission can be expected in most cases, 90% of children with ADHD in MTA continued to experience residual symptoms into young adulthood

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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.

Anadolu Psikiyatr Derg. 2022;23:67-73.

PATHOLOGICAL INTERNET USE, AGGRESSION, AND CYBERBULLYING IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yasin A, Yasin YK, Demirkaya SK.

Objective: The aim of this study was to evaluate the relationship between pathological internet use, aggression, and cyberbullying/victimization in children with attention deficit hyperactivity disorder.

Methods: Male children (10-18 years old) with attention deficit hyperactivity disorder (n = 30) and without any diagnosis (n = 30) were evaluated using Questionnaire of Computer/Internet Use of Children and Adolescents (Children-Adolescent Form and Parent Form), Children's Aggression Scale-Parent Version, Young Internet Addiction Scale, and Cyber Bullying and Online Aggression Survey Instrument.

Results: Weekly internet/computer using time, Young Internet Addiction Scale scores, Children's Aggression Scale-Parent Version scores were higher in the attention deficit hyperactivity disorder group. When all participants included in the study were compared for the availability of rules related to the PC/internet use at their homes, it was determined that there were rules by 53.3%, and the rate of setting rules was higher in the control group than attention deficit hyperactivity disorder group. There is a high level of positive correlation between Internet Addiction Scale score and duration in internet use in the attention deficit hyperactivity disorder group. Those who experienced cyberbullying throughout their lives were at a higher rate in the attention deficit hyperactivity disorder group compared to the control group. Physical aggression without provoking subgroup of Children's Aggression Scale-Parent Version is correlated with cyberbullying in the attention deficit hyperactivity disorder group and cyber victimization in the control group.

Conclusion: Children with attention deficit hyperactivity disorder have higher levels of aggression and pathological internet use than healthy controls, but there is no difference between cyberbullying and victimization. Cyberbullying/victimization is independent of diagnosis. For this reason, it is necessary to create awareness and preventive measures of cyberbullying

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Appl Neuropsychol Adult. 2022 Jan;29:10-22.

DISCRIMINATING MALINGERED ATTENTION DEFICIT HYPERACTIVITY DISORDER FROM GENUINE SYMPTOM REPORTING USING NOVEL PERSONALITY ASSESSMENT INVENTORY VALIDITY MEASURES.

Harrison AG, Harrison KA, Armstrong IT.

It is now widely understood that ADHD can be feigned easily and convincingly. Despite this, almost no methods exist to assist clinicians in identifying when such behavior occurs. Recently, new validity indicators specific to feigned ADHD were reported for the Personality Assessment Inventory (PAI). Derived from a logistic regression, these algorithms are said to have excellent specificity and good sensitivity in identifying feigned ADHD. However, these authors compared those with genuine ADHD only to nonclinical undergraduate students (asked to respond honestly or asked to simulate ADHD); no criterion group of definite malingerers was included. We therefore investigated these new validity indicators with 331 postsecondary students who underwent assessment for possible ADHD and compared scores of those who were eventually diagnosed with ADHD (n = 111) to those who were not [Clinical controls (66), Definite malingerers (36); No diagnosis (117)]. The two proposed PAI algorithms were found to have poor positive predictive value (.19 and .17). Self-report validity measures from the Connors' Adult Attention Rating Scale, and the Negative Impression Management scale on the PAI returned more positive results. Overall, more research is needed to better identify noncredible ADHD presentation, as the PAI-based methods proposed by Aita et al. appear inadequate as symptom validity measures

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Asia Pac J Clin Nutr. 2022 Mar;31:108-17.

NUTRITIONAL COMPLEXITY IN CHILDREN WITH ADHD RELATED MORBIDITIES IN CHINA: A CROSS-SECTIONAL STUDY.

Shen LX, Li F, Xue MB, et al.

BACKGROUND AND OBJECTIVES: To assess the general and nutritional health of children with attention deficit/ hyperactivity disorder (ADHD).

METHODS AND STUDY DESIGN: The National Multicenter Sleep Research Database for 23791 school-age children in grades 1-6 from 9 cities in China was accessed. Children with a specialist diagnosis of ADHD

or not (non-ADHD) in 2005 were studied. National anthropometric growth standards for children aged 2-18 years classified children as underweight, wasted, stunted (short stature presumed nutritional), or overweight/obesity. Independent variables were preterm birth, sleep quality and prior disease and ADHD was the dependent variable. Binary logistic regression models were developed along with interaction analyses for associated disorder or disease on overweight/obesity, and stunted.
RESULTS: Some 18731 records were analyzed for 808 children with ADHD. The comparative prevalences for ADHD with non-ADHD children were stunted 9.8% vs 5.9% (p<0.001) and overweight/ obesity (32.6% vs 29.6%, p=0.002) respectively. ADHD boys were more often underweight (7.5% vs 5.3%, p=0.027), but not in girls. ADHD likelihood Odds Ratios, ORs (with 95%CI) were for premature birth 1.838, (1.393-2.423), allergic diseases 1.915 (1.526-2.399), otitis media 1.54 (1.118- 2.146), tonsillar or adenoid hypertrophy1.662 (1.348-2.050), gastroesophageal reflux 3.008(1.792-1.792-5.049), and sleep disorder 2.201(1.847-2.623) were ADHD risk factors. Only poor sleep quality and ADHD exhibited an interaction for stunted with OR=0.409 (0.233-0.719).
CONCLUSIONS: Compromised and complex nutritional health in ADHD children challenges clinical nutrition with a range of health problems, albeit coherent with the needed nutritional emphasis in the 'first 1000 days'

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Biol Psychiatry. 2022.

GENETIC ASSOCIATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND MAJOR DEPRESSION WITH SUICIDAL IDEATION AND ATTEMPTS IN CHILDREN: THE ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY.

Lee PH, Doyle AE, Li X, et al.

Background: Suicide is among the leading causes of death in children and adolescents. There are well-known risk factors of suicide, including childhood abuse, family conflicts, social adversity, and psychopathology. While suicide risk is also known to be heritable, few studies have investigated genetic risk in younger individuals.
Methods: Using polygenic risk score analysis, we examined whether genetic susceptibility to major psychiatric disorders is associated with suicidal behaviors among 11,878 children enrolled in the ABCD (Adolescent Brain Cognitive Development) Study. Suicidal ideation and suicide attempt data were assessed using the youth report of the Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5. After performing robust quality control of genotype data, unrelated individuals of European descent were included in analyses (n = 4344).
Results: Among 8 psychiatric disorders we examined, depression polygenic risk scores were associated with lifetime suicide attempts both in the baseline (odds ratio = 1.55, 95% CI = 1.10–2.18, p = 1.27 10-2) and in the follow-up year (odds ratio = 1.38, 95% CI = 1.08-1.77, p = 1.05 10–2), after adjusting for children's age, sex, socioeconomic backgrounds, family history of suicide, and psychopathology. In contrast, attention-deficit/hyperactivity disorder polygenic risk scores were associated with lifetime suicidal ideation (odds ratio = 1.15, 95% CI = 1.05-1.26, p = 3.71 +ù 10-3), suggesting a distinct contribution of the genetic risk underlying attention-deficit/hyperactivity disorder and depression on suicidal behaviors of children.
Conclusions: The largest genetic sample of suicide risk data in U.S. children suggests a significant genetic basis of suicide risk related to attention-deficit/hyperactivity disorder and depression. Further research is warranted to examine whether incorporation of genomic risk may facilitate more targeted screening and intervention efforts

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Biol Psychiatry. 2022.

ALTERED PERIODIC DYNAMICS IN THE DEFAULT MODE NETWORK IN AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Curtin P, Neufeld J, Curtin A, et al.

Background: Altered resting-state functional connectivity in the default mode network (DMN) is characteristic of both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Standard analytical pipelines for resting-state functional connectivity focus on linear correlations in activation time courses between neural networks or regions of interest. These features may be insensitive to temporally lagged or nonlinear relationships.

Methods: In a twin cohort study comprising 292 children, including 52 with a diagnosis of ASD and 70 with a diagnosis of ADHD, we applied nonlinear analytical methods to characterize periodic dynamics in the DMN. Using recurrence quantification analysis and related methods, we measured the prevalence, duration, and complexity of periodic processes within and between DMN regions of interest. We constructed generalized estimating equations to compare these features between neurotypical children and children with ASD and/or ADHD while controlling for familial relationships, and we leveraged machine learning algorithms to construct models predictive of ASD or ADHD diagnosis.
Results: In within-pair analyses of twins with discordant ASD diagnoses, we found that DMN signal dynamics were significantly different in dizygotic twins but not in monozygotic twins. Considering our full sample, we found that these patterns allowed a robust predictive classification of both ASD (81.0% accuracy; area under the curve = 0.85) and ADHD (82% accuracy; area under the curve = 0.87) cases.
Conclusions: These findings indicate that synchronized periodicity among regions comprising the DMN relates both to neurotypical function and to ASD and/or ADHD, and they suggest generally that a dynamical analysis of network interconnectivity may be a useful methodology for future neuroimaging studies

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2022.

LONGITUDINAL CHANGES OF RESTING-STATE NETWORKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TYPICALLY DEVELOPING CHILDREN.

Soman SM, Vijayakumar N, Ball G, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent childhood neurodevelopmental disorder. Given the profound brain changes that occur across childhood and adolescence, it is important to identify functional networks that exhibit differential developmental patterns in children with ADHD. This study sought to examine whether children with ADHD exhibit differential developmental trajectories in functional connectivity compared with typically developing children using a network-based approach.
Methods: This longitudinal neuroimaging study included 175 participants (91 children with ADHD and 84 control children without ADHD) between ages 9 and 14 and up to 3 waves (173 total resting-state scans in children with ADHD and 197 scans in control children). We adopted network-based statistics to identify connected components with trajectories of development that differed between groups.
Results: Children with ADHD exhibited differential developmental trajectories compared with typically developing control children in networks connecting cortical and limbic regions as well as between visual and higher-order cognitive regions. A pattern of reduction in functional connectivity between corticolimbic networks was seen across development in the control group that was not present in the ADHD group. Conversely, the ADHD group showed a significant decrease in connectivity between predominantly visual and higher-order cognitive networks that was not displayed in the control group.
Conclusions: Our findings show that the developmental trajectories in children with ADHD are characterized by a subnetwork involving different trajectories predominantly between corticolimbic regions and between visual and higher-order cognitive network connections. These findings highlight the importance of examining the longitudinal maturational course to understand the development of functional connectivity networks in children with ADHD

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Biomarkers. 2022.

MICRORNA PROFILE AS POTENTIAL MOLECULAR SIGNATURE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Zhu P, Pan J, Cai QQ, et al.

Aims: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder of neurodevelopment in children. The diagnosis of ADHD mainly relies on the symptoms and some may be misdiagnosed due to age-based variation in behaviours. This study aimed to explore biomarkers that are greatly needed for the accurate diagnosis of ADHD.
Methods: Seven hundred and forty-two samples were retrospectively investigated in three independent cohorts, screening, training, and validation, for circulation microRNA measurement using microarray, Taqman polymerase chain reaction, and regression analysis.

Results: A panel of five miRNAs (miR-4516, miR-6090, miR-4763-3p, miR-4281, and miR-4466) were identified as ADHD independent risk factors that provided a high diagnostic accuracy and specificity of ADHD (AUC = 0.940 and 0.927 in the training and validation datasets, respectively). This panel of miRNAs differentiated ADHD well from control groups. After clinical improvement by treatment, the panel of miRNAs in patients and AUC changed significantly and were close to those in healthy controls. Importantly, the targets of the miRNAs identified were commonly enriched in receptor signalling pathways, ion channels, and synapse structures.
Conclusion: Our study identified a useful panel of miRNAs that have considerable clinical value in evaluating ADHD and provide important evidence for aberrant epigenetic regulation in ADHD

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Biomedical Signal Processing and Control. 2022;76.

COMPARISON OF DOMAIN SPECIFIC CONNECTIVITY METRICS FOR ESTIMATION BRAIN NETWORK INDICES IN BOYS WITH ADHD-C.

Aydin S, et al.

The goal of the present study is to propose the use of global connectivity measures as quantitative indicators of long-term medication in pediatric patients with Attention-Deficit-Hyperactivity Disorder, combined type (ADHD-C). For this purpose, graph theoretical brain connectivity indices are computed from connectivity estimations across eyes-opened resting-state EEG recordings measured before and after the treatment with osmotic release oral system-methylphenidate for a month in 18 boys (aged between 7-12 years). In order to present the reliable results, neurofunctional correlations are firstly estimated in time (Pearson Correlation (PC), Spearman Correlation), frequency (Directed Transfer Function, Partial Directed Coherence) and phase (Phase Locking Value, Phase Lag Index) domains in between short segments of 2sec over single trials of 1min. Later, transitivity, clustering coefficients, assortativity, global efficiency and modularity are computed from EEG based connectivity matrices produced by each approach. Since the highest classification accuracy of 83.79% is provided by PC, statistical tests (one-way Anova, pair-wise multiple comparison) and step-wise logistic regression modelling are all examined to detect significant differences between pre- and post-treatment relevant connectivity measures. Statistical boxplots are also shown, as well. Overall results reveal that global brain connectivity can be increased by long-term medication in pediatric ADHD-C in terms of increased segregation & resilience. This is the first study to demonstrate that long-term medication can normalize the functional brain connectivity in ADHD, which is characterized by decreased connectivity compared to controls

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BMC Med. 2022;20.

HIGH POLYGENIC PREDISPOSITION FOR ADHD AND A GREATER RISK OF ALL-CAUSE MORTALITY: A LARGE POPULATION-BASED LONGITUDINAL STUDY.

Ajnakina O, Shamsutdinova D, Wimberley T, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a highly heritable, neurodevelopmental disorder known to associate with more than double the risk of death compared with people without ADHD. Because most research on ADHD has focused on children and adolescents, among whom death rates are relatively low, the impact of a high polygenic predisposition to ADHD on accelerating mortality risk in older adults is unknown. Thus, the aim of the study was to investigate if a high polygenetic predisposition to ADHD exacerbates the risk of all-cause mortality in older adults from the general population in the UK.
Methods: Utilising data from the English Longitudinal Study of Ageing, which is an ongoing multidisciplinary study of the English population aged 50 years, polygenetic scores for ADHD were calculated using summary statistics for (1) ADHD (PGS-ADHDsingle) and (2) chronic obstructive pulmonary disease and younger age of giving first birth, which were shown to have a strong genetic correlation with ADHD using the multi-trait analysis of genome-wide association summary statistics; this polygenic score was referred to as PGS-ADHDmulti-trait. All-cause mortality was ascertained from the National Health Service central register that captures all deaths occurring in the UK.
Results: The sample comprised 7133 participants with a mean age of 64.7 years (SD = 9.5, range = 50-101); of these, 1778 (24.9%) died during a period of 11.2 years. PGS-ADHDsingle was associated with a

greater risk of all-cause mortality (hazard ratio [HR] = 1.06, 95% CI = 1.02-1.12, p= 0.010); further analyses showed this relationship was significant in men (HR = 1.07, 95% CI = 1.00-1.14, p= 0.043). Risk of all-cause mortality increased by an approximate 11% for one standard deviation increase in PGS-ADHDmulti-trait (HR = 1.11, 95% CI = 1.06-1.16, p< 0.001). When the model was run separately for men and women, the association between PGS-ADHDmulti-trait and an increased risk of all-cause mortality was significant in men (HR = 1.10, 95% CI = 1.03-1.18, p= 0.003) and women (HR = 1.11, 95% CI = 1.04-1.19, p= 0.003).
Conclusions: A high polygenetic predisposition to ADHD is a risk factor for all-cause mortality in older adults. This risk is better captured when incorporating genetic information from correlated traits

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BMC Psychiatry. 2022 Mar;22:166.

INVESTIGATING THE ASSOCIATIONS BETWEEN IRRITABILITY AND HOT AND COOL EXECUTIVE FUNCTIONING IN THOSE WITH ADHD.

Colonna S, Eyre O, Agha SS, et al.

BACKGROUND: Irritability is especially pertinent to those with Attention Deficit Hyperactivity Disorder (ADHD) as it is highly prevalent and associated with a more severe clinical presentation and poorer longitudinal outcomes. Preliminary evidence suggests that top-down cognitive processes taking place in emotional contexts (i.e., hot executive functions) as opposed to those evoked in abstract scenarios (i.e., cool executive functions) may be relevant to the presentation of irritability in ADHD. This study explored the cognitive mechanisms underlying irritability in young people with ADHD, hypothesising that irritability would be associated with hot, but not cool, executive function impairments.
METHODS: Our sample included 219 individuals with ADHD. A composite irritability score was derived extracting items from a parent interview, with scores ranging from 0 to 5. Associations were investigated using linear regression analyses, between irritability and four hot tasks measuring sensitivity to risk, risk-taking behaviour following reward or punishment, acceptance of reward delay and reaction to unfair behaviour from others, and two cool tasks measuring set-shifting and motor inhibition.
RESULTS: As hypothesised, there were no significant associations between irritability and cool executive functions in those with ADHD; however, contrary to expectations, there was also no significant evidence that hot executive functions were associated with irritability.
CONCLUSIONS: These results, in a large well characterised sample and using a comprehensive task battery, suggest that the variation in irritability in those with ADHD may not be associated with differences in hot or cool executive function performance

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BMC Psychiatry. 2022;22.

TRANSDIAGNOSTIC SYMPTOM SUBTYPES ACROSS AUTISM SPECTRUM DISORDERS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: VALIDATED BY MEASURES OF NEUROCOGNITION AND STRUCTURAL CONNECTIVITY.

Zhang M, Huang Y, Jiao J, et al.

Backgrounds: Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders that exhibit within-disorder heterogeneity and cross-disorder phenotypic overlap, thus suggesting that the current disease categories may not fully represent the etiologic essence of the disorders, especially for highly comorbid neurodevelopmental disorders. In this study, we explored the subtypes of a combined sample of ASD and ADHD by integrating measurements of behavior, cognition and brain imaging.
Methods: A total of 164 participants, including 65 with ASD, 47 with ADHD, and 52 controls, were recruited. Unsupervised machine learning with an agglomerative hierarchical clustering algorithm was used to identify transdiagnostic symptom clusters. Neurocognition and brain structural connectivity measurements were used to assess symptom clusters. Mediation analysis was used to explore the relationship between transdiagnostic symptoms, neurocognition and brain structural connectivity.
Results: We identified three symptom clusters that did not fall within the diagnostic boundaries of DSM. External measurements from neurocognition and neuroimaging domains supported distinct profiles, including fine motor function, verbal fluency, and structural connectivity in the corpus callosum between these symptom

clusters, highlighting possible biomarkers for ASD and ADHD. Additionally, fine motor function was shown to mediate the relationship between the corpus callosum and perseveration symptoms.
Conclusions: In this transdiagnostic study on ASD and ADHD, we identified three subtypes showing meaningful associations between symptoms, neurocognition and brain white matter structural connectivity. The fine motor function and structural connectivity of corpus callosum might be used as biomarkers for neurodevelopmental disorders with social skill symptoms. The results of this study highlighted the importance of precise phenotyping and further supported the effects of fine motor intervention on ASD and ADHD

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BMJ Open. 2022 Mar;12:e054424.

DEFICITS IN ATTENTION, MOTOR CONTROL AND PERCEPTION CHILDHOOD TO AGE 30 YEARS: PROSPECTIVE CASE-CONTROL STUDY OF OUTCOME PREDICTORS.

Landgren V, Fernell E, Gillberg C, et al.

OBJECTIVE: Investigate predictors of adverse outcome in children with and without attention-deficit/hyperactivity disorder (ADHD) combined with developmental coordination disorder (DCD) at 6 years of age.
DESIGN: Prospective population-based cohort study.
SETTING: Western Sweden.
PARTICIPANTS: From a screening-based population cohort of 589 individuals, 62 (11 female) diagnosed with ADHD+DCD at mean age 6.6 years, and a comparison group of 51 population-matched (10 female) children were followed prospectively.
OUTCOME MEASURES: Drawn from a clinical reassessment at age 9 years of 110 of the 113 individuals, neuropsychiatric symptoms, continuous performance test results and measures of motor function were used as predictors of outcome in linear regression models. Participants were followed in national registers up to 30-31 years of age for outcomes in adulthood. Predictors were regressed onto an adverse outcome score (range 0-7) comprising seven binary endpoints, and when applicable onto each continuous outcome separately (low educational attainment, low occupation level, psychiatric disorder, psychotropic medication prescription, sick pension, high dependence on social benefits and criminal conviction).
RESULTS: Of the 110 individuals, 3 had died. In univariable regression onto the adverse outcome score, the strongest predictors at age 9 years were symptoms of conduct disorder, oppositional defiant disorder, ADHD and motor dysfunction, with an R(2) around 25%, followed by autistic traits (R(2)=15%) and depressive symptoms (R(2)=8%). Combining these six strongest predictors in a multivariable model yielded an adjusted R(2)=38%. Subgroup analyses were similar, except for a strong association of autistic traits with the adverse outcome score in females (n=20, R(2)=50%).
CONCLUSION: Several neurodevelopmental symptoms, including ADHD severity at age 9 years, accounted for a considerable amount of the variance in terms of adulthood adverse outcome. Broad neurodevelopmental profiling irrespective of diagnostic thresholds should inform research and clinical practice. The study highlights the importance of considering associated comorbidities and problems in ADHD

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Brain Sciences. 2022;12.

TRANSIENT DESTABILIZATION OF DECLARATIVE MEMORY-OPPOSING IMPACT OF PHYSICAL EXERCISE OR REST AFTER ENCODING IN TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER BUT NO DIFFERENCE AFTER SUBSEQUENT SLEEP.

Munz M, Baving L, Prehn-Kristensen A.

Background: Children are especially sensitive to a broad range of influences and show a remarkable capacity for learning. One prominent example is declarative memory, which may be influenced by a variety of factors and is impaired in attention deficit hyperactivity disorder (ADHD). Exercise and sleep, or both combined, might foster declarative memory.
Methods: Here, 12 typically developing children (TDC) and 12 age-matched children with ADHD participated in an exercise and rest condition before a night in the sleep laboratory. Declarative memory was encoded before exercise or rest and retrieved before and after a night of sleep.

Results: Exercise in TDC but rest in ADHD lead to a transient destabilization of declarative memory, while there were no more differences after a night of sleep. Rapid eye movement (REM) sleep latency was prolonged after exercise in both groups.
Conclusions: Exercise leads to opposing effects on immediate declarative memory formation. The factors or contexts that promote or hinder declarative memory formation in children ADHD and TDC differ, and further work is needed to determine the recommendations for declarative learning in children with ADHD

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Child Neuropsychol. 2022.

IMPROVING ACCURACY OF ADHD SUBTYPE DIAGNOSES WITH THE ADHD SYMPTOM RATING SCALE.

Rogers EA, Graves SJ, Freeman AJ, et al.

Neuropsychologists evaluate children and adults with ADHD to establish a diagnosis, quantify cognitive deficits associated with ADHD and other common comorbid conditions, and provide recommendations for education and vocational planning. Standardized instruments that align with DSM ADHD symptom criteria are recommended for increasing ADHD diagnostic accuracy. This study examined whether a brief DSM-based symptom rating scale would assist in differentiating subtypes of ADHD. Participants were 253 children diagnosed with ADHD-Inattentive (n =163) or ADHD-Combined (n =90). Parents completed the Behavior Assessment System for Children, Second Edition (BASC-2) and DSM-IV ADHD Symptom Rating Scale (SRS) as part of a comprehensive evaluation to establish ADHD diagnoses. The SRS displayed expected convergent and discriminant validity with BASC-2 subscales. The diagnostic accuracy of the SRS subscales to differentiate ADHD was also examined and compared with the BASC-2. Results indicated that SRS Impulsivity, SRS Hyperactivity, and BASC-2 Hyperactivity had significantly better classification accuracy than BASC-2 Attention Problems and SRS Inattention, although they did not differ from each other. The SRS produced symptom profiles consistent with ADHD-Inattentive and Combined subtypes with good classification accuracy when differentiating subtypes. Overall, the SRS is an economical measure that can assist in ADHD presentation differentiation when used as a component of ADHD evaluations

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Child Neuropsychol. 2022.

ATTENTION CONTROL IN CHILDREN WITH ADHD: AN INVESTIGATION USING FUNCTIONAL NEAR INFRARED SPECTROSCOPY (FNIRS).

Calub CA, Rapport MD, Irurita C, et al.

Attention problems are a predominant contributor to near- and far-term functional outcomes in attention-deficit/hyperactivity disorder (ADHD); however, most interventions focus on improving the alerting attentional network, which has failed to translate into improved learning for a majority of children with ADHD. Comparatively less is known regarding the executive attentional network and its overarching attention control process, which governs the ability to maintain relevant information in a highly active, interference-free state, and is intrinsic to a broad range of cognitive functions. This is the first study to compare attention control abilities in children with ADHD and typically developing (TD) children using the Visual Array Task (VAT) and to simultaneously measure hemodynamic functioning (oxyHb) using functional Near-Infrared Spectroscopy (fNIRS). Nineteen children with ADHD Combined type and 18 typically developing (TD) children aged 8 to 12-áyears were administered the VAT task while prefrontal activity was monitored using fNIRS. Results revealed that children with ADHD evinced large magnitude deficits in attention control and that oxyHb levels in the left dorsal lateral prefrontal cortex (dlPFC) were significantly greater in children with ADHD relative to TD children. These findings suggest that poor attention control abilities in children with ADHD may be related to increased left dlPFC activation in response to an underdeveloped and/or inefficient right dlPFC. The need to design interventions that target and strengthen attention control and its corresponding neural network is discussed based on the likelihood that attention control serves as the potential quaesitum for understanding a wide array of ADHD-related deficits

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Child Neuropsychol. 2022.

PATTERNS OF PERFORMANCE OF CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 ON THE K-CPT AND K-CPT 2.

Pardej SK, Glad DM, Lee KM, et al.

Children with neurofibromatosis type 1 (NF1) often have attention difficulties with emerging evidence that these difficulties can be seen even in early childhood. This study aimed to explore the relative utility of two versions of a commonly used computerized attention measure for young children with NF1 and to explore relations with parent-reported attention in young children with NF1. Two independent samples of young children with NF1 participated. One sample (Study 1; N =22; M age=4.95 (SD=0.66)) completed the Conner's Kiddie Continuous Performance Test (K-CPT). A second and separate sample (Study 2; N =19; M age=5.46 (SD=0.74)) completed the K-CPT second edition (K-CPT 2). Relations of the K-CPT and K-CPT 2 with concurrent parent-reported attention (Kiddie Disruptive Behavior Disorder Schedule; Conners parent report questionnaires) were explored. The K-CPT sample's scores significantly differed from the normative median on Commissions, Hit Rate Standard Error, Variability, Detectability, Perseverations, and Hit Rate Inter Stimulus Interval. No relations with parent-report were identified. The K-CPT 2 sample's scores were significantly worse than normative data on every score except Hit Rate Block Change. Multiple scores on the K-CPT 2 were significantly related to parent-report of inattention and hyperactivity with some evidence of construct validity for the distinction between inattention and hyperactivity. The K-CPT 2 may be more useful for the assessment of attention problems in young children with NF1 as more challenges were observed and performance was more closely related to parent-reported attention difficulties than its predecessor the K-CPT

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Child Neuropsychol. 2022.

A PRELIMINARY STUDY: RELATIONSHIP BETWEEN INATTENTION/HYPERACTIVITY AND FAMILIAL MEDITERRANEAN FEVER IN CHILDREN AND ADOLESCENTS.

Durcan G, Barut K, Haslak F, et al.

Although Familial Mediterranean Fever (FMF) progresses with attacks, its subclinical inflammation may continue in attack-free periods. To date, increased inflammatory cytokines have been reported in many psychiatric diseases. In this study, we aimed to evaluate the psychological symptoms, especially inattention/hyperactivity, in patients with FMF. The study included 272 children and adolescents with FMF and 250 healthy peers as a control group. The Strengths and Difficulties Questionnaire-Parent Form was used to assess emotion, behavior and peer related problems, as well as inattention/hyperactivity and prosocial behavior in participants. The age and gender of the children were similar across groups. The emotional and behavioral problem subscale scores of patients with FMF were significantly higher than those of healthy controls. The inattention/hyperactivity scores of patients with FMF were also significantly higher than those of the control group (3.99-¦2.34 vs 2.93-¦2.26, p <0.001). When patients with FMF were compared according to the presence of attacks in the last year, presence of exertional leg pain, no differences were found in terms of inattention/hyperactivity scores. However, patients whose FMF symptoms started before 6 years of age had significantly higher inattention/hyperactivity scores than those whose symptoms begun after 6 years of age. This research demonstrated that FMF patients had increased inattention/hyperactivity, which was unaffected by FMF-related variables, except for age of onset. The FMF-inattention/hyperactivity relationship may be due to a common etiology in which proinflammatory cytokines play a role

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Child Psychiatry Hum Dev. 2022 Feb;53:3-15.

ACADEMIC, INTERPERSONAL, RECREATIONAL, AND FAMILY IMPAIRMENT IN CHILDREN WITH TOURETTE SYNDROME AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ricketts EJ, Wolicki SB, Danielson ML, et al.

This study describes impairment in academic, interpersonal, recreational, and family financial or occupational domains across children in three mutually exclusive diagnostic groups: ever diagnosed with Tourette syndrome (TS), attention-deficit/hyperactivity disorder (ADHD), and both disorders. In 2014, parents reported on impairment and diagnostic status of children aged 4–17 years (n = 3014). Weighted analysis and pairwise t-tests showed more children with ADHD (with or without TS) experienced impairment in overall school

performance, writing, and mathematics, relative to children with TS but not ADHD. More children with TS and ADHD had problematic handwriting relative to children with ADHD but not TS. More children with TS and ADHD had problematic interpersonal relationships relative to those with ADHD but not TS. Children with TS and ADHD had higher mean impairment across domains than children with either TS or ADHD. Findings suggest assessing disorder-specific contributions to impairment could inform targeted interventions for TS and ADHD

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Child Psychiatry Hum Dev. 2022 Feb;53:109-23.

TEMPERAMENT PROFILES ASSOCIATED WITH INTERNALIZING SYMPTOMS AND EXTERNALIZING BEHAVIOR IN ADOLESCENTS WITH ADHD.

Deotto A, Eastwood JD, Toplak ME.

The current study investigated temperament profiles associated with internalizing symptoms and externalizing behavior in adolescents with ADHD. Participants were 121 adolescents (90 males) with ADHD, ranging in age from 13 to 18 years (M = 15.40, SD = 1.59). Emotional and behavioral ratings were obtained using the Strengths and Difficulties Questionnaire (SDQ) and temperament profiles were assessed by administering the Temperament and Character Inventory (TCI). Multivariate profile analyses and post hoc tests revealed that youth high in internalizing symptoms were significantly higher in harm avoidance and lower in self-directedness. Youth high in externalizing behavior were significantly lower in cooperativeness. No cognitive differences were observed across groups, but youth high in externalizing behavior had more ADHD symptoms and greater impairment in daily life. Findings reveal unique temperament factors associated with comorbid concerns, which may have implications for adapting and personalizing intervention efforts based on these different profiles within adolescents with ADHD

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Clin EEG Neurosci. 2022;53:NP23.

MAXIMUM DOWNWARD SLOPES OF SLEEP SLOW WAVES AS A POTENTIAL MARKER OF ATTENTION DEFICIT HYPERACTIVITY DISORDER CLINICAL PHENOTYPES.

Fasano A, Biancardi C, Masi G, et al.

Sleep problems are common in children with Attention Deficit Hyperactivity Disorder (ADHD) [Cortese, 2015], possibly due to shared pathophysiology. However, few differences in the macrostructure of the sleep EEG have emerged between ADHD and healthy children [Diaz-Roman et al., 2016]. We wanted to verify that the slope of Slow Waves (SW) was a potential predictive parameter of psychiatric comorbidities and neuropsychological dimensions in ADHD. 70 children (8.76-¦2.77 y) with ADHD, with no epilepsy and no intellectual disabilities, underwent psychiatric and neurologic evaluation and were assessed through the CBCL 6-18, the CPRS-R, the WISC-IV rating scales, and a standard 10-20 EEG during naps. We grouped the extracted SW in bins of equal amplitude and then measured associations, through generalized linear regression, between their maximum downward slopes (MDS) and the clinical scores. Sorted by degree of significance: negative association between the Processing Speed Index and the MDS (0.30++V) in anterior and temporal right areas; positive association between the Processing Speed Index and the MDS (20.50++V) in temporal and posterior left areas; positive association between autistic traits and the MDS (50.90++V) in anterior and temporal left areas; negative association between internalizing symptoms (CBCL 6-18) and the MDS (0.40++V) in temporal and posterior left areas; positive association between comorbid multiple anxiety disorder and the MDS (50.60++V) in posterior and temporal left areas. Consistency of clusters'f localization suggests that alterations in local cortical synchronization, revealed by MDS, could underlie specific neurodevelopmental trajectories resulting in different ADHD clinical phenotypes

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Clin EEG Neurosci. 2022.

PHASE-AMPLITUDE COUPLING BRAIN NETWORKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Liu X, Sun L, Zhang D, et al.

In cognitive neuroscience, there is an increasing interest in identifying and understanding the synchronization of distinct neural oscillations with different frequencies that might support dynamic communication within the brain. This study explored the cross-frequency phase-amplitude coupling brain network characteristics of resting-state electroencephalograms between 30 children with attention-deficit/hyperactivity disorder (ADHD) and 30 age-matched typically developing children. Compared with control group, children with ADHD show increased coupling intensity and altered distribution patterns of dominant paired channels, especially in the δ-γH, θ-γH, α-γH, βL-γH, and βH-γH coupling networks. Regarding graph theory properties, the characteristic path length, the mean clustering coefficient, the global efficiency, and the mean local efficiency significant difference in many cross-frequency coupling networks, especially in the δ-γH, θ-γH, α-γH, βL-γH, and βH-γH coupling networks. The area under the receiver operating characteristic curve (AUC) in low-frequency coupling with a high-gamma frequency was larger than that in coupling with low-gamma frequency (AUC values of δ-γL, θ-γL, α-γL, βL-γL, βH-γL, δ-γH, θ-γH, α-γH, βL-γH, and βH-γH were 0.794, 0.722, 0.666, 0.570, 0.881, 0.992, 0.998, 0.998, 0.989, and 0.974, respectively). These findings demonstrate altered coupling intensity and disrupted topological organization of coupling networks, support the altered brain network theory in children with ADHD. The coupling intensity and graph theory properties of low-frequency coupling with high-gamma frequency were promising resting-state electroencephalogram biomarkers of ADHD in children

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Clin EEG Neurosci. 2022;53:NP4.

ASSESSMENT OF OSCILLATIONS AND ATTENTION IN ADHD.

Lenartowicz A.

One of the most powerful features of concurrent EEG-fMRI methodology is the complementary nature of signals recorded, offering the opportunity for a richer, more comprehensive perspective on neural systems. In this talk I will discuss new perspectives gained in our understanding of the attention system, through the analysis of network correlates of alpha-range (8-12 Hz) oscillations during working memory encoding, and their modifications in individuals with attention-deficit hyperactivity disorder (ADHD). I will discuss both insights gained regarding the neural circuitry of attention deficits and the knowledge gained in understanding the disorder behaviorally, considering broader progress in this research domain. As part of this effort, I will discuss the unique challenges and potential solutions of application of concurrent EEG-fMRI methodology to pediatric and neuropsychiatry populations

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Clin EEG Neurosci. 2022;53:NP2.

PATHOGENETIC ROLE OF BRAIN AROUSAL REGULATION IN AFFECTIVE DISORDERS AND ADHD.

Hegerl U, Jawinski P, Ulke C, et al.

The conceptual framework and empirical evidence for the pathogenetic role of arousal and wakefulness dysregulation in both affective disorders and ADHD will be presented. Converging evidence from preclinical as well as clinical studies indicate that in major depression (MD) an upregulated brain arousal and in ADHD an unstable brain arousal regulation play a central pathogenetic role. The hyperactivity and sensation seeking observed in overtired children, ADHD and mania is interpreted as an autoregulatory attempt of the organism to stabilize brain arousal level by increasing external stimulation. Correspondingly the withdrawal and sensation avoidance in MD is interpreted as a reaction to a state of tonically upregulated arousal. The EEG-based algorithm VIGALL 2.1 (Vigilance Algorithm Leipzig) allows to objectively assess the level as well as the regulation of brain arousal within a 20-minutes EEG recording under quiet rest. Further support for this concept is provided by a GWAS showing that the genetic variant most closely associated with upregulated brain arousal (assessed with VIGALL 2.1.) has also been found by others to be associated with depression. An upregulated brain arousal at baseline in major depression predicts response to antidepressants, and low arousal levels are related to hypomanic personality as well as to extraversion and openness to experience

in healthy subjects. Wakefulness regulation as assessed with VIGALL 2.1 is an important transdiagnostic, pathogenetic and response-predictive biomarker

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Clin Neurophysiol. 2022;135:e13.

EVALUATING SPATIAL CUING EFFECTS OF SOCIAL CUES IN CHILDREN WITH ADHD: PRE-TEST OF THREE VERSIONS OF A NEUROPSYCHOLOGICAL TOOL IN CHILDREN WITHOUT DISORDERS.

Haza B, Mersali J, Pinabiaux C, et al.

Our aim was to pre-test three versions of an evaluative tool designed to identify children with ADHD who are sensitive to cuing effects triggered by social cues (gaze and pointing finger). Method: Children without disorders, aged from 7 to 9 years, had to press a button as soon as an object appeared on the screen, at the left or the right of an individual. In two thirds of the trials, the side of the object appearance was cued by the individual either by deviating her gaze or by pointing with her finger. In the first version (19 children), these congruent trials were compared to neutral trials in which the individual did not move before the object appearance. In the second version (18 children), congruent trials were compared to moving trials in which the individual pointed her finger towards the children before the object appearance. In the third version (15 children), congruent trials were compared to incongruent trials in which the individual gazed or pointed towards the opposite side of the object appearance. Results: Congruent pointing finger triggered strong cuing effects compared to neutral, moving or incongruent trials. By contrast, the strength of the gaze cuing effect depended on the comparison trials. When compared to incongruent trials, congruent gazing and pointing led to similar and robust effects. Conclusion: The version manipulating incongruent trials, which controls for alerting effect induced by gaze or finger movements respectively, was the most appropriate to measure social cuing effects and was chosen to calibrate the tool

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Clin Pharmacol Ther. 2022;111:S10.

POPULATION PHARMACOKINETICS OF ATOMOXETINE AND ITS METABOLITES IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD).

Al-Kofahi M, Cheng S, Leeder S, et al.

BACKGROUND: Atomoxetine (ATX) is a non-stimulant used to treat attention-deficit/ hyperactivity disorder (ADHD), and is a substrate for cytochrome p450 2D6 (CYP2D6). Variation in CYP2D6 results in a range of function from poor to ultra-rapid metabolizers. The primary objective of this study was to characterize the time course of ATX and metabolites (4-hydroxyatomoxetine, 4-OH; N-desmethylatomoxetine, NDM; and 2-COOH, 2-carboxymethylatomoxetine) exposure following oral ATX dosing in children with ADHD.

METHODS: A nonlinear mixed-effect modeling approach was used to analyze ATX, 4-OH, NDM and 2-COOH plasma and urine concentrations obtained over 24 to 72 hours from children with ADHD (n = 23) following a single 0.5 mg/kg oral dose of ATX. Demographics, clinical factors, and CYP2D6 activity score (AS) were evaluated for their influence on ATX, 4-OH, NDM and 2-COOH.

RESULTS: A simultaneous PK approach was employed in which a model for plasma and urine ATX, 4-OH, NDM and 2-COOH was developed. Plasma ATX, 4-OH, and NDM were modeled using two-compartment models with first order elimination. CYP2D6 AS was a significant determinant of ATX bioavailability, fraction metabolized, and Cl/F as well as NDM Cl/F. Cl/F across the CYP2D6 AS groups were: AS 2: 19.04 L/h; AS 1: 18.02 L/h; AS 0.5: 6.49 L/hr; and AS 0: 2.12 L/hr. CYP2D6 normal metabolizers (AS = 2) had a 9-fold higher ATX clearance and a 20-fold higher NDM clearance compared to poor metabolizers (AS = 0).

CONCLUSION: The developed model closely captures observed ATX, 4-OH, NDM and 2-COOH plasma and urine concentrations. The 20-fold reduction in clearance of NDM in CYP2D6 poor metabolizers suggests that CYP2D6 is the primary enzyme responsible for this pathway

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CNS Spectr. 2022.

SEX DIFFERENCES IN PATIENTS WITH TOURETTE SYNDROME.

Baizabal-Carvallo JF, Jankovic J.

Background: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the presence of motor and phonic tics. It is at least three times more common in males" compared with females; however, the clinical phenomenology between sexes has not been" fully examined. We aimed to contrast the clinical features between males and females with" TS and chronic tic disorder."

Methods: We studied 201 consecutive patients fulfilling the diagnostic criteria for TS," persistent (or chronic) motor and vocal tic disorder and provisional tic disorder that were" considered within the TS spectrum disorder. We performed blinded evaluations of video-" recordings and retrospectively reviewed the clinical charts of all patients."

Results: Age ranges between 4-65 years. Males represented 77.6% of patients in the cohort. Overall, no differences were observed in the frequency, distribution and complexity of tics" between sexes, except for a higher frequency of ADHD (P=0.003) among males. Patients" younger than 18-years old, in addition to a higher frequency of ADHD (P=0.026), males" had a statistically higher frequency of complex motor tics (P=0.049) and earlier age at" onset (P=0.072) than females in the multivariate regression analysis. However, these differences were lost in patients older than 18 years, due to increased complexity of tics in" females with ageing."

Conclusions: A sexual dimorphism was observed between patients with TS mainly before" age of 18 years, suggesting an earlier onset of some types of tics and of ADHD in males" compared to females."

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Cogn Behav Pract. 2022.

FROM THE CLINIC TO SCHOOLS: ITERATIVE DEVELOPMENT OF A DEPRESSION PREVENTION PROGRAM FOR ADOLESCENTS WITH ADHD WITHIN AN URBAN SCHOOL SYSTEM.

Meinzer MC, Schwartz KTG, Triece P, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder, particularly among Black youth and youth in urban settings. In addition to well-documented academic and social dysfunction, ADHD is associated with increased risk for depression and suicide. However, there is a stark mismatch between services available and need among adolescents with ADHD, especially those from low-income backgrounds. Implementation of services in schools is one promising way to overcome barriers to care, decrease stigma associated with mental health care, and offer the ability to practice mental health skills in a more natural environment. As such, the current study aims to (a) describe the iterative development of a school-based depression prevention program (i.e., Behaviorally Enhancing Adolescents Mood in Schools [BEAMS]) for adolescents with ADHD in an underresourced, urban school district using stakeholder feedback; and (b) evaluate the preliminary effectiveness of an open trial of BEAMS. Raw data for all participants (n = 6; 83% Black, 17% biracial; 83% male) with indications for significant Reliable Change Indices are presented in addition to two case vignettes to illustrate treatment components and exemplify participant response. Pre- and posttreatment focus group data are presented to depict the development of the BEAMS program, lessons learned, and modifications made to BEAMS, in preparation for a larger randomized trial. Future directions are discussed

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Computers in Biology and Medicine. 2022;140.

AUTOMATED CLASSIFICATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND CONDUCT DISORDER USING ENTROPY FEATURES WITH ECG SIGNALS.

Koh JEW, Ooi CP, Lim-Ashworth NS, et al.

Background: The most prevalent neuropsychiatric disorder among children is attention deficit hyperactivity disorder (ADHD). ADHD presents with a high prevalence of comorbid disorders such as conduct disorder (CD). The lack of definitive confirmatory diagnostic tests for ADHD and CD make diagnosis challenging. The distinction between ADHD, ADHD + CD and CD is important as the course and treatment are different. Electrocardiography (ECG) signals may become altered in behavioral disorders due to brain-heart autonomic

interactions. We have developed a software tool to categorize ADHD, ADHD + CD and CD automatically on ECG signals.
Method: ECG signals from participants were decomposed using empirical wavelet transform into various modes, from which entropy features were extracted. Robust ten-fold cross-validation with adaptive synthetic sampling (ADASYN) and z-score normalization were performed at each fold. Analysis of variance (ANOVA) technique was employed to determine the variability within the three classes, and obtained the most discriminatory features. Highly significant entropy features were then fed to classifiers.
Results: Our model yielded the best classification results with the bagged tree classifier: 87.19%, 87.71% and 86.29% for accuracy, sensitivity and specificity, respectively.
Conclusion: The proposed expert system can potentially assist mental health professionals in the stratification of the three classes, for appropriate intervention using accessible ECG signals

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Dev Psychobiol. 2022 Apr;64:e22228.

ELECTROENCEPHALOGRAM APERIODIC POWER SPECTRAL SLOPE CAN BE RELIABLY MEASURED AND PREDICTS ADHD RISK IN EARLY DEVELOPMENT.

Karalunas SL, Ostlund BD, Alperin BR, et al.

The aperiodic exponent of the electroencephalogram (EEG) power spectrum has received growing attention as a physiological marker of neurodevelopmental psychopathology, including attention-deficit/hyperactivity disorder (ADHD). However, its use as a marker of ADHD risk across development, and particularly in very young children, is limited by unknown reliability, difficulty in aligning canonical band-based measures across development periods, and unclear effects of treatment in later development. Here, we investigate the internal consistency of the aperiodic EEG power spectrum slope and its association with ADHD risk in both infants (n = 69, 1-month-old) and adolescents (n = 262, ages 11-17 years). Results confirm good to excellent internal consistency in infancy and adolescence. In infancy, a larger aperiodic exponent was associated with greater family history of ADHD. In contrast, in adolescence, ADHD diagnosis was associated with a smaller aperiodic exponent, but only in children with ADHD who had not received stimulant medication treatment. Results suggest that disruptions in cortical development associated with ADHD risk may be detectable shortly after birth via this approach. Together, findings imply a dynamic developmental shift in which the developmentally normative flattening of the EEG power spectrum is exaggerated in ADHD, potentially reflecting imbalances in cortical excitation and inhibition that could contribute to long-lasting differences in brain connectivity

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Dev Med Child Neurol. 2022;64:12.

MUTATIONS ENCODING DOPAMINE RECEPTORS CAUSE COMPLEX CHILDHOOD-ONSET HYPERKINETIC DISORDERS.

Reid KM, Steel DBD, Barwick KES, et al.

Objective: Dopamine receptors, especially D1 (encoded by DRD1) and D2 (encoded by DRD2) are a key component of the neurological networks controlling voluntary movement. Until 2021, however, no monogenic disorders associated with their malfunction had been reported. We describe the first family affected by disease due to a DRD1 variant, and another due to DRD2.
Methods: Whole-genome sequencing was performed in a cohort of well-phenotyped patients with movement disorders believed to be genetic in origin. In silico prediction tools and structure-function modelling were used to predict impact of candidate variants. For DRD1, over-expression of the variant in HEK-293T cells was used to assess production of the receptor protein by Western blotting, cell-membrane localisation by biotinylation and immunofluorescence, and ligand binding response by luminescence-based measurement of cAMP production. For DRD2, case matching confirmed the relevance of the variant.
Results: In a child with a phenotype strongly suggestive of dysfunction of the dopaminergic system (generalised dystonia, oculogyric crises), but with normal neurotransmitter levels, a homozygous missense variant in DRD1 was identified (c.110C>A; p.Thr37Lys). Functional investigations confirmed near-normal cellular protein levels and appropriate localisation to the cell surface membrane; however, second-messenger (cAMP) production in response to dopamine binding was significantly reduced compared with the wild-type, confirming a functional deficiency of the mutant protein. A heterozygous missense variant (c.1121-T->-G; p.Met374Arg) in DRD2 was identified in a female with an infant-onset choreiform disorder

and neurodevelopmental delay. The same variant, predicted to cause gain of function, was identified by another team in an unrelated individual with matching clinical features.
Conclusion: Variants in DRD1 and DRD2 are associated with characteristic movement disorders. It is reasonable to speculate that additional phenotypes - involving gain-of-function in DRD1 and loss-of-function in DRD2 - may be identified in future. Identification of these new genetic syndromes is a first step towards developing targeted therapies

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Drug Metabolism and Personalized Therapy. 2022.
CYP450 2D6 AND 2C19 GENOTYPES IN ADHD: NOT RELATED WITH TREATMENT RESISTANCE BUT WITH OVER-REPRESENTATION OF 2C19 ULTRA-METABOLIZERS.
Kutuk MO, Tufan AE, Topal Z, et al.
Cytochrome P450 (CYP450) is a major enzyme system involved in drug metabolism as well as regulation of brain function. Although individual variability in CYP enzymes have been studied in terms of personality traits and treatment effects, no study up to now evaluated CYP polymorphisms in children with attention deficit/hyperactivity disorder (ADHD). We aimed to define the genetic profiles of CYP2D6 and CYP2C19 relevant alleles in children with ADHD according to treatment status and compare the frequencies according to past results. Three hundred and seventeen patients with ADHD-Combined Presentation were enrolled; symptom severity was evaluated by parents and clinicians while adverse effects of previous treatments were evaluated with parent and child reports. Reverse blotting on strip assays was used for genotyping and descriptive and bivariate analyses were conducted. A p-value was set at 0.05 (two-tailed). Children were divided into treatment-na+»ve (n=194, 61.2%) and treatment-resistant (n=123, 38.8%) groups. Within the whole sample PM, EM and UM status according to 2D6 were 3.8% (n=12), 94.3% (n=299) and 21.9% (n=6); respectively. PM, IM, EM and UM status according to 2C19 were 2.5% (n=8), 19.8% (n=63), 48.6% (n=154) and 29.0% (n=92), respectively. No relationship with treatment resistance, comorbidity or gender could be found. Importantly, CYP2C19 UMs were significantly more frequent in ADHD patients compared to previous studies in the general population. CYPs may be a rewarding avenue of research to elucidate the etiology and treatment of patients with ADHD

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Egypt J Neurol , Psychiatr Neurosurg. 2022;58.
STUDY OF SERUM NEOPTERIN IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISTIC SPECTRUM DISORDER: FAYOUM GOVERNORATE, EGYPT.
Abdel Ghaffar HMGE, Abdelghaffar NK, Ahmed HH, et al.
Background: There is evidence supporting that cellular immunity may play a role in the pathophysiology of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Neopterin, a pteridine mainly synthesized by activated macrophages, is a marker of inflammation, immune system activation that may be involved in the pathophysiology of both disorders.
Methods: Fifty drug-naïve patients were diagnosed according to DSM-5 (25 with ASD, 25 with ADHD), in addition to 25 healthy volunteers matched in age and gender with the patients were included. The CARS, Conners' scales used to assess the severity of the disorders, respectively. Serum neopterin level was measured using ELISA technique for all participants.
Results: Statistically nonsignificant difference in mean neopterin level between control and both patients groups with significant negative correlation between neopterin level and younger ages in ASD group were found. Statistically nonsignificant difference also was found between its levels among subtypes of ADHD as well and with the degree of ASD symptoms severity.
Conclusions: There was no statistically significant difference between serum neopterin level in ADHD, ASD patients groups and control group reference

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Encephale. 2022.

ADHD AND ADDICTIVE BEHAVIOR IN CRACK-COCAINE USERS.

Fond G, El-Maamar M, Korchia T, et al.

Background: Crack consumption is a major public health issue in Martinique with a poor prognosis. A preliminary study has found a high prevalence of history of childhood ADHD (C-ADHD) in crack users. Objective: To determine the prevalence of C-ADHD and adult ADHD (A-ADHD) in crack users and their potential associations with substance use behavior.

Methods: All consecutive patients consulting in the public academic hospital covering 376,000 inhabitants were included in the present study and received a comprehensive battery measuring addictive behavior, psychiatric and somatic comorbidities. C-ADHD groups and A-ADHD groups were defined with the Wender-Utah Rating Scale-25 and the Brown ADD Rating Scale, respectively. Impulsivity was evaluated with the Barratt Impulsiveness Scale (BIS-11).

Findings: In total, 111 participants were evaluated. Among them, 50 (45%) were classified in the C-ADHD group and 20 (18%) in the A-ADHD group. Compared to the patients without ADHD, those with ADHD were found to have higher impulsivity (C-ADHD: BIS total score 67.90 (10.1) vs. 63.28 (10.5), P = 0.021, BIS attentional score 17.5 (3.6) vs. 15.3 (3.4), P = 0.002, A-ADHD: BIS total score 75.1 (11.3) vs. 63.4 (9.2), P < 0.001, BIS motor impulsivity 26.9 (5.3) vs. 22.6 (4.3), P < 0.001, BIS attentional score 19.3 (3.3) vs. 15.6 (3.5), P < 0.001, BIS planification 28.9 (5.7) vs. 25.10 (4.7), P = 0.003). Fifty percent of A-ADHD patients were found with high impulsivity vs. 15% of patients without A-ADHD (P < 0.001). However, ADHD was not associated with more severe addictive behavior or history of legal consequences.

Interpretation: ADHD prevalence is high in cocaine-crack users and associated with increased impulsivity. However, neither ADHD nor impulsivity explains addictive behaviors or legal consequences

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Environ Int. 2022;161.

NEIGHBORHOOD ENVIRONMENTAL EXPOSURES AND INCIDENCE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A POPULATION-BASED COHORT STUDY.

Yuchi W, Brauer M, Czekajlo A, et al.

Background: Emerging studies have associated low greenspace and high air pollution exposure with risk of child attention deficit/hyperactivity disorder (ADHD). Population-based studies are limited, however, and joint effects are rarely evaluated. We investigated associations of ADHD incidence with greenspace, air pollution, and noise in a population-based birth cohort.

Methods: We assembled a cohort from administrative data of births from 2000 to 2001 (N Γê+ 37,000) in Metro Vancouver, Canada. ADHD was identified by hospital records, physician visits, and prescriptions. Cox proportional hazards models were applied to assess associations between environmental exposures and ADHD incidence adjusting for available covariates. Greenspace was estimated using vegetation percentage derived from linear spectral unmixing of Landsat imagery. Fine particulate matter (PM2.5) and nitrogen dioxide (NO2) were estimated using land use regression models; noise was estimated using a deterministic model. Exposure period was from birth until the age of three. Joint effects of greenspace and PM2.5 were analysed in two-exposure models and by categorizing values into quintiles.

Results: During seven-year follow-up, 1217 ADHD cases were diagnosed. Greenspace was associated with lower incidence of ADHD (hazard ratio, HR: 0.90 [0.81-0.99] per interquartile range increment), while PM2.5 was associated with increased incidence (HR: 1.11 [1.06-1.17] per interquartile range increment). NO2 (HR: 1.01 [0.96, 1.07]) and noise (HR: 1.00 [0.95, 1.05]) were not associated with ADHD. There was a 50% decrease in the HR for ADHD in locations with the lowest PM2.5 and highest greenspace exposure, compared to a 62% increase in HR in locations with the highest PM2.5 and lowest greenspace exposure. Effects of PM2.5 were attenuated by greenspace in two-exposure models.

Conclusions: We found evidence suggesting environmental inequalities where children living in greener neighborhoods with low air pollution had substantially lower risk of ADHD compared to those with higher air pollution and lower greenspace exposure

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Eur Arch Psychiatry Clin Neurosci. 2022.

EMERGING FINDINGS OF GLUTAMATE-GLUTAMINE IMBALANCE IN THE MEDIAL PREFRONTAL CORTEX IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: SYSTEMATIC REVIEW AND META-ANALYSIS OF SPECTROSCOPY STUDIES.

Vidor MV, Panzenhagen AC, Martins AR, et al.

One of the main challenges in investigating the neurobiology of ADHD is our limited capacity to study its neurochemistry in vivo. Magnetic resonance spectroscopy (MRS) estimates metabolite concentrations within the brain, but approaches and findings have been heterogeneous. To assess differences in brain metabolites between patients with ADHD and healthy controls, we searched 12 databases screening for MRS studies. Studies were divided into children and adolescents and adults and meta-analyses were performed for each brain region with more than five studies. The quality of studies was assessed by the Newcastle-Ottawa Scale. Thirty-three studies met our eligibility criteria, including 874 patients with ADHD. Primary analyses revealed that the right medial frontal area of children with ADHD presented higher concentrations of a composite of glutamate and glutamine ($p = 0.02$, SMD = 0.53). Glutamate might be implicated in pruning and neurodegenerative processes as an excitotoxin, while glutamine excess might signal a glutamate depletion that could hinder neurotrophic activity. Both neuro metabolites could be implicated in the differential cortical thinning observed in patients with ADHD across all ages. Notably, more homogeneous designs and reporting guidelines are the key factors to determine how suitable MRS is for research and, perhaps, for clinical psychiatry. Results of this meta-analysis provided an overall map of the brain regions evaluated so far, addressed the role of glutamatergic metabolites in the pathophysiology of ADHD, and pointed to new perspectives for consistent use of the tool in the field

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Eur Arch Psychiatry Clin Neurosci. 2022.

CLINICAL CHARACTERISTICS OF CHILDREN AND ADOLESCENTS WITH ADHD WITH OR WITHOUT METHYLPHENIDATE PRESCRIPTION AT THEIR FIRST DIAGNOSTIC ASSESSMENT.

De Rossi P, Pretelli I, Menghini D, et al.

Attention Deficit/Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder diagnosed in the scholar age. It is associated with significant impairment in global functioning, and in moderate/severe presentations the outcome is critically dependent on pharmacological optimization of the multi-modal treatment. Methylphenidate (MPH) is the first-choice pharmacological treatment in children and adolescents with ADHD, with substantial evidence of significant efficacy and effectiveness on global functioning and symptomsΓÇÖ severity. There is some evidence supporting a few clinical and socio-demographic variables as predictors of pharmacological treatment prescription in children with ADHD independently of ADHD symptoms severity. However, it is warranted to investigate clinical and general psychopathological characteristics potentially associated with negative outcomes and the need for pharmacological treatment to inform appropriate prescription strategies. In this context, we compared 268 children and adolescents who were prescribed MPH (ADHD/MPH) for the first time after their first diagnostic assessment at our center, and 444 children and adolescents with ADHD (ADHD/noMPH) who were recommended non-pharmacological evidence-based interventions alone. ADHD/MPH group had higher severity of non-ADHD psychopathological symptoms compared to the ADHD/noMPH group, as documented by higher scores on the Child Behavior Checklist (CBCL) subscales, higher severity of ADHD symptoms, lower average IQ and lower adaptive levels independently of IQ. More specifically, beside externalizing symptoms, also internalizing symptoms were significantly higher in the ADHD/MPH group. The presence of significant non-ADHD psychopathology should be considered as a clinical factor associated with the need for MPH prescription in children and adolescents with ADHD

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Eur Child Adolesc Psychiatry. 2022.

ASSOCIATION BETWEEN PRETERM INFANT SIZE AT 1-ÁYEAR AND ADHD LATER IN LIFE: DATA FROM 1993 AND 2004 PELOTAS BIRTH COHORTS.

Soldateli B, Silveira RC, Procianoy RS, et al.

The objective of this study is to examine the association between preterm infantsΓÇÖ size at 1 year and attention-deficit/hyperactivity disorder (ADHD) assessed categorically and dimensionally in childhood and

adolescence. We studied infants born < 37-áweeksΓÇÖ gestation from two Brazilian birth cohorts (n = 653). ADHD was evaluated using the Development and Well-Being Assessment (DAWBA) interview at the age of 6-áyears in one cohort and by a structured interview according to-áDSM-5 criteria at 18-áyears in the other one. The presence of child attention difficulties was measured by the Strengths and Difficulties Questionnaire (SDQ) at 6 and 11-áyears in the 2004 and 1993 cohorts, respectively. We estimated associations of weight, length, head circumference, and BMI z-scores at 1-year chronological age with ADHD using Poisson Regression Model; and with attention difficulties using Linear Regression, adjusting for covariates. Mean birth weight was 2500-ág and gestational age was 34.5-áweeks. The aggregated ADHD prevalence in the two cohorts was 2.7%, and the median score for attention difficulties was 3.0. We found that increased head circumference at 1 year was associated with a lower risk of ADHD diagnosis (RR = 0.7, 95% CI 0.4, 0.9; p = 0.04 per standard deviation difference) and with fewer dimensional attention symptoms. In sensitivity analysis with other mental disorders, head circumference was associated with depression, but not with anxiety. Our findings emphasize poor head growth in the first year of life as a potential determinant of attentional difficulties in the preterm infant population

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European Journal of Health Psychology. 2022 Feb.

ADHD SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE OF ADOLESCENTS AND YOUNG ADULTS.

Krauss A, Schellenberg C.

Background: Adolescence and young adulthood present particularly challenging periods for individuals affected by attention-deficit hyperactivity disorder (ADHD) symptoms. However, unlike childhood ADHD, ADHD among adolescents and young adults has been studied less frequently. A concept that can be used to characterize the experiences of individuals with ADHD symptoms is health-related quality of life (HRQoL), which encompasses well-being in various dimensions.

Aims: The present study used a school-based sample in the German-speaking part of Switzerland to investigate the association between ADHD symptoms and HRQoL of adolescents and young adults. Method: A total of 907 individuals aged 14–24 years (M = 17.69; SD = 1.66; 58.9% female) were surveyed regarding ADHD symptoms and HRQoL.

Results: Multiple hierarchical regression analyses disclosed that ADHD symptoms were negatively related to all subdimensions of HRQoL. Moreover, adolescents with clinically significant or subclinical ADHD symptoms showed lower values in all examined dimensions—physical, emotional, self-esteem, family, friends/peers, and school/education—than adolescents with unremarkable ADHD symptoms. An exception was the well-being concerning friends/peers.

Limitations: The present study used a cross-sectional design and a selective sample of school classes. ADHD symptoms were assessed using self-reports without any diagnostic judgment.

Conclusion: The results illustrate the comprehensive effects of ADHD symptoms on well-being during adolescence and young adulthood. They highlight the importance of focusing more on ADHD during these stages of age, also considering individuals with symptoms in the subclinical range

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Europ J Spec Needs Educ. 2022.

WHAT INFLUENCES DO PARENTS PERCEIVE AS SUPPORTIVE OF SCHOOL WELL-BEING AND THE INCLUSION OF CHILDREN WITH ADHD?: A QUALITATIVE STUDY.

Krtkova R, Krtek A, Pesoutova M, et al.

A growing body of a literature recognises the importance of special educational needs (SEN) of adolescents with attention-deficit/hyperactivity disorder (ADHD). Therefore, there is a current need for more in-depth insights into the factors that may help meet the SEN, well-being, and educational inclusion of ADHD students. The aim of this qualitative study was to assess the factors that parents perceive as being helpful for the school well-being, adaptation, and inclusion of their ADHD adolescents. The sample comprised 20 parents, aged from 30 to 60-áyears old, of ADHD adolescents. From the viewpoint of the parents, the teachersΓÇÖ knowledge of ADHD symptoms, the use of educational methods respecting the determination of ADHD, special school aids and equipment, and the help of various professionals and psychotherapy with social skills training were considered to be supportive for school well-being and the inclusion of ADHD adolescents.

Practical implications emerging from the results of the present study involve training focused on the development of secure attachment of teachers, awareness-raising campaigns about ADHD, and activities supporting teacher-parent cooperation

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European Thyroid Journal. 2019;8:86.

ATTENTION DEFICIT HYPERACTIVITY DISORDER, HYPERTHYROIDISM OR SOMETHING ELSE?

Yafi M.

The Case: A seven- year- old female had a history of early onset and severe attention deficit hyperactivity disorder (ADHD). A thyroid function test was obtained and showed elevated TSH and T4. The mother was told that hyperactivity was related to hyperthyroidism and was referred for a formal evaluation. The patient was not taking any medication and had no allergies. The family history was significant for hyperthyroidism in maternal grandmother and an unexplained case of thyroidectomy in maternal uncle. On physical examination, vital signs were normal; the weight was at 30th percentile while the height was at 40th percentile. There was no thyromegaly or tachycardia. Tanner Staging was I.

Laboratory work up showed: TSH 23.5 UIU/ml (normal range 0.5-4.5) T4 19.2 ugl/dl (normal range 4.5-12) Free T4 2.4 ng/dl (normal range 0.8-1.6) All levels of Antithyroid Peroxidase antibodies (Anti TPO), Thyroid Stimulating Immunoglobin (TSI) and Antithyroiglobulin (anti TG) were within normal range. Based on symptomatology and thyroid function test, the diagnosis of thyroid resistance was suspected. An MRI of the pituitary gland showed no pituitary adenoma. Genetic testing showed a heterozygous thyroid hormone receptor +¦ (THRB) gene mutation confirming the diagnosis. The mother was educated about this diagnosis; she revealed that many family members have had brain MRIs for the same suspicion. The patient was referred for behavioral therapy and special education school.

Discussion: Evaluation of thyroid axis is often performed in children with attention deficit-hyperactivity disorder. The result of thyroid tests should be evaluated based on the child's age -specific normal range and clinical symptoms. Attention deficit-hyperactivity disorder has been often associated with RTH. Resistance to the Thyroid Hormone (RTH) is a very rare disorder. This can be at the level of peripheral tissues, pituitary or both (glob al resistance). The symptoms of RTH may include same feature of hypo and hyperthryoidism based on affected tissues. Delayed bone maturation, learning disabilities and even mental retardation can be some features. The diagnosis of RTH is complicated and often misinterpreted as hyperthyroidism or pituitary adnoma, resulting in unnecessary therapy. Specific molecular genetic testing can confirm the diagnosis and understand the specific tissue related level of resistance. There are many reported genetic defects that can cause resistance to TH. Therapy is nonspecific, many therapeutic approach aim to control the symptoms of hyperthyroidism especially to control heart rate but generally speaking, there is no successful treatment for RTH itself

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Fertility and Sterility. 2022.

THE NEURODEVELOPMENTAL MORBIDITY OF CHILDREN BORN AFTER ASSISTED REPRODUCTIVE TECHNOLOGY: A NORDIC REGISTER STUDY FROM THE COMMITTEE OF NORDIC ASSISTED REPRODUCTIVE TECHNOLOGY AND SAFETY GROUP.

Rono K, Rissanen E, Bergh C, et al.

Objective: To assess the risk of neurodevelopmental disorders in singletons born after the use of assisted reproductive technology (ART) compared with singletons born without the use of ART.

Design: Nordic register-based study. Setting: Cross-linked data from Medical Birth Registers and National ART and Patient Registers; liveborn singletons in 1995-2014 in Denmark and Finland, 2005-2015 in Norway, and 1995-2015 in Sweden with follow-up to 2014 (Denmark and Finland) or 2015 (Norway and Sweden).

Patients: A total of 5,076,444 singletons: 116,909 (2.3%) born with and 4,959,535 (97.7%) born without the use of ART (non-ART). Interventions: In vitro fertilization, intracytoplasmic sperm injection, and fresh and frozen embryo transfer.

Main Outcome Measures: The primary outcomes (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, codes) were learning and motor functioning disorders (F80-F83), autism spectrum disorder (F84), attention-deficit/hyperactivity disorder and conduct disorders (F90-F92), and

tic disorders (F95). Crude hazard ratios (HRs) and adjusted hazard ratios (aHRs) with 95% confidence intervals were calculated.
Results: Singletons in the ART cohort had a higher adjusted risk of learning and motor functioning disorders (HR, 1.01 [0.96-1.07]; aHR, 1.17 [1.11-1.24]) and a tendency toward a higher risk of autism spectrum disorder (HR, 1.12 [1.04-1.21]; aHR, 1.07 [0.98-1.16]) and attention-deficit/hyperactivity disorder and conduct disorders (HR, 0.82 [0.77-0.86]; aHR, 1.17 [0.99-1.12]) but not of tic disorders (HR, 1.21 [1.06-1.38]; aHR, 1.17 [0.96-1.27]). No differences in risk were found between children born after in vitro fertilization and intracytoplasmic sperm injection or after fresh and frozen embryo transfer. Conclusions: Our findings of only small differences in neurodevelopment between ART and non-ART singletons are reassuring and in line with previous studies

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Front Human Neurosci. 2022 Feb;16.

PRIMARY SCHOOL CHILDREN'S SELF-REPORTS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER-RELATED SYMPTOMS AND THEIR ASSOCIATIONS WITH SUBJECTIVE AND OBJECTIVE MEASURES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Slobodin O, Davidovitch M.

Background: The diagnosis of Attention deficit hyperactivity disorder (ADHD) is primarily dependent on parents' and teachers' reports, while children's own perspectives on their difficulties and strengths are often overlooked. Goal: To further increase our insight into children's ability to reliably report about their ADHD-related symptoms, the current study examined the associations between children's self-reports, parents' and teachers' reports, and standardized continuous performance test (CPT) data. We also examined whether the addition of children's perceptions of ADHD-symptoms to parents' and teachers' reports would be reflected by objective and standardized data.
Methods: The study included 190 children with ADHD, aged 7–10 years, who were referred to a pediatric neurologic clinic. A retrospective analysis was conducted using records of a clinical database. Obtained data included children's self-reports of their attention level and ADHD-related symptoms, parent, and teacher forms of the Conners ADHD rating scales, Child Behavior Checklist (CBCL), Teacher's Report Form (TRF), and CPT scores.
Results: Children's self-evaluations of their functioning were globally associated with their teachers' and parents' evaluations, but not uniquely. Children's self-reports of ADHD symptoms were not uniquely linked to a specific CPT impairment index, but to a general likelihood of having an impaired CPT. The CPT performance successfully distinguished between the group of children who defined themselves as inattentive and those who did not.
Conclusion: Primary school children with ADHD are able to identify their limitations and needs difficulties and that their perspectives should inform clinical practice and research. The clinical and ethical imperative of taking children's perspectives into account during ADHD diagnosis and treatment is highlighted

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Frontiers in Medicine. 2022;8.

METHYLPHENIDATE USE AND INFECTIOUS DISEASES IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: A POPULATION-BASED STUDY.

Chen VCH, Kao KL, Chen YL, et al.

Objective: Children with attention deficit hyperactivity disorder (ADHD) have more visits to the emergency department (ED) due to injuries than those without ADHD. However, no study has investigated whether children with ADHD have more ED visits or hospitalizations due to infectious diseases (IDs) and whether methylphenidate (MPH) treatment may reduce the risk.
Method: The incidence of ID-related ED visits or hospitalizations was defined as the main outcome. The Cox regression and conditional Poisson regression models were calculated to estimate hazard ratios (HRs) in the population level and relative risks for the self-controlled case series design, respectively.
Results: Children with ADHD had higher rates of emergency visits (HR = 1.25, 95% CI: 1.23~1.27) and hospitalizations (HR = 1.28, 95% CI: 1.26~1.31) due to IDs than those without ADHD. In the ADHD subgroup, those who received MPH treatment have a reduced risk of emergency visits (HR = 0.10, 95% CI: 0.09~0.10)

and hospitalizations (HR = 0.73, 95% CI: 0.71~0.75), compared to those without treatment. The risk of ID-related emergency visits decreased to 0.21 (95% CI: 0.21~0.22); and hospitalizations decreased to 0.71 (95% CI: 0.69~0.73). Within self-controlled analysis, it is demonstrated that compared with non-MPH exposed period, children with ADHD had significantly decreased risks for infection-related emergency visits (RR = 0.73, 95% CI: 0.68~0.78) or hospitalizations (RR = 0.19, 95% CI: 0.17~0.21) during MPH-exposed periods.

Conclusions and Relevance: This is the first study that reported an increased risk of ID-related healthcare utilizations in children with ADHD compared to those without, and that such risks may be significantly reduced in ADHD children that received MPH treatment

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Frontiers in Neuroscience. 2022;15.

ASSOCIATION OF EPIGENETIC DIFFERENCES SCREENED IN A FEW CASES OF MONOZYGOTIC TWINS DISCORDANT FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH BRAIN STRUCTURES.

Fujisawa TX, Nishitani S, Makita K, et al.

The present study examined the relationship between DNA methylation differences and variations in brain structures involved in the development of attention-deficit hyperactivity disorder (ADHD). First, we used monozygotic (MZ) twins discordant (2 pairs of 4 individuals, 2 boys, mean age 12.5 years) for ADHD to identify candidate DNA methylation sites involved in the development of ADHD. Next, we tried to replicate these candidates in a case-control study (ADHD: N = 18, 15 boys, mean age 10.0 years; Controls: N = 62, 40 boys, mean age 13.9 years). Finally, we examined how methylation rates at those sites relate to the degree of local structural alterations where significant differences were observed between cases and controls. As a result, we identified 61 candidate DNA methylation sites involved in ADHD development in two pairs of discordant MZ twins, among which elevated methylation at a site in the sortilin-related Vps10p domain containing receptor 2 (SorCS2) gene was replicated in the case-control study. We also observed that the ADHD group had significantly reduced gray matter volume (GMV) in the precentral and posterior orbital gyri compared to the control group and that this volume reduction was positively associated with SorCS2 methylation. Furthermore, the reduced GMV regions in children with ADHD are involved in language processing and emotional control, while SorCS2 methylation is also negatively associated with emotional behavioral problems in children. These results indicate that SorCS2 methylation might mediate a reduced GMV in the precentral and posterior orbital gyri and therefore influence the pathology of children with ADHD

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Frontiers in Neuroscience. 2022;15.

IDENTIFICATION AND CHARACTERIZATION OF INFLUENTIAL FACTORS IN SUSCEPTIBILITY TO ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG PRESCHOOL-AGED CHILDREN.

Deng X, Yang M, Wang S, et al.

Attention deficit hyperactivity disorder (ADHD) is the most common childhood-onset neurodevelopmental disorder. Currently, increasing amounts of attention have been focused on the epidemiologic profiling of ADHD in children, viewed as a continuously distributed risk dimension throughout the whole lifespan. This study aimed to identify and characterize potential influential factors susceptible to ADHD-related symptoms among preschool-aged children. A comprehensive questionnaire was self-designed for both children and their parents or guardians and was distributed to 30 kindergartens from Beijing and Hebei, collecting potential influential factors in susceptibility to ADHD. ADHD was assessed by the ConnerΓÇÖs Abbreviated Symptom Questionnaire (C-ASQ), and 7,938 children were analyzed. Least absolute shrinkage and selection operator (LASSO) regression and hierarchical degree of adjustment were used to control possible covariates. Five factors, namely, childrenΓÇÖs secondhand smoking exposure, breastfeeding duration, sleep mode, maternal pregnancy smoking exposure, and parental self-rating for patience, were identified to be independently and significantly associated with ADHD susceptibility. Meanwhile, doseΓÇôresponse relationships were observed between breastfeeding duration, parental self-rating for patience, and ADHD-related symptoms. Finally, a nomogram model was created for predicting ADHD susceptibility based on significant and conventional attributes under each criterion

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Frontiers in Pediatrics. 2022;9.

EFFECTS OF COMBING GROUP EXECUTIVE FUNCTIONING AND ONLINE PARENT TRAINING ON SCHOOL-AGED CHILDREN WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.

Chu L, Zhu P, Ma C, et al.

Objective: The acceptance of drug treatment for younger children with attention-deficit/hyperactivity disorder (ADHD) in China remains low. Here, we explored the clinical benefits of a non-pharmaceutical intervention method combining a group and executive function training and an online parent training program, termed group executive functioning and online parent training (GEF-OPT), for school-aged students with ADHD through a randomized controlled trial.

Method: A total of 145 children (aged 6-8 years) were formally registered and randomized to the intervention group (n = 73) and waitlist group (n = 72). The enrolled children received eight sessions of GEF-OPT treatment, which consists of a hospital-based children executive function (EF) training program and an online parent training program. Treatment outcome was assessed by a parent/teacher report questionnaire and neurophysiological experiment.

Results: After eight sessions of intervention, children in the intervention group showed a significant improvement in inattentive symptom compared to the waitlist group (14.70 -¦ 4.35 vs. 16.03 -¦ 2.93; p = 0.024), but an insignificant difference in hyperactive-impulsivity (9.85 -¦ 5.30 vs. 10.69 -¦ 5.10; p = 0.913). Comorbid oppositional defiant disorder was significantly reduced in the intervention group (7.03 -¦ 4.39 vs. 8.53 -¦ 4.41; p = 0.035). Children in the intervention group had greater reduction in the scores of behavioral regulation index (inhibition, emotional control) and metacognition index (working memory, planning/organization, monitoring) in executive function than those in the waitlist group (p < 0.05). Significant effects were also found in learning problem of Weiss Functional Impairment ScaleΓÇôParent form and parental distress between two groups at post-treatment (p < 0.05). In line with this, the result of go/no-go task showed significant improvements in accuracy change (4.45 -¦ 5.50% vs. 1.76 -¦ 3.35%; p = 0.001) and reaction time change (47.45 -¦ 62.25 s vs. 16.19 -¦ 72.22 s; p = 0.007) in the intervention group compared with the waitlist group.

Conclusion: We conclude that participants in the GEF-OPT program improved outcomes for inattentive symptom, executive function, learning problems, and parental distress. GEF-OPT is a promising non-pharmaceutical therapeutic option for younger children.

Trial Registration: ChiCTR2100052803

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Front Psychiatry. 2022;12.

THE MECHANISM, CLINICAL EFFICACY, SAFETY, AND DOSAGE REGIMEN OF ATOMOXETINE FOR ADHD THERAPY IN CHILDREN: A NARRATIVE REVIEW.

Fu D, Wu DD, Guo HL, et al.

Atomoxetine, a selective norepinephrine (NE) reuptake inhibitor, was approved for attention deficit/hyperactivity disorder (ADHD) treatment in children, adolescents and adults. We searched the database PubMed/MEDLINE (2000 to October 1, 2021). Only publications in English were considered. Atomoxetine inhibits the presynaptic norepinephrine transporter (NET), preventing the reuptake of NE throughout the brain along with inhibiting the reuptake of dopamine in specific brain regions such as the prefrontal cortex (PFC). The novel mechanism of atomoxetine also includes several new brain imaging studies and animal model studies. It is mainly metabolized by the highly polymorphic drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Atomoxetine is effective and generally well tolerated. ADHD is often accompanied by multiple comorbidities. A series of studies have been published suggesting that atomoxetine is effective in the treatment of ADHD symptoms for children with various types of comorbidity. In some cases, it is possible that atomoxetine may have a positive influence on the symptoms of comorbidities. Atomoxetine can be administered either as a single daily dose or split into two evenly divided doses, and has a negligible risk of abuse or misuse. The latest guideline updated that clinical dose selection of atomoxetine was recommended based on both CYP2D6 genotype and the peak concentration. To have a more comprehensive understanding of atomoxetine, this review sets the focus on the mechanism, clinical efficacy and dosage regimen in detail, and also touches on those studies regarding adverse reactions of atomoxetine

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Front Psychiatry. 2022;13.

SELF-MEDICATION OF ADHD SYMPTOMS: DOES CAFFEINE HAVE A ROLE?

Agoston C, et al.

Objective: Stimulants are the most effective treatment for Attention Deficit/ Hyperactivity disorder (ADHD). In addition, studies have shown that nicotine dependence in patients with ADHD is probably best explained by self-medication. The question is whether this is also true for caffeine use and caffeine dependence. The aim of our study was, therefore, to examine the relationship of ADHD symptoms, caffeine consumption, caffeine use disorder (CUD) and well-being. We hypothesized that those who have more ADHD symptoms and regularly consume caffeine have higher psychological well-being than those who have more ADHD symptoms, but do not consume caffeine.

Methods: A general population sample (N = 2,259, 70.5% male, mean age 34.0) filled out the 10-item Caffeine Use Disorder Questionnaire (CUDQ), the Adult ADHD Self-report Scale (ASRS) and the WHO-5 Well-Being Index (WHO-5) and were asked about their caffeine consumption habits in an online survey.

Results: There were no associations between ADHD and coffee, tea, energy drink or cola consumption or daily caffeine consumption. However, the results of the path analysis showed that the level of ADHD symptoms was positively associated with the level of CUD (+¦ = 0.350) and negatively with the WHO-5 (+¦ = ΓêÆ0.259).

Conclusions: Caffeine consumption was not associated with ADHD symptom severity and thus not likely to represent self-medication. On the contrary, caffeine use disorder severity is associated with more ADHD symptoms and both caffeine use disorder and ADHD are associated with lower well-being

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Front Psychiatry. 2022;12.

UTILIZATION OF DRUGS FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER AMONG YOUNG PATIENTS IN CHINA, 2010-2019.

Wang Z, Wu X, Yu Z, et al.

Objective: The use of attention-deficit hyperactivity disorder (ADHD) medication is increasing worldwide, but its status in China is unknown. This research aimed to assess the trends of ADHD medication use in young Chinese patients between 2010 and 2019.

Methods: Dispensing data related to ADHD medication use were extracted from the Hospital Prescription Analysis Cooperative Project of China. The trends in the yearly prescription number of ADHD drugs and corresponding cost were analyzed. We further stratified the data by age, sex, and specific drug.

Results: From 2010 to 2019, sampled prescriptions for ADHD medication increased from 902 to 4531, and the total expenditure increased rapidly from 276,580 to 2,412,308 Chinese Yuan. Prescriptions for males were almost fourfold more than that for females. Patients aged 6ΓÇô11 years had the highest number of prescriptions for ADHD medication each year, accounting for more than 50% of the total number of prescriptions. The percentage of methylphenidate prescriptions decreased from 91.9% in 2010 to 76.9% in 2019, and the corresponding cost declined from 77.3% to 66.8%. In contrast, atomoxetine prescriptions increased progressively and accounted for about 24.5% of the total prescriptions at the end of the study.

Conclusions: The use of ADHD drugs and the corresponding cost increased rapidly in China, and methylphenidate was the most frequently prescribed medicine. The increase in ADHD prescriptions requires attention to ensure that it reflects appropriate use, especially in patients aged 6-11 years

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Front Psychiatry. 2022;13.

THE NURSE ROLE IN THE MANAGEMENT OF ADHD IN CHILDREN AND ADOLESCENT: A LITERATURE REVIEW.

Kleve L, et al.

Objective: To review literature regarding existing and recommended roles for nurses in the management of children with ADHD.

Methods: MEDLINE and CINAHL were searched from 2010 to the end of 2019 with the following keywords: ADHD, nurse, child, and inclusion criteria published in an English journal.

Results: Forty-three records were found. However, only five articles scientifically evaluated the nurse role. The nurse role in ADHD management seemed to vary across countries with nurses working independently or as part of a team with delegated responsibility.
Conclusion: The literature review gave information to suggest that nurses can have a significant role in providing a range of medical and non-medical management

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Global Pediatric Health. 2022;9.
COMORBIDITIES ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS AT A TERTIARY CARE SETTING.
Jogia J, Sharif AH, Nawaz FA, et al.
Studies have revealed high rates of neurodevelopmental and psychiatric comorbid conditions among individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD). However, research on this topic in the Arab world has been limited. This study evaluates the medical, neurodevelopmental, and psychiatric comorbidities in children and adolescents diagnosed with ADHD in Dubai, United Arab Emirates (UAE). A total of 428 pediatric patients diagnosed with ADHD were included. Children and adolescents with ADHD had high rates of comorbid disorders. Twenty comorbid conditions were identified. More than 3 quarters of the study sample had at least 1 comorbid disorder. The most common comorbidity among children was autism spectrum disorder, and among adolescents was anxiety disorders. Comprehensive assessments are highly warranted to identify and manage associated comorbid conditions. Further research is needed in exploring the biopsychosocial factors contributing to the elevated rate of comorbidity in children and adolescents with ADHD

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Hong Kong J Occup Ther. 2022.
EFFECTIVENESS OF MINDFULNESS PARENT TRAINING ON PARENTING STRESS AND CHILDREN'S ADHD-RELATED BEHAVIORS: A SYSTEMATIC REVIEW AND META-ANALYSIS.
Lee CSC, Ng KH, Chan PCK, et al.
Background/Objective: Literature shows that there is a circular relationship between childrenΓÇÖs ADHD-related behaviors and parenting stress. This systematic review and meta-analysis aimed to understand if mindfulness parent trainings have benefits for both parenting stress and the problem behaviors in children with ADHD.
Methods: Five databases, CINAHL, Embase, PsycINFO, PubMED, and Web of Science, were searched. Within-group effects at post-treatment and follow-up assessment, and between-group effects at post-treatment were analyzed. Effect sizes (Hedges g) were also calculated.
Results: Ten studies (5 RCTs and 5 non-RCTs) met the selection criteria and were selected for systematic review, and nine of them were included for meta-analysis. Among these 10 studies, five studies involved mindfulness training for both parents and children, while the other five studies involved mindfulness training for parents only. Within-group effects at post-treatment were small-to-large for all outcomes. Hedges g ranged between 0.17 [95% CI (0.98, 0.64)] and 4.70 [95% CI (3.59, 5.81)] for parenting stress; 0.17 [95% CI (0.03, 0.37)] and 4.03 [95% CI (2.97, 5.09)] for children's problem behaviors; and 0.20 [95% CI (0.10, 0.50)] and 2.98 [95% CI (2.16, 3.80)] for children's ADHD symptoms. Between-group comparisons showed mindfulness parent training was superior to other active controls on all outcomes.
Conclusion: Findings suggest that mindfulness parent training may be beneficial for parenting stress and children's ADHD-related behaviors, and due to the small number of studies reviewed, cautions should be taken when interpreting the results

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Hum Brain Mapp. 2022 Mar;43:1256-64.

ALTERED SINGLE-SUBJECT GRAY MATTER STRUCTURAL NETWORKS IN DRUG-NAÏVE ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN.

Chen Y, Lei D, Cao H, et al.

Altered topological organization of brain structural covariance networks has been observed in attention deficit hyperactivity disorder (ADHD). However, results have been inconsistent, potentially related to confounding medication effects. In addition, since structural networks are traditionally constructed at the group level, variabilities in individual structural features remain to be well characterized. Structural brain imaging with MRI was performed on 84 drug-naïve children with ADHD and 83 age-matched healthy controls. Single-subject gray matter (GM) networks were obtained based on areal similarities of GM, and network topological properties were analyzed using graph theory. Group differences in each topological metric were compared using nonparametric permutation testing. Compared with healthy subjects, GM networks in ADHD patients demonstrated significantly altered topological characteristics, including higher global and local efficiency and clustering coefficient, and shorter path length. In addition, ADHD patients exhibited abnormal centrality in corticostriatal circuitry including the superior frontal gyrus, orbitofrontal gyrus, medial superior frontal gyrus, precentral gyrus, middle temporal gyrus, and pallidum (all $p < .05$, false discovery rate [FDR] corrected). Altered global and nodal topological efficiencies were associated with the severity of hyperactivity symptoms and the performance on the Stroop and Wisconsin Card Sorting Test tests (all $p < .05$, FDR corrected). ADHD combined and inattention subtypes were differentiated by nodal attributes of amygdala ($p < .05$, FDR corrected). Alterations in GM network topologies were observed in drug-naïve ADHD patients, in particular in frontostriatal loops and amygdala. These alterations may contribute to impaired cognitive functioning and impulsive behavior in ADHD

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IEEE Trans Neural Syst Rehabil Eng. 2022;30:668-77.

SIGNIFICANT LOW-DIMENSIONAL SPECTRAL-TEMPORAL FEATURES FOR SEIZURE DETECTION.

Yan X, Yang D, Lin Z, et al.

Absence seizure as a generalized onset seizure, simultaneously spreading seizure to both sides of the brain, involves around ten-second sudden lapses of consciousness. It common occurs in children than adults, which affects living quality even threats lives. Absence seizure can be confused with inattentive attention-deficit hyperactivity disorder since both have similar symptoms, such as inattention and daze. Therefore, it is necessary to detect absence seizure onset. However, seizure onset detection in electroencephalography (EEG) signals is a challenging task due to the non-stereotyped seizure activities as well as their stochastic and non-stationary characteristics in nature. Joint spectral-temporal features are believed to contain sufficient and powerful feature information for absence seizure detection. However, the resulting high-dimensional features involve redundant information and require heavy computational load. Here, we discover significant low-dimensional spectral-temporal features in terms of mean-standard deviation of wavelet transform coefficient (MS-WTC), based on which a novel absence seizure detection framework is developed. The EEG signals are transformed into the spectral-temporal domain, with their low-dimensional features fed into a convolutional neural network. Superior detection performance is achieved on the widely-used benchmark dataset as well as a clinical dataset from the Chinese 301 Hospital. For the former, seven classification tasks were evaluated with the accuracy from 99.8% to 100.0%, while for the latter, the method achieved a mean accuracy of 94.7%, overwhelming other methods with low-dimensional temporal and spectral features. Experimental results on two seizure datasets demonstrate reliability, efficiency and stability of our proposed MS-WTC method, validating the significance of the extracted low-dimensional spectral-temporal features

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Indian Journal of Clinical Biochemistry. 2021;36:S85.

A STUDY TO ASSESS THE PRESENCE OF HEAVY METALS IN URINE AND HAIR OF PATIENTS DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN EASTERN INDIA.

Nayak S, Sahu S, John J, et al.

Objectives: 1. To estimate levels of heavy metals in urine and hair in the study population 2. To evaluate the association between excretion of heavy metals in urine, and accumulation in hair, with ADHD.

Methods: 24 children diagnosed with ADHD were taken as cases and matched with 24 healthy controls. Hair and urine samples were analysed for lead, cadmium, zinc, nickel, copper, and arsenic. The samples were collected in sterile containers following standardised protocols. Acid digestion of hair samples and extraction of heavy metals from urine were performed. The levels of heavy metals were measured using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES).
Results: The levels of lead (p = 0.004), cadmium (p = 0.020), nickel (p = 0.016) and copper (p = 0.013) of hair samples were higher in the cases while Zinc levels were lower in the cases (p < 0.001) compared to controls. In urine too the heavy metals except zinc were significantly higher, lead (p = 0.003), cadmium (p < 0.001), zinc (p < 0.001), nickel (p < 0.001) and copper (p = 0.006) while. Zinc levels were lower in cases (p<0.001) than controls. The zinc to copper ratio was lower in cases (p < 0.001 in both hair and urine).
Conclusion: The heavy metals level in hair and urine are significantly higher than controls in ADHD

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Int J Environ Res Public Health. 2022;19.

EARLY AND OBJECTIVE EVALUATION OF THE THERAPEUTIC EFFECTS OF ADHD MEDICATION THROUGH MOVEMENT ANALYSIS USING VIDEO RECORDING PIXEL SUBTRACTION.

Lee YH, Ouyang CS, Chiu YH, et al.

Attention-deficit/hyperactivity disorder (ADHD) affects approximately 5-7% of school-age children. ADHD is usually marked by an ongoing pattern of inattention or hyperactivityΓÇô impulsivity, leading to functioning or developmental problems. A common ADHD assessment tool is the Swanson, Nolan, and Pelham (SNAP) questionnaire. However, such scales provide only a subjective perspective, and most of them are used to evaluate therapeutic effects at least 3-12 months after medication initiation. Therefore, we employed an objective assessment method to provide more accurate evaluations of therapeutic effects in 25 children with ADHD (23 boys and 2 girls). To evaluate the participants improvement and treatment's effectiveness, the pixel subtraction technique was used in video analysis. We compared the efficacy of 1-month Ritalin or Concerta treatment by evaluating the movement in each video within 3 h of medication administration. The movement value was defined as the result of a calculation when using the pixel subtraction technique. Based on behavior observation and SNAP scores, both parent-and teacher-reported scores decreased after 1 month of medication (reduction rates: 19.61% and 16.38%, respectively). Specifically, the parent-reported hyperactivity subscale and teacher-reported oppositional subscale decreased more significantly. By contrast, the reduction rate was 39.27%, as evaluated using the average movement value (AMV). Considering symptomatic improvement as a >25% reduction in scores, the result revealed that the AMV decreased in 18 patients (72%) compared with only 44% and 56% of patients based on parent-and teacher-reported hyperactivity subscale scores. In conclusion, the pixel subtraction method can serve as an objective and reliable evaluation of the therapeutic effects of ADHD medication in the early stage

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Int J Gen Med. 2021;14:10503-09.

THE RELATIONSHIP BETWEEN BLOOD LIPID AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN AN OBESE POPULATION OF CHINESE CHILDREN: AN OBESITY-STRATIFIED CROSS-SECTIONAL STUDY.

Xu Y, Bao L, Liu C.

Background: Although obesity has been related to attention-deficit/hyperactivity disorder (ADHD), few studies have examined the relationship between blood lipid levels and ADHD in children. We aimed to evaluate whether increased blood lipid levels are associated with the prevalence of ADHD in children.
Methods: A total of 1179 children were studied in the cross-sectional analysis. Multivariate logistic regression and linear regression analyses were performed to evaluate the association of blood lipid levels with the prevalence of ADHD in children.
Results: In 1179 children, the average age was 10.4 years, and the percentage of boys was 50.3%. 97 (8.2%) of the children were diagnosed with ADHD. The logistic regression analysis demonstrated that elevated levels of total cholesterol (OR=2.001, 95% CI 1.247-3.541, P-trend=0.024), triglycerides (OR=1.776, 95% CI 1.448-2.187, P-trend=0.003) and LDL (low density lipoprotein; OR=2.016, 95% CI 1.335-3.966, P-trend<0.001) and reduced levels of HDL (high density lipoprotein; OR=0.577, 95% CI 0.298-0.948, P-trend=0.023) were associated with the prevalence of ADHD after adjustments were made for age, sex,

body mass index (BMI), residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, and marital status of parents in Model 3. The stratified analysis using obese as a covariate showed that elevated levels of total cholesterol, triglycerides and LDL and reduced levels of HDL were independently associated with an increased risk of ADHD in obese children.
Conclusion: Increased blood lipid levels were associated with ADHD in obese children

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Int J Gen Med. 2022;15:2187-95.

ASSOCIATIONS OF EPSTEIN-BARR VIRUS INFECTION WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, LEARNING DISABILITY, AND SPECIAL EDUCATION IN US CHILDREN.

Wang J, Li Y, Geng X, et al.

Background: Most infections of Epstein-Barr virus (EBV), which is potentially neurotropic, occur in childhood, but little is known about its association with child neurodevelopmental outcomes. Patients and
Methods: We investigated whether EBV seropositivity was associated with parent-reported attention deficit hyperactivity disorder (ADHD), learning disability, or special education utilization among children, using data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004. Potential confounding factors were adjusted using survey logistic regression models.
Results: EBV seroprevalence was 69.6% (95% CI, 67.1-72.1%) for US children aged 6-19. The prevalence was 8.86% (95% CI, 7.47-10.47%) for ADHD among 6ΓÇô19 year olds, 11.70% (95% CI, 9.84-13.87%) for learning disability among 6-15 year olds, and 10.18% (95% CI, 8.58-12.05%) for special education among 6-17 year olds. Children with positive anti-EBV had higher crude prevalence rates of learning disability and special education but not ADHD compared with those with negative anti-EBV. The adjusted odds ratios were 2.76 (95% CI, 1.53-4.96) for learning disability, 3.58 (95% CI, 1.92-6.55) for special education, and 0.77 (95% CI, 0.42-1.38) for ADHD, when comparing children with positive and negative anti-EBV.
Conclusion: EBV seropositivity was associated with learning disability and special education among US children. Future studies that longitudinally examine the associations are warranted

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Int J Obes. 2022.

ADHD IN CHILDHOOD PREDICTS BMI AND BODY COMPOSITION MEASUREMENTS OVER TIME IN A POPULATION-BASED BIRTH COHORT.

Martins-Silva T, dos Santos Vaz J, Sch+ñfer JL, et al.

Background/Objectives: Obesity has been reported as an attention-deficit hyperactivity disorder (ADHD) comorbidity. So far, few studies have aimed to explore the potential causal relationship between ADHD and obesity, as well as used other measures of body composition like fat-free mass (FFM) and fat mass (FM) as measures of obesity. This study aimed to test the association between ADHD and body composition (body mass index [BMI] and others) and to evaluate the potential causal relationship with obesity.
Subjects/Methods: Data from the 1993 Pelotas (Brazil) birth cohort at age 11-, 15-, 18-, and 22-year follow-up was used. We performed a cross-lagged panel model (CLPM) analysis between ADHD symptoms and BMI to explore the causal relationship between both traits. Finally, we tested whether ADHD, inattention, and hyperactivity symptom scales were associated with BMI, FM, and FFM at 22 years.
Results: In the CLPM, higher ADHD scores at age 11 predicted higher BMI at age 15 (+¦ = 0.055, 95% CI [0.037; 0.073]). ADHD symptoms at age 11 was also associated with a decrease in the FFM (+¦ = 0.16, 95% CI [0.28; 0.05]), and an increase in the BMI (+¦ = 0.17, 95% CI [0.10; 0.23]) and FM (+¦ = 0.17, 95% CI [0.06; 0.29]) at 22 years. At 22 years of age, ADHD was associated with FFM and FM. Moreover, an increase in BMI was observed with an increase in several symptoms of ADHD in general (+¦ = 0.06, 95% CI [0.004; 0.12]), and hyperactivity symptoms (+¦ = 0.15, 95% CI [0.05; 0.25]).
Conclusion: ADHD at 11 years predicted a higher BMI at 15 years, and body fat composition in adulthood, suggesting higher scores on ADHD symptoms in early life may be a critical point for body composition in early adulthood. The hyperactivity symptoms may play an important role in the BMI increase

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Iran J Psychiatry. 2021;16:374-82.

ANALYSIS OF EFFECTIVE CONNECTIVITY STRENGTH IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER USING PHASE TRANSFER ENTROPY.

Ekhlasi A, Nasrabadi AM, Mohammadi MR.

Objective: This study aimed to investigate differences in brain networks between healthy children and children with attention deficit hyperactivity disorder (ADHD) during an attention test.

Method: To fulfill this, we constructed weighted directed graphs based on Electroencephalography (EEG) signals of 61 children with ADHD and 60 healthy children with the same age. Nodes of graphs were 19 EEG electrodes, and the edges were phase transfer entropy (PTE) between each pair of electrodes. PTE is a measure for directed connectivity that determines the effective relationship between signals in linear and nonlinear coupling. Connectivity graphs of each sample were constructed using PTE in the five frequency bands as follows: delta, theta, alpha, beta, and gamma. To investigate the differences in connectivity strength of each node after the sparsification process with two values (0.5 and 0.25), the permutation statistical test was used with the statistical significance level of $p<0.01$.

Results: The results indicate stronger inter-regional connectivity in the prefrontal brain regions of the control group compared to the ADHD group. However, the strength of inter-regional connectivity in the central regions of the ADHD group was higher. A comparison of the prefrontal regions between the two groups revealed that the areas of the Fp1 electrode (left prefrontal) in healthy individuals play stronger transmission roles.

Conclusion: Our research can provide new insights into the strength and direction of connectivity in ADHD and healthy individuals during an attention task

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Iran J Psychiatry. 2022;17:110-17.

RELATION BETWEEN ADHD AND COVID-19: A NARRATIVE REVIEW TO GUIDE ADVANCING CLINICAL RESEARCH AND THERAPY.

Davoody S, Goeschl S, Dolatshahi M, et al.

Objective: To cope with the COVID-19 pandemic, national health authorities temporarily closed cultural, religious, and educational institutions such as universities and schools. Children and adolescents with ADHD were challenged with the restrictions caused by the Covid-19 pandemic such as homeschooling and reduced physical activity. The present narrative review aimed to summarize the state-of-the-art regarding associations between COVID-19-related social restrictions and possible psychological and behavioral issues in children and adolescents with ADHD. Additionally, we discussed the underlying possible reasons of the association focusing on the role of parental influence and physical activity, vulnerabilities of individuals with ADHD to Covid-19 infection and to school closure and remote learning.

Method: To collect data for the present narrative review, recent publications on these topics between February 1st, 2020 and January 10th, 2021 were retrieved from the most popular search engines (PubMed; Scopus; Google Scholar; Psych Info; Embase) through a comprehensive search using relevant keywords.

Results: During confinement, children and adolescents with ADHD reported increased behavioral and ADHD-related symptoms and overall decreased psychological well-being. Factors negatively impacting children's and adolescents behavioral symptoms and well-being were: less physical activity, adverse parental behavior, difficulties in coping with preventive guidelines, and school closure and remote learning consequences.

Conclusion: Children and adolescents with ADHD and their caregivers faced both specific and general psychological issues related to the school lockdowns and homeschooling. Additionally, Individuals with ADHD seem to be more vulnerable to Covid-19 infection which highlights the need for better healthcare adaptation

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Ital J Pediatr. 2022 Mar;48:50.

ADHD SYMPTOMS AND SCHOOL IMPAIRMENT HISTORY IN PARENTS OF ADHD CHILDREN ARE A FUNDAMENTAL DIAGNOSTIC AND THERAPEUTIC CLUE.

Wiel LC, Rispoli F, Peccolo G, et al.

BACKGROUND: Attention Deficit and Hyperactivity Disorder (ADHD) is a multi-factorial condition, with inheritance playing a major role. Recognizing parents' ADHD represents a clue not only for an earlier diagnosis of the disease in their children, but also to optimize psycho-educational therapy outcomes, by addressing the impairment of parenting related to untreated ADHD. This study aimed to assess the frequency of features suggestive of ADHD during childhood among parents of affected children, and the presence of school and emotional impairment.

METHODS: We administered the Wender Utah Rating Scale-25, a self-assessment tool for the retrospective identification of symptoms consistent with ADHD during childhood, to a cohort of 120 parents of 60 children with ADHD, and to a consistent number of "controls".

RESULTS: The WURS-25 proved positive in 49.1% of fathers and 30.0% of mothers of ADHD patients, compared to 1.7% of fathers and 1.7% of mothers of non-ADHD patients ($p<0.0001$). The questions addressing learning and emotional impairment provided significantly higher scores in parents with an overall positive test compared to those with negative test ($p<0.0001$).

CONCLUSIONS: This study demonstrates a remarkably high rate of symptoms consistent with ADHD during childhood in parents of affected children. Physicians should be aware that this is a relevant anamnestic clue and, given the relevance of parents' role in the management of children with ADHD, an important issue to address in order to optimize patients' treatment

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J Child Adolesc Psychopharmacol. 2022 Mar;32:98-106.

A LONG-TERM, OPEN-LABEL SAFETY AND TOLERABILITY STUDY OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AGED 4-5 YEARS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Lloyd E, Johnson SA, Jr., et al.

Objective: To evaluate the long-term safety and tolerability of lisdexamfetamine dimesylate (LDX) in preschool-aged children (4-5 years of age inclusive) diagnosed with attention-deficit/hyperactivity disorder (ADHD).

Methods: This phase 3 open-label study (ClinicalTrials.gov registry: NCT02466386) enrolled children aged 4-5 years meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for a primary ADHD diagnosis and having baseline ADHD Rating Scale-IV Preschool version total scores (ADHD-RS-IV-PS-TS) ≥24 for girls or ≥28 for boys and baseline Clinical Global Impressions-Severity scores ≥4. Participants were directly enrolled or enrolled after completing one of two antecedent short-term LDX studies. Over 52 weeks of treatment, participants received once-daily dose-optimized LDX (5-30 mg). Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and vital sign changes. Clinical outcomes included ADHD-RS-IV-PS-TS changes from baseline.

Results: Among 113 participants in the safety set, optimized LDX dose was 5, 10, 15, 20, and 30 mg in 1 (0.9%), 12 (10.6%), 21 (18.6%), 26 (23.0%), and 53 (46.9%) participants, respectively. Of the safety set, 69 participants (61.1%) completed the study. TEAEs were reported in 76.1% of participants; no serious TEAEs were reported. Only one type of TEAE was reported in >10% of participants (decreased appetite, 15.9%). Mean ± standard deviation (SD) changes in vital signs and body weight from baseline to week 52/or early termination (ET; n = 101) were 1.9 ± 7.73 mmHg for systolic blood pressure, 3.1 ± 7.58 mmHg for diastolic blood pressure, 4.7 ± 11.00 bpm for pulse, and 0.6 ± 1.38 kg for body weight. Over the course of the study, mean ± SD change in ADHD-RS-IV-PS-TS from baseline to week 52/ET was -24.2 ± 13.34 (n = 87).

Conclusions: In this long-term 52-week study of children aged 4-5 years with ADHD, dose-optimized LDX (5-30 mg) was well tolerated and associated with reductions from baseline in ADHD symptoms

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J Healthc Eng. 2022;2022:1818693.

CLINICAL EFFICACY EVALUATION OF PSYCHOLOGICAL NURSING INTERVENTION COMBINED WITH DRUGS TREATMENT OF CHILDREN WITH ADHD UNDER ARTIFICIAL INTELLIGENCE.

Guo Y, Wang J, Yan S, et al.

ADHD in children is one of the most common neurodevelopmental disorders. It is manifested as inattention, hyperactivity, impulsiveness, and other symptoms that are inconsistent with the developmental level in different occasions, accompanied by functional impairment in social, academic, and occupational aspects. At present, the treatment for children with ADHD is mainly based on psychological nursing intervention combined with drug therapy. Therefore, the actual efficacy evaluation of this treatment regimen is very important. Neural networks are widely used in smart medical care. This work combines artificial intelligence with the evaluation of clinical treatment effects of ADHD children and designs an intelligent model based on neural networks for evaluating the clinical efficacy of psychological nursing intervention combined with drug treatment of children with ADHD. The main research is that, for the evaluation of clinical treatment effect of ADHD in children, this paper proposes a 1D Parallel Multichannel Network (1DPMN), which is a convolutional neural network. The results show that network models can extract different data features through different channels and can achieve high accuracy evaluation of clinical efficacy of ADHD in children. On the basis of the model, performance is improved through the study of Adam optimizer to speed up the model convergence, adopts batch normalization algorithm to improve stability, and uses Dropout to improve the generalization ability of the network. Aiming at the problem of too many parameters, the 1DPMN is optimized through the principle of local sparseness, and the model parameters are greatly reduced

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J Korean Med Sci. 2022 Mar;37:e89.

EFFECT OF MATERNAL ANXIETY ON PARENTING STRESS OF FATHERS OF CHILDREN WITH ADHD.

Lee YJ, Kim J.

BACKGROUND: Hyperactivity, inattention, and impulsivity of children with attention deficit hyperactivity disorder (ADHD) increase parenting stress and familial conflict. Among parent-related factors, maternal mental health has been studied in-depth, but studies on paternal factors in this context are scarce. This cross-sectional study was conducted of children with ADHD and their parents in South Korea. We investigated the relationships between ADHD symptom severity of children and the mental health of their mothers and fathers.

METHODS: The study included 70 children with ADHD and their 140 married heterosexual parents (70 fathers and 70 mothers). Children completed the Child Depression Inventory and State-Anxiety Inventory for children, and their parents completed the Korean ADHD rating scale-IV, Adult ADHD self-report scale, State-Anxiety Inventory, Patient Health Questionnaire-9, and Parental Stress Scale.

RESULTS: There was a significant positive correlation between children's ADHD symptoms and maternal anxiety symptom severity, whereby more severe ADHD symptoms were associated with more severe maternal anxiety symptoms. There was also a significant positive correlation between maternal anxiety symptom severity and paternal parenting stress severity, whereby more severe maternal anxiety was associated with more severe paternal parenting stress. A mediation model showed that paternal parenting stress severity was not directly related to children's ADHD symptoms, but the severity of maternal anxiety mediated this relationship.

CONCLUSION: The present study found the importance of mental health in mothers of children with ADHD and the interrelatedness of mental health within families. Future assessments and treatment of children with ADHD should include both the children and their parents

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J Med Internet Res. 2022 Mar;24:e33560.

USE OF MOBILE AND WEARABLE ARTIFICIAL INTELLIGENCE IN CHILD AND ADOLESCENT PSYCHIATRY: SCOPING REVIEW.

Welch V, Wy TJ, Ligezka A, et al.

BACKGROUND: Mental health disorders are a leading cause of medical disabilities across an individual's lifespan. This burden is particularly substantial in children and adolescents because of challenges in

diagnosis and the lack of precision medicine approaches. However, the widespread adoption of wearable devices (eg, smart watches) that are conducive for artificial intelligence applications to remotely diagnose and manage psychiatric disorders in children and adolescents is promising.
OBJECTIVE: This study aims to conduct a scoping review to study, characterize, and identify areas of innovations with wearable devices that can augment current in-person physician assessments to individualize diagnosis and management of psychiatric disorders in child and adolescent psychiatry.
METHODS: This scoping review used information from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search of several databases from 2011 to June 25, 2021, limited to the English language and excluding animal studies, was conducted. The databases included Ovid MEDLINE and Epub ahead of print, in-process and other nonindexed citations, and daily; Ovid Embase; Ovid Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews; Web of Science; and Scopus.
RESULTS: The initial search yielded 344 articles, from which 19 (5.5%) articles were left on the final source list for this scoping review. Articles were divided into three main groups as follows: studies with the main focus on autism spectrum disorder, attention-deficit/hyperactivity disorder, and internalizing disorders such as anxiety disorders. Most of the studies used either cardio-fitness chest straps with electrocardiogram sensors or wrist-worn biosensors, such as watches by Fitbit. Both allowed passive data collection of the physiological signals.
CONCLUSIONS: Our scoping review found a large heterogeneity of methods and findings in artificial intelligence studies in child psychiatry. Overall, the largest gap identified in this scoping review is the lack of randomized controlled trials, as most studies available were pilot studies and feasibility trials

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J Affective Disord. 2021;295:1407-14.
BIPOLAR WOMEN'S ANTEPARTUM PSYCHOTROPIC EXPOSURE AND OFFSPRING RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.
Yeh TC, Bai YM, Hsu JW, et al.
Background: Women with bipolar disorder (BD) may continue psychotropics during pregnancy. The association of exposure to antidepressant, antipsychotics, and mood stabilizers with offspring risks of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) remains unexplored in mothers with BD.
Methods: A total of 5669 pregnant women with BD and 5669 psychiatrically healthy controls were identified between 2002 and 2011 from the Taiwan Longitudinal Health Insurance Database. We analyzed the odds ratios (ORs) of psychotropic types and exposure periods (3 months before pregnancy [3MbPreg] and first, second, and third trimesters [T1, T2, T3, respectively]) on the risk of ADHD and ASD by using adjusted logistic regression analyses.
Results: Antidepressant exposure during 3MbPreg (OR=2.15, 95% CI=1.45-3.20), T1 (OR=2.62, 95% CI=1.68-4.09), T2 (OR=2.33, 95% CI=1.18-4.63), and T3 (OR=2.33, 95% CI=1.67-6.61) was associated with increased offspring risk of ADHD, particularly for selective serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor. Mood stabilizer exposure during 3MbPreg increased the risks of ADHD (OR=2.39, 95% CI=1.45-3.95) and ASD (OR=3.89, 95% CI=1.30-11.65); a higher ADHD risk was associated with valproic acid (OR=2.43, 95% CI=1.32-4.47) and lamotrigine exposure (OR=8.24, 95% CI = 1.49-45.67); ASD risk was higher for lithium exposure (OR=6.75, 95% CI=1.41-32.28). Limitation: In claims-data analyses, several clinical parameters or potential confounders may be incompletely captured.
Conclusions: Antidepressants were associated with higher offspring risk of ADHD over all gestation periods among mothers with BD than psychiatrically healthy controls, while mood stabilizers were associated with higher risk of ADHD and ASD during 3MbPreg

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J Autism Dev Disord. 2022.

PARENT-REPORTED EARLY ATYPICAL DEVELOPMENT AND AGE OF DIAGNOSIS FOR CHILDREN WITH CO-OCCURRING AUTISM AND ADHD.

Sainsbury WJ, Carrasco K, Whitehouse AJO, et al.

Autism and attention-deficit/hyperactivity disorder (ADHD) often co-occur. This survey of 288 New Zealand parents of children diagnosed with autism (n = 111), ADHD (n = 93), or both conditions (n = 84), examined the relations between age of diagnosis and early atypical development, the age specialist consultation was needed and types of specialists seen. Co-occurring autism and ADHD was associated with an earlier ADHD diagnosis and a later autism diagnosis. Parents of children with both diagnoses reported less atypical development in language and social behaviours compared to parents of children of autism, and this co-occurring group also experienced longer wait times to diagnosis, and saw more types of specialists prior to a diagnosis, than those with autism

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J Child Adolesc Psychopharmacol. 2022;32:89-97.

EFFICACY AND SAFETY OF DEXTROAMPHETAMINE TRANSDERMAL SYSTEM FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: RESULTS FROM A PIVOTAL PHASE 2 STUDY.

Cutler AJ, Suzuki K, Starling B, et al.

Objectives: To assess efficacy and safety of the new Dextroamphetamine Transdermal System (d-ATS) to treat children and adolescents (aged 6-17 years) with attention-deficit/hyperactivity disorder (ADHD).

Methods: In this phase 2, randomized, placebo-controlled study, 4 d-ATS patches of differing doses (5, 10, 15, and 20 mg) were evaluated. Patients began a 5-week, open-label, stepwise dose-optimization period in which they received a 5-mg d-ATS patch (applied to hip) for 9 hours. During weekly visits, patients were evaluated for possible adjustments to the next dose level based on efficacy and safety. Once at the optimal dose, that dose was maintained during a 2-week, crossover double-blind treatment period. Primary endpoint was to assess efficacy of d-ATS versus placebo as measured by Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) total score; key secondary endpoints included assessing onset and duration of efficacy by SKAMP total score, and additional secondary endpoints included Permanent Product Measure of Performance (PERMP) scores. Safety was assessed throughout.

Results: d-ATS treatment resulted in significant improvements versus placebo in ADHD symptoms as measured by SKAMP total score, with overall least-squares mean difference (95% confidence interval) versus placebo of -5.87 (6.76, -4.97; $p < 0.001$) over the 12-hour assessment period. Onset of efficacy was observed at 2 hours postdose ($p < 0.001$), and duration of effect continued through 12 hours (patch removed at 9 hours), with significant differences between d-ATS and placebo at all time points from 2 hours onward (all p 0.003). Significant improvements versus placebo in PERMP-A and PERMP-C scores were also observed from 2 to 12 hours postdose with d-ATS treatment. d-ATS was safe and well-tolerated, with a systemic safety profile similar to that observed with oral amphetamines.

Conclusions: This study demonstrates that d-ATS is an effective and well-tolerated treatment for children and adolescents with ADHD. These data indicate that d-ATS can deliver sustained levels of efficacy along with the advantages of transdermal drug delivery, making it a beneficial new treatment option

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J Child Adolesc Psychopharmacol. 2022;32:107-16.

THE EFFECTS OF METHYLPHENIDATE TREATMENT ON BULLYING PERPETRATION AND VICTIMIZATION IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Karaosman T, Gumus YY.

Objective: Although it is known that attention-deficit/hyperactivity disorder (ADHD) increases the risk of bullying perpetration and victimization, the data on the effect of methylphenidate (MPH) treatment, which is frequently used in the treatment of ADHD, on bullying perpetration and victimization, are very limited. The aim of this study was to investigate the effect of MPH treatment on bullying perpetration and victimization in children and adolescents with ADHD.

Methods: Children and adolescents with ADHD, aged 8-16 years, who had not been treated for ADHD for at least 1 year and prescribed only MPH treatment were invited to participate in this open-label naturalistic

study. After 3 months of MPH treatment, peer bullying involvement status was analyzed in comparison with the pretreatment data.
Results: There was a significant decrease in all subscales of the Conners' Parent Rating Scale (CPRS) and Conners' Teacher Rating Scale after MPH treatment. Being a bully decreased from 50% to 18% and being a victim decreased from 80% to 46%. It was determined that for every 1 point decrease in the CPRS Conduct Problems subscale, the risk of being a bully was reduced Γê+2-fold, and every 1 point decrease in the CPRS Anxiety subscale reduced the risk of being a victim 2.44-fold.
Conclusions: This is the first longitudinal study examining the effect of MPH treatment on bullying perpetration and victimization in children and adolescents with ADHD. It appears that MPH treatment may be effective in improving the situations of bullying perpetration and victimization in ADHD patients. In addition, the fact that the decrease in behavioral problems reduces the risk of being a bully and the decrease in anxiety symptoms reduces the risk of being a victim, suggests that prevention and intervention programs for bullying perpetration and victimization should target these problem areas

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J Child Adolesc Psychopharmacol. 2022 Feb;32:45-51.
RELATIVE AGE AND THE USE OF SECOND-GENERATION ANTIPSYCHOTICS FROM 7 TO 17 YEARS OF AGE: A POPULATION-BASED REGISTER STUDY.
Vuori M, Sourander A, Aronen ET, et al.
Objective: The youngest children in a classroom have a higher risk of attention-deficit/hyperactivity disorders (ADHDs) and depression than their relatively older peers. However, there has been a lack of research on how relative age is related to second-generation antipsychotic (SGA) medication use.
Methods: This study used the Finnish National Prescription Register data and comprised all 669,726 Finnish children and adolescents aged 7–17 in 2018. We extracted data for those who were dispensed SGAs (risperidone, quetiapine, aripiprazole, and olanzapine) and ADHD medication (methylphenidate, atomoxetine, dexamphetamine, and lisdexamfetamine). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for medication dispensed to schoolchildren born from January to April (the relatively oldest), May to August, and September to December (the relatively youngest). Dispensed prescriptions were a proxy for medication use.
Results: SGAs were dispensed to 9146 (1.4%) individuals in 2018. Their use was lower among girls aged 12–17 years born from September to December than January to April (OR 0.89; 95% CI 0.83–0.97), with no association between SGA use and birth month among boys. However, younger relative age was associated with combined SGA and ADHD medication, which was used by 2556 (0.4%) of the cohort: 2074 (0.6%) boys and 482 (0.1%) girls. The OR was 1.27 for boys aged 12–17 born from September to December (95% CI 1.10–1.46), compared with January to April. The OR for girls born from May to August was 1.35 (95% CI 1.04–1.76) and from September to December it was 1.33 (95% CI 1.02–1.74), compared with January to April.
Conclusions: A novel discovery of this study was that using both SGA and ADHD medication at the age of 12–17 years was more common among the youngest subjects in a school year than their relatively older peers

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J Child Psychol Psychiatry. 2022 Feb;63:229-37.
HOW MUCH IMPAIRMENT IS REQUIRED FOR ADHD? NO EVIDENCE OF A DISCRETE THRESHOLD.
Arildskov TW, Sonuga-Barke EJS, Thomsen PH, et al.
Background: A diagnosis of attention-deficit/hyperactivity disorder (ADHD) requires the presence of impairment alongside symptoms above a specific frequency and severity threshold. However, the question of whether that symptom threshold represents anything more than an arbitrary cutoff on a continuum of impairment requires further empirical study. Therefore, we present the first study investigating if the relationship between ADHD symptom severity and functional impairment is nonlinear in a way that suggests a discrete, nonarbitrary symptom level threshold associated with a marked step increase in impairment.

Methods: Parent reports on the ADHD-Rating Scale (ADHD-RS-IV), the Weiss Functional Impairment Rating Scale (WFIRS-P), and the Strengths and Difficulties Questionnaire were collected in a general population sample of 1st, 2nd, and 3rd graders (N = 1,914–2,044).
Results: Piecewise linear regression analyses and nonlinear regression modeling both demonstrated that the relationship between symptom severity (ADHD-RS-IV total score) and impairment (WFIRS-P mean score) was characterized by a gradual linear increase in impairment with higher symptom severity and no apparent step increase or changing rate of increase in impairment at a certain high ADHD-RS-IV total score level. Controlling for socioeconomic status, sex, and co-occurring conduct and emotional symptoms did not alter these results, though comorbid symptoms had a significant effect on impairment.
Conclusions: There was no clear evidence for a discrete, nonarbitrary symptom severity threshold with regard to impairment. The results highlight the continued need to consider both symptoms and impairment in the diagnosis of ADHD

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J Child Psychol Psychiatry. 2022 Feb;63:238-40.

THE CONCEPTUAL AND DIAGNOSTIC IMPORTANCE OF ADHD-RELATED IMPAIRMENT: A COMMENTARY ON ARILDSKOV ET AL (2021).

DuPaul GJ.

Comments on an article by Arildskov, Sonuga-Barke, Thomsen, Virring, and Østergaard (see record [rid]2021-51033-001[/rid]). The premise of this commentary is that if we want to gain comprehensive understanding of ADHD as well as address the primary needs of youth with this disorder, we must raise the status of functional impairment to be equal to symptoms in terms of assessment focus, treatment targets, and research attention. The study conducted by Arildskov, Sonuga-Barke, Thomsen, Virring, and Østergaard (2021) provides important evidence in support of this premise in multiple ways. The conceptualization and assessment of ADHD-related impairment are far from the simple dichotomy (i.e., present vs. absent) exemplified by DSM-5 and our research literature. The impairment construct is complex in being comprised of multiple domains of functioning (e.g., academic, social, occupational) that are exhibited in a dimensional fashion within and across individuals. Findings from the Arildskov et al. (2021) investigation provide compelling evidence of the complexity of ADHD-related impairment in terms of the nature and magnitude of the relationship with symptoms

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Journal of Clinical Neuroscience. 2022;98:149-53.

TREATMENT WITH REHACOM COMPUTERIZED REHABILITATION PROGRAM IMPROVES RESPONSE CONTROL, BUT NOT ATTENTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Mozaffari M, Hassani-Abharian P, Kholghi G, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder in children. ADHD impairs attention, response control, emotion regulation, and other cognitive functions. On the other hand, RehaCom is a cognitive rehabilitation software that has therapeutic effects on cognitive dysfunctions in many diseases such as stroke, multiple sclerosis, and schizophrenia. The goal of the present study was to investigate the effect of treatment with RehaCom on auditory and visual response control, and auditory and visual attention in children with ADHD. Forty patients were selected. The participants were assigned to control (n = 20) and experimental (n = 20) groups, while only the participants in the experimental group were trained by RehaCom for five weeks (ten 45-min sessions, two sessions per week). At weeks 0 and 5, performance of the participants of experimental group was compared with the participants of control group. The results showed that treatment with RehaCom significantly improved auditory and visual response control in children with ADHD, with no effect on auditory and visual attention. In conclusion, RehaCom may alter brain's structural and functional properties that are related to response control. We suggest that attention deficit in ADHD may be a result of more complicated dysfunctions in the brain, that are not affected by RehaCom

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J Isfahan Med Sch. 2021;39:496-503.

THE INVESTIGATION OF EFFICACY OF IMPULSE CONTROL GAME ON IMPULSIVITY AND BEHAVIORAL PROBLEMS AS AN ADJUVANT THERAPY AMONG 8-12-YEAR-OLD CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Najafi M, Tarrahi MJ, Taraffoe A.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurological disorder that affects children, adolescents, and adults. As the impulse control is a major part of their problems, they must learn how to control these impulses. The aim of this study was to determine the effectiveness of impulse control game on impulsivity and behavioral problems of children with ADHD.

Methods: This study was a randomized clinical trial. The statistical population included 60 children with ADHD at the range of 8-12 years. They were randomly divided into two equal groups of intervention and control. For the children in intervention group, the impulse control game was performed for eight weeks, twice a week for 45 minutes each time. After the intervention, the Strengths and Difficulties Questionnaire (SDQ) and Continuous Performance Test (CPT) were completed by the parents and teachers. Assessments were repeated one month later to track the effects of the intervention. At the same time, a neutral game was played in the control group. During the study, both groups took Ritalin 10 mg daily.

Finding: There was not significant difference in impulse control between subjects in the intervention group and control group. However, in terms of grades of general problems, behavioral problems, problems with peers, and increasing socially desirable behavior in terms of parents, significant differences were obtained with ($P < 0.05$). According to the teacher, there was a significant difference in the scores of general problems ($P < 0.05$), but no significant difference was observed in other subgroups.

Conclusion: Impulse control game in improved behavioral problems over time in children with ADHD. However, it did not have a significant effect on impulsivity in these patients

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J Neural Transm. 2022.

TRYPTOPHAN MODULATION IN INDIVIDUALS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Dinu LM, Phattharakulnij N, Dommett EJ.

The serotonergic system is implicated in ADHD, but the impact of serotoninΓÇÖs precursor molecule, tryptophan, on ADHD symptomology remains unclear. Systematic searches of randomised controlled trials with an experimental tryptophan intervention in children and adults with ADHD identified 14 studies measuring core and related symptoms of the condition. Risk of bias was assessed using the Cochrane Risk of Bias tool. The 14 studies all used acute tryptophan depletion procedures, and most did not investigate core ADHD symptoms (inattention, impulsivity, hyperactivity) as primary outcome measures. Only two studies examined attention and revealed mixed effects of tryptophan. Similar effects were found for impulsivity in a small number of studies. No studies investigated hyperactivity. Most studies focused on reactive aggression, but samples were heterogenous and small, rendering potential meta-analyses inconclusive or misleading. However, the narrative analysis indicates tryptophan interventions may impact reactive aggression. More research is needed on the effect of tryptophan modulation on core ADHD symptoms, especially in adults, using more diverse samples to determine potential as an intervention. From current data, tryptophan modulation appears to alter aggressive behaviour in ADHD; however, the available studies were insufficient for the planned meta-analysis

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J Neurodevelopmental Disord. 2022;14.

THE EFFECT OF AUTISTIC TRAITS ON RESPONSE TO AND SIDE-EFFECTS OF PHARMACOLOGICAL ADHD TREATMENT IN CHILDREN WITH ADHD: RESULTS FROM A PROSPECTIVE CLINICAL COHORT.

Lilja MM, Sandblom E, Lichtenstein P, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common childhood behavioral condition that globally affects an average of around 5% of children and is associated with several adverse life outcomes. Comorbidity with autism spectrum disorder (ASD) is highly prevalent. Pharmacological treatment for ADHD symptoms has been shown to be effective. However, the prevailing perception is that children with

ADHD and concomitant ASD symptoms report poorer efficacy and more side effects. This has been supported by studies on this population, but prospective studies directly comparing children with ADHD and different levels of ASD symptoms are lacking. We aimed to assess if children with ADHD and concomitant ASD symptoms differ regarding effects and side-effects of pharmacological ADHD treatment compared to children with ADHD without ASD traits. This is to our knowledge the second study to directly compare the effect of ADHD medication between ADHD patients with different levels of ASD symptoms.
Methods: In a non-randomized, observational, prospective cohort study, 323 patients aged 6 to 17 years who were diagnosed with ADHD and starting pharmacological treatment were divided into two groups: one with high level of ASD symptoms (ASD group, N=71) and one with low level of ASD symptoms (non-ASD group, N = 252). Treatment outcome was measured as ADHD symptoms, and evaluated using the Swanson, Nolan and Pelham Teacher and Parent ADHD rating scale-version IV (SNAP-IV). Side-effects were evaluated using the Pediatric Side Effects Checklist (P-SEC), at 3 months follow-up.
Results: From baseline to 3 months, there was no significant difference in neither treatment effect nor number of clinically significant adverse events experienced between the ASD group and the non-ASD group.
Conclusions: Our results did not implicate that ADHD patients with concomitant ASD symptoms have decreased treatment effect of ADHD medication than patients with ADHD without concomitant ASD symptoms. Neither did the results support that ADHD patients with ASD symptoms experienced significantly more side-effects than ADHD patients without ASD symptoms. Although, we did not analyze different medications separately, this is in line with the only previous study directly comparing methylphenidate treatment in children with or without ASD.
Trial registration: NCT02136147, May 12, 2014

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Journal of Neuroscience Research. 2022.
CLINICAL CHARACTERISTICS, NEUROIMAGING FINDINGS, AND NEUROPSYCHOLOGICAL FUNCTIONING IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER: SEX DIFFERENCES.
Carucci S, Narducci C, Bazzoni M, et al.
Recent clinical studies, in both children/adolescents and adults, have shown the extreme neuropsychological heterogeneity of attention-deficit hyperactivity disorder (ADHD): specific neuropsychological deficits have been found only in a minority of individuals, with no direct correlation between discrete cognitive performances and the trajectory of clinical symptoms. Deficits in specific neuropsychological functions may be common in ADHD, but nevertheless no cognitive or neuropsychological profile may fully explain the disorder. Sex differences in the ADHD presentation, both at a neuropsychological and clinical level, also contribute to this clinical and neuropsychological heterogeneity. At a neuropsychological level, females with ADHD may show greater working memory problems, poorer vocabulary skills and worse visual spatial reasoning. Structural and functional imaging study also show discrete differences across sex; however, the great majority of clinical studies mainly or exclusively include male participants with insufficient data to draw firm conclusions on sex differences within the disorder. Here, we report the recent literature data, discussing still open research questions about the clinical presentation, neuroimaging findings, and neuropsychological functioning in ADHD with a focus on the impact of sex differencesΓÇöa deeper insight in these unresolved issues may have relevant clinical and therapeutic implications for tailored, effective, and long-lasting interventions

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Journal of Pediatric Pharmacology and Therapeutics. 2022;27:132-40.
TRAZODONE PRESCRIBING FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER ON MEDICAID IN OREGON.
Klein TA, Graves JM, Panther S.
OBJECTIVE To examine trazodone prescribing to Medicaid-insured children with a diagnosis of attention deficit hyperactivity disorder (ADHD) from 2012 to 2016 for patient-level factors, including coexisting diagnoses associated with trazodone prescriptions.
METHODS A retrospective cohort study used de-identified claims data from the Oregon Health Authority to analyze associations, frequency, and likelihood of new trazodone fills.

RESULTS A total of 16,547 trazodone prescriptions were identified, representing 8.4% (n = 2,705) of 32,134 children. Most were filled for children ages 10 years and older. Children with ADHD were predominantly male (70.7%); however, more female children had a filled trazodone prescription compared with males (10.1% vs 7.7%). Female and male children with a filled trazodone prescription shared common diagnoses in the top 10 rank, although episodic mood disorders, such as bipolar disorder (International Classification of Diseases, Ninth Revision, Clinical Modification, diagnosis code 296) were only noted for female children. Female children were significantly older at the time of the first filled trazodone prescription (12.5 years; 95% CI, 12.3-12.7) compared with male children (12.0 years; 95% CI, 11.8ΓÇô12.1). Modified Poisson regression models found children with ADHD and a filled trazodone prescription were 3 times more likely to have a sleep-related diagnosis as their most common diagnosis (excluding ADHD), compared with those of the same age and sex without a trazodone prescription (RR, 2.94; 95% CI, 2.44ΓÇô3.54).
CONCLUSIONS Children with ADHD are prescribed trazodone off label and for conditions with no national guidelines or clinical evidence of efficacy. Female children on Medicaid may be prescribed trazodone for concurrent mental health conditions, and further research is warranted regarding potential correlates

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J Pediatr Urol. 2022.

ACCURACY OF THE SHORT SCREENING INSTRUMENT FOR PSYCHOLOGICAL PROBLEMS (SSIPPE) IN ENURESIS IN THE IDENTIFICATION OF ATTENTION-DEFICIT/ HYPERACTIVITY SYMPTOMS IN THE ENURETIC POPULATION.

de Carvalho Mrad FC, da Silva GS, de Souza Rodrigues GK, et al.

Introduction: Enuresis prevalence is approximately 5-15% in children aged 6-7 years. The presence of attention deficit hyperactivity disorder (ADHD) in enuretic children is associated with 3 times greater risk of persistent enuresis. The Multimodal Treatment Study for ADHD (MTA) Swanson, Nolan, and Pelham version IV (SNAP-IV) is one of the most used instruments to evaluate ADHD symptoms, but it is a time-consuming questionnaire.
Objective: This study aims to compare the accuracy of an easy questionnaire named Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE) to MTA-SNAP-IV in identifying ADHD symptoms in children and adolescents with enuresis.
Methods: ADHD symptoms screening was performed by applying SSIPPE and MTA-SNAP-IV in 160 children and adolescents with enuresis, aged 6-14 years, who regularly attended a specialized clinic for pediatric urology.
Results: A total of 153 individuals with enuresis were included in the study (52% males), among them 55 (35.9%) were considered positive for inattention and hyperactivity-impulsivity by the MTA-SNAP-IV. Sensitivity for SSIPPE concerning MTA-SNAP-IV was 85.5%, and specificity was 84.7%, with an overall accuracy of 85% in identifying ADHD symptoms. Discussion: In the present study, we found high accuracy of SSIPPE in relation to MTA-SNAP-IV in identifying ADHD symptoms in the enuretic population, with substantial agreement between instruments. Its sensitivity and specificity were considered high for a screening method. However, there are some limitations. The population studied is composed of a group of children with enuresis, which can lead to an overestimation of the test's accuracy, as the disorder under investigation is more prevalent in this population. This can be explained by the high specificity of the test (84.7%) associated with the fact that the SSIPPE is an instrument tailored for an enuretic population, unlike the MTA-SNAP IV.
Conclusion: The SSIPPE has proven to be a reliable tool in identifying ADHD symptoms in the enuretic population. In addition to being a quick and easily applicable instrument

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J Psychiatr Res. 2022;149:28-36.

ADHD-INATTENTIVE VERSUS ADHD-COMBINED SUBTYPES: A SEVERITY CONTINUUM OR TWO DISTINCT ENTITIES? A COMPREHENSIVE ANALYSIS OF CLINICAL, COGNITIVE AND NEUROIMAGING DATA.

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

The current study aimed to explore the multimodal differences between the inattentive ADHD (ADHD-I) subtype and the combined ADHD (ADHD-C) subtype. A large sample of medication-na+»ve children with pure ADHD (i.e., without any comorbidity) (145 with ADHD-I, 132 with ADHD-C) and healthy controls (n =

98) were recruited. A battery of multiple scales and cognitive tests were utilized to assess the clinical and cognitive profiles of each individual. In addition, structural and diffusion magnetic resonance imaging (MRI) were acquired for 120 subjects with ADHD and 85 controls. Regional gray matter volume, white matter volume, and diffusion tensors, e.g., axial diffusivity (AD), were compared among the three groups in a whole-brain voxel-wise manner. Compared with healthy controls, both ADHD groups exhibited elevated levels of behavioral and emotional problems. The ADHD-C group had more behavioral problems and emotional liability, as well as less anxiety, than the ADHD-I group. The two ADHD groups were equally impaired in most cognitive domains, with the exception of sustained attention. Compared with healthy controls, the ADHD-C group showed a high gray matter volume (GMV) in the bilateral thalamus and a high white matter volume in the body of the corpus callosum, while the ADHD-I group presented an elevated GMV mainly in the left precentral gyrus and posterior cingulate cortex. Compared with participants with ADHD-C and healthy controls, subjects with ADHD-I showed increased AD in widespread brain regions. Our study has revealed a distinct, interconnected pattern of behavioral, cognitive, and brain structural characteristics in children with different ADHD subtypes

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J Psychiatr Res. 2022;149:217-25.

STRESS-RELATED BIOMARKERS AND COGNITIVE FUNCTIONING IN ADOLESCENTS WITH ADHD: EFFECT OF CHILDHOOD MALTREATMENT.

Llorens M, Barba M, Torralbas J, et al.

Our study aimed to explore whether stress-related hormones (hypothalamic-pituitary-adrenal [HPA] axis hormones and prolactin) are associated with poorer cognitive functioning in adolescents with attention deficit and hyperactivity disorder (ADHD) and to test the potential moderating effect of childhood maltreatment. Seventy-six adolescents with ADHD were studied. The ADHD rating scale (ADHD-RS) and Childhood Trauma Questionnaire (CTQ) were administered. Seven cognitive tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered, and two cognitive factors (attention and memory as well as executive functioning) were identified by confirmatory factor analysis. Stress-related hormone levels were assessed at the clinic (plasma prolactin and cortisol levels and salivary cortisol levels) before cognitive testing and at home for two consecutive days (cortisol awakening response [CAR] and diurnal cortisol slope). Multiple linear regression analyses were used to explore the association between hormone levels and ADHD severity or cognitive functioning while adjusting for sex and childhood maltreatment. Regarding hormonal measurements obtained at the clinic, female sex moderated the relationship between salivary cortisol levels and executive functioning, whereas childhood maltreatment moderated the relationship between salivary cortisol levels and inattention symptoms of patients with ADHD. Prolactin levels were not associated with cognitive functioning or the severity of ADHD. Regarding HPA axis measurements performed at home, lower cortisol levels at awakening were associated with poorer executive functioning. Neither CAR nor the cortisol diurnal slope were associated with cognitive functioning or ADHD severity. Our study suggests that HPA axis hormone levels are associated with the severity of cognitive and inattention symptoms of patients with ADHD and that childhood maltreatment and sex exert distinct moderating effects depending on the symptom type

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J Psychiatr Res. 2022;149:1-9.

STRESS-RELATED GENETIC COMPONENTS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): EFFECTS OF THE SERPINA6 AND SERPINA1 GENETIC MARKERS IN A FAMILY-BASED BRAZILIAN SAMPLE.

Carpena MX, S+ínchez-Luquez KY, Martins-Silva T, et al.

SERPINA6 and SERPINA1 were recently identified as the main genes associated with plasma cortisol concentration in humans. Although dysregulation in the HypothalamusΓÇôPituitary-Adrenal (HPA) axis has been observed in Attention Deficit/Hyperactivity Disorder (ADHD), the molecular mechanisms underlying this relationship are still unclear. Evaluation of the SERPINA6/SERPINA1 gene cluster in ADHD may provide relevant information to uncover them. We tested the association between the SERPINA6/SERPINA1 locus, including 95 single nucleotide polymorphisms (SNPs), and ADHD, using data from a Brazilian clinical sample of 259 ADHD probands and their parents. The single SNP association was tested using binary logistic

regression, and we performed Classification and Regression Tree (CART) analysis to evaluate genotype combinations' effects on ADHD susceptibility. We assessed SNPsΓÇÖ regulatory effects through the Genotype-Tissue Expression (GTEx) v8 tool, and performed a complementary look-up analysis in the largest ADHD GWAS to date. There was a suggestive association between ADHD and eight variants located in the SERPINA6 region and one in the intergenic region between SERPINA6 and SERPINA1 after correction for multiple tests ($p < 0.032$). CART analysis showed that the combined effects of genotype GG in rs2144833 and CC in rs10129500 were associated with ADHD (OR = 1.78; CI95% = 1.24ΓÇô2.55). The GTEx assigned the SNPs as eQTLs for genes in different tissues, including SERPINA6, and the look-up analysis revealed two SNPs associated with ADHD. These results suggest a shared genetic component between cortisol levels and ADHD. HPA dysregulation/altered stress response in ADHD might be mediated by upregulation of corticosteroid binding globulin (CBG, encoded by SERPINA6) expression

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J Psychiatr Res. 2022;149:252-59.

THE EFFECTS OF PSYCHOSTIMULANTS ON COGNITIVE FUNCTIONS IN INDIVIDUALS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Mckenzie A, Meshkat S, Lui LMW, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of deficits in cognitive functions which has significant implications for quality of life. Psychostimulants are demonstrated to improve symptoms of inattention and hyperactivity/impulsivity, however, their impact on cognition remains incompletely characterized. Herein, the aim of this systematic review is to synthesize the extant literature reporting on the effects of psychostimulants on cognitive function in individuals with ADHD.

Method: A systematic search of PubMed, Scopus, and Web of Science from inception to July 2021 was conducted. Additional studies were identified through Google Scholar and a manual search of the reference lists of relevant articles. Inclusion criteria were original studies that evaluated the cognitive function of individuals with ADHD taking psychostimulants drugs. We assessed the quality of the included papers using the NewcastleΓÇôOttawa scale (NOS).

Results: A total of 10 studies involving 753 subjects with ADHD and 194 healthy controls were identified and eligible for inclusion. Nine studies evaluated the impact of methylphenidate on cognitive function and one study investigated the use of lisdexamfetamine. Results indicated that attentional deficits such as memory, vigilance, divided attention, phasic and tonic alertness, and focused attention were improved in ADHD patients treated with psychostimulants. The efficacy of psychostimulants in improving other domains of cognition remains inconclusive due to conflicting evidence or insignificant findings (ie. academic performance and executive function). Overall, results indicate that psychostimulants may improve only select domains of cognition (ie. memory and attention).

Conclusion: Psychostimulants are reported to improve several disparate aspects of cognition among individuals with ADHD. Further research is needed to better understand the complex relationships between cognition and behavior in ADHD, as well as the impact of medication on these distinct aspects of functioning. Further research is also needed to determine whether the pro-cognitive effect of stimulants would be transferable to other mental disorders

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J Psychopathol Behav Assess. 2022.

HARMONIZED PHENOTYPES FOR ANXIETY, DEPRESSION, AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Jovi-ç M, Agarwal K, Whitehouse A, et al.

In multi-cohort consortia, the problem often arises that a phenotype is measured using different questionnaires. This study aimed to harmonize scores based on the Child Behaviour Check List (CBCL) and the Strength and Difficulties Questionnaire (SDQ) for anxiety/depression and ADHD. To link the scales, we used parent reports on 1330 children aged 10ΓÇô11.5-áyears from the Raine study on both SDQ and CBCL. Harmonization was done based on Item Response Theory. We started from existing CBCL and SDQ scales related to anxiety/depression and ADHD (theoretical approach). Next, we conducted a data-driven approach using factor analysis to validate the theoretical approach. Both approaches yielded similar scales, validating

the combination of existing scales. In addition, we studied the impact of harmonized (IRT-based) scores on the statistical power of the results in meta-analytic gene-finding studies. The results showed that the IRT-based harmonized scores increased the statistical power of the results compared to sum scores, even with an equal sample size. These findings can help future researchers to harmonize data from different samples and/or different questionnaires that measure anxiety, depression, and ADHD, in order to obtain the larger sample sizes, to compare research results across subpopulations or to increase generalizability, the validity or statistical power of research results. We recommend using our item parameters to estimate harmonized scores that represent commensurate phenotypes across cohorts, and we explained in detail how other researchers can use our results to harmonize data in their studies

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J Am Acad Child Adolesc Psychiatry. 2022 Feb;61:144-58.

AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS: BEHAVIORAL TREATMENTS FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Groenman AP, Hornstra R, Hoekstra PJ, et al.

Objective: Behavioral interventions are well established treatments for children with attention-deficit/hyperactivity disorder (ADHD). However, insight into moderators of treatment outcome is limited.

Method: We conducted an individual participant data meta-analysis (IPDMA), including data of randomized controlled behavioral intervention trials for individuals with ADHD <18 years of age. Outcomes were symptoms of ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) and impairment. Moderators investigated were symptoms and impairment severity, medication use, age, IQ, sex, socioeconomic status, and single parenthood.

Results: For raters most proximal to treatment, small- to medium-sized effects of behavioral interventions were found for symptoms of ADHD, inattention, hyperactivity/impulsivity (HI), ODD and CD, and impairment. Blinded outcomes were available only for small preschool subsamples and limited measures. CD symptoms and/or diagnosis moderated outcome on ADHD, HI, ODD, and CD symptoms. Single parenthood moderated ODD outcome, and ADHD severity moderated impairment outcome. Higher baseline CD or ADHD symptoms, a CD diagnosis, and single parenthood were related to worsening of symptoms in the untreated but not in the treated group, indicating a protective rather than an ameliorative effect of behavioral interventions for these children.

Conclusion: Behavioral treatments are effective for reducing ADHD symptoms, behavioral problems, and impairment as reported by raters most proximal to treatment. Those who have severe CD or ADHD symptoms, a CD diagnosis, or are single parents should be prioritized for treatment, as they may evidence worsening of symptoms in the absence of intervention

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J Am Acad Child Adolesc Psychiatry. 2022;61:187-226.

SYSTEMATIC REVIEW AND META-ANALYSIS: THE SCIENCE OF EARLY-LIFE PRECURSORS AND INTERVENTIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shephard E, Zuccolo PF, Idrees I, et al.

Objective: To evaluate which early neurocognitive and behavioral precursors are associated with the development of attention-deficit/hyperactivity disorder (ADHD) and whether these are currently targeted in early interventions.

Method: We conducted 2 systematic reviews and meta-analyses of empirical studies to examine the following: (1) early-life (0-5 years) neurocognitive and behavioral precursors associated with familial likelihood for ADHD, an early ADHD diagnosis/elevated ADHD symptoms, and/or the presence of later-childhood ADHD; and (2) interventions delivered to children aged 0 to 5 years targeting the identified precursors or measuring these as outcomes. Standardized mean differences (HedgesΓÇÖ g) and pre-post-treatment change scores (SMD) were computed.

Results: A total of 149 studies (165,095 participants) investigating 8 neurocognitive and behavioral domains met inclusion criteria for part 1. Multi-level random-effects meta-analyses on 136 studies revealed significant associations between ADHD and poorer cognitive (g = 0.46 [95% CIs: 0.59, 0.33]), motor (g = 0.35 [CIs: 0.48, 0.21]) and language (g = 0.43 [CIs: 0.66, 0.19]) development, social (g = 0.23 [CIs: 0.03, 0.43]) and

emotional (g = 0.46 [CIs: 0.33, 0.58]) difficulties, early regulatory (g = 0.30 [CIs: 0.18, 0.43]) and sleep (g = 0.29 [CIs: 0.14, 0.44]) problems, sensory atypicalities (g = 0.52 [CIs: 0.16, 0.88]), elevated activity levels (g = 0.54 [CIs: 0.37, 0.72]), and executive function difficulties (g = 0.34 [CIs: 0.05, 0.64] to ΓêÆ0.87 [CIs: 1.35, 0.40]). A total of 32 trials (28 randomized, 4 nonrandomized, 3,848 participants) testing early interventions that targeted the identified precursors met inclusion criteria for part 2. Multi-level random-effects meta-analyses on 22 studies revealed significant intervention-related improvements in ADHD symptoms (SMD = 0.43 [CIs: 0.22, 0.64]) and working memory (SMD = 0.37 [CIs: 0.06, 0.69]).
Conclusion: Children aged 0 to 5 years with current or later-emerging ADHD are likely to experience difficulties in multiple neurocognitive/behavioral functions. Early interventions show some effectiveness in reducing ADHD symptoms, but their effects on neurocognitive/behavioral difficulties require further study

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J Int Neuropsychol Soc. 2022 Jan;28:12-21.

FEEDBACK-BASED LEARNING OF TIMING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND NEUROFIBROMATOSIS TYPE 1.

Prochnow A, Bluschke A, Novotna B, et al.

Objective: Patients with Neurofibromatosis Type 1 (NF1) frequently display symptoms resembling those of Attention Deficit/Hyperactivity Disorder (ADHD). Importantly, these disorders are characterised by distinct changes in the dopaminergic system, which plays an important role in timing performance and feedback-based adjustments in timing performance. In a transdiagnostic approach, we examine how far NF1 and ADHD show distinct or comparable profiles of timing performance and feedback-based adjustments in timing.
Method: We examined time estimation and learning processes in healthy control children (HC), children with ADHD with predominantly inattentive symptoms and those with NF1 using a feedback-based time estimation paradigm.
Results: Healthy controls consistently responded closer to the correct time window than both patient groups, were less variable in their reaction times and displayed intact learning-based adjustments across time. The patient groups did not differ from each other regarding the number of in-time responses. In ADHD patients, the performance was rather unstable across time. No performance changes could be observed in patients with NF1 across the entire task.
Conclusions: Children with ADHD and NF1 differ in feedback learning-based adjustments of time estimation processes. ADHD is characterised by behavioural fluctuations during the learning process. These are likely to be associated with inefficiencies in the dopaminergic system. NF1 is characterised by impairments of feedback learning which could be due to various neurotransmitter alterations occurring in addition to deficits in dopamine synthesis. Results show that despite the strong overlap in clinical phenotype and neuropsychological deficits between NF1 and ADHD, the underlying cognitive mechanisms are different

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J Int Neuropsychol Soc. 2022 Feb;28:109-22.

LEARNING AND ATTENTION DEFICIT/HYPERACTIVITY DISORDERS AS RISK FACTORS FOR PROLONGED CONCUSSION RECOVERY IN CHILDREN AND ADOLESCENTS.

Martin AK, Petersen AJ, Sesma HW, et al.

Objective: Examine pre-existing learning disorders (LD) and attention deficit/hyperactivity disorders (ADHD) as risk factors for prolonged recovery and increased symptomology following pediatric mild traumatic brain injury (mTBI).
Methods: We conducted a retrospective cohort study of children/adolescents (5-17 years) with mTBI who presented to a Children's Minnesota Concussion Clinic between April 2018 and March 2019. Differences across strata of pre-existing conditions (present vs. absent) in time to recovery measures were estimated via Kaplan–Meier and Cox proportional hazards analyses and differences in symptom trajectories were examined via linear mixed-effects regression models. Regression models were adjusted for age, sex and other confounders.
Results: In our cohort of 680 mTBI patients, those with LD (n = 70) or ADHD (n = 107) experienced significantly longer median durations of symptoms (58 and 68 days, respectively) than those without (43 days). Accordingly, LD was significantly associated with delayed symptom recovery (adjusted hazard ratio

(aHR) = 1.63, 95% CI: 1.16–2.29), return to school (1.47, 1.08–2.00), and return to physical activity (1.50, 1.10–2.04). Likewise, ADHD was associated with delayed recovery (1.69, 1.28–2.23), return to school (1.52, 1.17–1.97) and physical activity (1.55, 1.19–2.01). Further, patients with LD or ADHD reported, on average, significantly more concussion symptoms and higher vision symptom scores throughout recovery versus those without. There was no evidence that concussion or vision symptom recovery trajectories varied over time between those with/without LD or ADHD (joint P-interactions > 0.05).
Conclusion: Pre-existing LD and ADHD are risk factors for prolonged and more symptomatic mTBI recovery in youth. These results can inform clinical concussion management and recovery expectations

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Medicina (Argentina). 2022;82:23-27.

NEUROPSYCHOLOGICAL DEFICITS, SYMPTOM INTENSITY AND FUNCTIONAL IMPAIRMENT IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Albert J, S+ínchez-Carmona AJ, L+¦pez-Mart+¡n S, et al.

This study aims to contribute to a better understanding of attention deficit hyperactivity disorder (ADHD) by comprehensively examining the relationship between two of the main cognitive deficits of the disorder (attention and inhibitory control), symptomatology (inattention and hyperactivity/impulsivity) and functional impairment in 85 children and adolescents with ADHD without other comorbid disorders. We found, independent of general intellectual functioning and age, that i) greater atten-tional and inhibitory deficits predicted greater severity of ADHD symptoms, ii) greater attentional and inhibitory deficits predicted greater functional impairment, but not in a direct way but through symptoms, and iii) greater symptomatic severity predicted greater functional impairment. Beginning to explore and understand the complexity of ADHD is key to advance our knowledge of the disorder and for correct clinical decision making

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Neural Netw. 2022 May;149:157-71.

JOINT LEARNING OF MULTIPLE GRANGER CAUSAL NETWORKS VIA NON-CONVEX REGULARIZATIONS: INFERENCE OF GROUP-LEVEL BRAIN CONNECTIVITY.

Manomaisaowapak P, Songsiri J.

This paper considers joint learning of multiple sparse Granger graphical models to discover underlying common and differential Granger causality (GC) structures across multiple time series. This can be applied to drawing group-level brain connectivity inferences from a homogeneous group of subjects or discovering network differences among groups of signals collected under heterogeneous conditions. By recognizing that the GC of a single multivariate time series can be characterized by common zeros of vector autoregressive (VAR) lag coefficients, a group sparse prior is included in joint regularized least-squares estimations of multiple VAR models. Group-norm regularizations based on group- and fused-lasso penalties encourage a decomposition of multiple networks into a common GC structure, with other remaining parts defined in individual-specific networks. Prior information about sparseness and sparsity patterns of desired GC networks are incorporated as relative weights, while a non-convex group norm in the penalty is proposed to enhance the accuracy of network estimation in low-sample settings. Extensive numerical results on simulations illustrated our method's improvements over existing sparse estimation approaches on GC network sparsity recovery. Our methods were also applied to available resting-state fMRI time series from the ADHD-200 data sets to learn the differences of causality mechanisms, called effective brain connectivity, between adolescents with ADHD and typically developing children. Our analysis revealed that parts of the causality differences between the two groups often resided in the orbitofrontal region and areas associated with the limbic system, which agreed with clinical findings and data-driven results in previous studies

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Neuropsychiatr Enfance Adolesc. 2022.

PREVALENCE OF TICS AMONG ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN TREATED WITH METHYLPHENIDATE.

Kahrizi MS, Ghanbari Mardasi K, Ghanbari Merdasi P, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is one of the most common psychoneurological disorders in children. Psychostimulants such as methylphenidate, used for the treatment of ADHD, but can increase the incidence of tics.

Objectives: The aim of this study was to investigate the relationship between methylphenidate consumption in patients with ADHD and the incidence of motor and phonic tics with regard to differences in gender, age and drug dosage in these patients.

Method: This study was a cross-sectional study where ADHD patients referred to (XXX) and medical Center for the treatment of ADHD were included. The patients underwent methylphenidate treatment and were asked to come in for follow up four weeks after the treatment. The data collection tools were a demographic questionnaire and a comprehensive Yale Global Tic Severity Scale (YGTSS) questionnaire.

Results: One hundred and fourteen patients with ADHD were included in the study of whom 78.07% were male. The prevalence of tic disorder before treatment was 16.7% (19 patients) and was 21.9% (25 patients) during treatment. The number of phonic tics was significantly different based on the age of the patients before and during the treatment. In total, the mean score of the questionnaire before and during treatment was 51.63 and 58.44, which was significantly different.

Conclusion: Our study reported a significant difference in the prevalence of tics before and during the treatment. However, based on previous studies, this difference may not be clinically significant

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Neuropsychology. 2022 Mar.

CENTRAL EXECUTIVE TRAINING FOR ADHD: EFFECTS ON ACADEMIC ACHIEVEMENT, PRODUCTIVITY, AND SUCCESS IN THE CLASSROOM.

Singh LJ, Gaye F, Cole AM, et al.

Objective: Central executive training (CET) is a 'Level 2' evidence-based treatment for improving ADHD-related executive dysfunction and behavioral symptoms, but the extent to which these gains extend to the disorder's well-documented academic difficulties is unknown.

Method: Across two clinical trials, 108 children with attention-deficit/hyperactivity disorder (ADHD) 8–13 years old (M = 10.29, SD = 1.50; 32 girls; 75% White/Non-Hispanic) were treated with CET (n = 52), inhibitory control training (ICT; n = 29), or gold-standard behavioral parent training (BPT; n = 27).

Results: CET was superior to BPT and ICT (d = 0.62–0.88) for improving masked teacher perceptions of academic success, impulse control, and academic productivity at 1–2 months posttreatment. At 2–4-month follow-up, CET (d = 0.76) and ICT (d = 0.54) were superior to BPT for improving objectively-tested academic achievement overall (reading comprehension, math problem-solving, language comprehension), and CET was superior to ICT (d = 0.56) for improving math problem-solving. The significant benefits of CET on academic success, academic productivity, reading comprehension, and math problem-solving replicated across both trials and were clinically significant as evidenced by low number needed to treat estimates (Needed to Treat; NNT = 3–7) and significantly higher proportions of individual cases demonstrating reliable improvements in academic success/productivity (33%–36% vs. 0%–18%) and achievement (38%–72% vs. 18%–54%) across outcomes (all p = .01).

Conclusions: Results across the two trials provide strong support for the efficacy of CET for ADHD, and are consistent with model-driven hypotheses that academic difficulties in ADHD are due, in part, to these children's underdeveloped executive functioning abilities.

Question: Central executive training (CET) improves the 'working' components of working memory and has been shown to improve ADHD-related executive dysfunction and behavioral symptoms, but do these gains extend to the disorder's well-documented academic difficulties? Findings: CET was superior to behavioral parent training (BPT) and/or inhibitory control training (ICT) for improving masked teacher perceptions of academic success and academic productivity as well as objectively-assessed academic achievement in reading comprehension and math problem-solving across two clinical trials. Importance: CET yields direct benefits for children with attention-deficit/hyperactivity disorder (ADHD) and demonstrates academic far-transfer benefits relative to both gold-standard BPT and an active, credible, and adaptive neurocognitive

training intervention (ICT). Next Steps: Future work is needed to evaluate CET's potential benefits across a broader array of academic skills as well as other domains of functional impairment associated with ADHD (e.g., peer, family, organizational skills).

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New Zealand Medical Journal. 2020;133:84-95.

MEDICATION DISPENSING FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TO NEW ZEALAND YOUTH.

D'Souza S, Bowden N, Gibb S, et al.

AIMS: Global trends show an increase in medication dispensing for attention-deficit/hyperactivity disorder (ADHD) in young people over time. The current study aimed to examine whether similar trends were observed in New Zealand youth over the period of 2007/08 to 2016/17.

METHODS: We estimated the prevalence in ADHD medication dispensing using national pharmaceutical data for each fiscal year from 2007/08 to 2016/17 in approximately 2.4 million New Zealand youth aged 1-24 years. We also examined whether trends varied by sociodemographic factors.

RESULTS: The total dispensing prevalence almost doubled from 516 per 100,000 to 996 per 100,000 over the study period. Males had a consistently higher dispensing prevalence relative to females. Young people aged 7-17 years had the highest dispensing prevalence. The most deprived quintile had a slightly lower dispensing prevalence relative to other quintiles. Ethnic differences in dispensing prevalence were apparent, with deprivation differences also existing within most ethnic groups.

CONCLUSIONS: Overall, our study showed an increase in ADHD medication use by young people in New Zealand, similar to international findings. Further research is needed into why disparities in dispensing prevalence occur across ethnic and socioeconomic groups

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Noropsikiyatr Ars. 2022;59:63-67.

SERUM HEAT SHOCK PROTEIN 70 LEVEL IN CHILDREN WITH ATTENTION DEFICIENCY HYPERACTIVITY DISORDER.

Ozaslan A, Guney E, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) have quite complicated etiology. The relationship between ADHD and immune and oxidative imbalances is discussed in current researches investigating the pathophysiology of ADHD. The aim of the study is to determine whether heat shock protein 70 (HSP70) has a potential role in pathophysiologic mechanisms of attention deficit hyperactivity disorder.

Methods: This study included 41 children that were diagnosed with ADHD and 32 typically developing children. ConnersΓÇÖ Teacher Rating Scale (CTRS) was used to evaluate ADHD presentation and severity. Additionally, an enzyme-linked immunosorbent assay (ELISA) kit was used to evaluate serum HSP70 level.

Results: We have detected that the serum HSP70 levels of children with ADHD were lower than the typically developing group ($p<0.01$). No relationship was determined between HSP70 levels and either the severity of ADHD or predominantly ADHD presentations ($p>0.05$).

Conclusion: With these findings, it can be proposed that HSP70 might have a crucial role in the etiological mechanisms of ADHD. Moreover, these changes in peripheral blood may have therapeutic and/or diagnostic value. However, more detailed prospective studies are needed to explain the link between ADHD and heat shock proteins

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Nutrients. 2022 Mar;14.

DO CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FOLLOW A DIFFERENT DIETARY PATTERN THAN THAT OF THEIR CONTROL PEERS?

Rojo-Marticella M, Arija V, Alda JÃ, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and adolescents. A current area of interest is the association between ADHD and food consumption. The aim of this study was to determine the food consumption and dietary patterns of children with and without ADHD in relation to their age and ADHD presentation. The study involved 259 preschoolers aged 3 to 6 years old (57 with ADHD and 202 controls) and 475 elementary-school-age children, aged 10 to 12 years old (213 with ADHD and 262 controls) from Spain. ADHD was diagnosed in accordance with the Diagnostic

and Statistical Manual of Mental Disorders (5th edition) from Schedule for Affective Disorders and Schizophrenia for School-Age Children interviews. Eating data were collected using a food consumption frequency questionnaire, and principal component analysis was carried out to analyze dietary patterns. Western-like, sweet, and healthy patterns were identified. The ADHD group was negatively associated with the healthy pattern (p < 0.001) and positively associated with the Western-like diet (p = 0.004). Children with inattentive presentation showed lower adherence (12.2%) to a healthy pattern than that of the control group (39.9%) (p < 0.001). There is an association between ADHD and dietary habits; children with inattentive presentation may particularly be at risk of unhealthy eating habits

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Nutrients. 2022 Jan;14.

ASSOCIATION OF FOOD ALLERGY, RESPIRATORY ALLERGY, AND SKIN ALLERGY WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AMONG CHILDREN.

Xu G, Liu B, Yang W, et al.

BACKGROUND: Previous studies have predominately examined associations of respiratory allergy and skin allergy with ADHD, but little is known about the association between food allergy and ADHD.

METHODS: We included 192,573 children aged 4-17 years from the National Health Interview Survey (NHIS), a leading health survey in a nationally representative sample of the US population. Allergy conditions and ADHD were defined based on an affirmative response in the NHIS questionnaire. We used weighted logistic regression to estimate the odds ratio (OR) of ADHD.

RESULTS: Among the 192,573 children, 15,376 reported ADHD diagnosis. The prevalence of ADHD was higher among children with allergic conditions: 12.66% vs. 7.99% among children with and without food allergy; 12.16% vs. 7.63% among children with and without respiratory allergy; and 11.46% vs. 7.83% among children with and without skin allergy. After adjusting for covariates, the OR of ADHD was 1.72 (95% CI, 1.55-1.91) comparing children with and without food allergy, 1.50 (95% CI, 1.41-1.59) comparing children with and without respiratory allergy, and 1.65 (95% CI, 1.55-1.75) comparing children with and without skin allergy. The observed associations remained significant after mutual adjustment for other allergic conditions.

CONCLUSIONS: In a nationally representative sample of US children, we found a significant association of common allergic conditions (food allergy, respiratory allergy, and skin allergy) with ADHD

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Nutrients. 2022 Mar;14.

HOUSEHOLD FOOD INSECURITY IS ASSOCIATED WITH SYMPTOMS OF EMOTIONAL DYSREGULATION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: THE MADDY STUDY.

Hatsu IE, Eiterman L, Stern M, et al.

The association of household food insecurity with symptoms of attention deficit hyperactivity disorder (ADHD) and emotional dysregulation in children was examined in this study. We utilized baseline data from 134 children aged 6-12 years who were enrolled in a clinical trial investigating multinutrient supplementation as a treatment for ADHD and emotional dysregulation. Household food security status was assessed using the 18-item US Household Food Security Survey Module. The symptoms of ADHD and emotional dysregulation disorders (oppositional defiant disorder (ODD) and disruptive mood dysregulation disorder (DMDD)) were assessed using the Child and Adolescent Symptom Inventory-5 and other comorbid emotional dysregulation symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ). Multiple linear regression determined associations between household food security status and symptoms of ADHD, ODD and DMDD, emotional symptoms and conduct problems. Household food insecurity was associated with more severe emotional symptoms (Î² = 2.30; 95% CI = 0.87-3.73; p = 0.002), conduct problems (Î² = 1.15; 95% CI = 0.01-2.30; p = 0.049) and total difficulties scores (Î² = 4.59; 95% CI = 1.82-7.37; p = 0.001) after adjusting for covariates (child's sex, parent marital status, household income, parental anxiety and other parental psychopathology). In unadjusted analyses, household food insecurity was also associated with increased ODD (Î² = 0.58; 95% CI = 0.21-0.95; p = 0.003) and DMDD symptoms (Î² = 0.69; 95% CI = 0.20-1.19; p = 0.006), but these associations attenuated to non-significance after adjusting for all covariates. Household food insecurity was associated with more severe emotional dysregulation symptoms. Discussing

and addressing food insecurity may be appropriate initial steps for youths with ADHD and emotional dysregulation

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Nutritional Neuroscience. 2022;25:11-21.

TOWARD "ŸELEMENT BALANCE" IN ADHD: AN EXPLORATORY CASE CONTROL STUDY EMPLOYING HAIR ANALYSIS.

Perham JC, Shaikh NI, Lee A, et al.

Background: Head hair analysis has been used for decades to clarify mineral relationships to symptoms of ADHD, but there is little consensus among findings. We sought to explore 33 hair element concentrations and their 528 calculated ratios among two groups of boys, one with ADHD and one without.

Method: 107 boys aged 7ΓÇô12 years were recruited; 55 with ADHD and 52 non-ADHD Controls. Hair minerals were compared using MannΓÇôWhitney U tests, p<0.01 was used for significance. Dietary data were obtained using a 138 item food frequency questionnaire (FFQ).

Results: There were three group differences on individual elements: bismuth/Bi: 8 fold higher in ADHD, chromium/Cr: 15% lower in ADHD and germanium/Ge: 11% lower in ADHD, Cr level being the strongest predictor of ADHD symptoms. We found thirty significant group differences in element ratios, two thirds involving Bi and eight of these showing that as ADHD severity increased, the ratios with Bi as the denominator decreased (r ranging from 0.263 to 0.433, p<0.01). From the FFQ, tinned fruit was consumed more often in the ADHD group. Hair arsenic levels were somewhat elevated across both ADHD and Control groups.

Discussion: While element imbalance appears to be associated with ADHD, we did not replicate any previous study results of group differences on individual elements. We have raised the possibility that the ratios may be far more important than any one individual element in better elucidating the effects that minerals may have on the pathogenesis of ADHD. These are cautionary findings requiring replication

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Pediatrics. 2021;148.

IMPROVING ENGAGEMENT IN ADHD CARE.

Chan E.

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Pediatrics. 2022 Apr;149.

INTEGRATING PEDIATRIC UNIVERSAL BEHAVIORAL HEALTH CARE AT FEDERALLY QUALIFIED HEALTH CENTERS.

Sheldrick RC, Bair-Merritt MH, Durham MP, et al.

BACKGROUND: Research supports integrated pediatric behavioral health (BH), but evidence gaps remain in ensuring equitable care for children of all ages. In response, an interdisciplinary team codeveloped a stepped care model that expands BH services at 3 federally qualified health centers (FQHCs).

METHODS: FQHCs reported monthly electronic medical record data regarding detection of BH issues, receipt of services, and psychotropic medications. Study staff reviewed charts of children with attention-deficit/hyperactivity disorder (ADHD) before and after implementation.

RESULTS: Across 47-437 well-child visits, >80% included a complete BH screen, significantly higher than the state's long-term average (67.5%; P < .001). Primary care providers identified >30% of children as having BH issues. Of these, 11.2% of children <5 years, 53.8% of 5-12 years, and 74.6% >12 years were referred for care. Children seen by BH staff on the day of referral (ie, "warm hand-off") were more likely to complete an additional BH visit than children seen later (hazard ratio = 1.37; P < .0001). There was no change in the proportion of children prescribed psychotropic medications, but polypharmacy declined (from 9.5% to 5.7%; P < .001). After implementation, diagnostic rates for ADHD more than doubled compared with baseline, follow-up with a clinician within 30 days of diagnosis increased (62.9% before vs 78.3% after; P = .03) and prescriptions for psychotropic medication decreased (61.4% before vs 43.9% after; P = .03).

CONCLUSIONS: Adding to a growing literature, results demonstrate that integrated BH care can improve services for children of all ages in FQHCs that predominantly serve marginalized populations

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Pediatrics. 2022 Apr;149.

EMERGENCY VISITS FOR AUTISTIC CHILDREN AND CHILDREN WITH ADHD.

Schott W, Tao S, Shea L.

BACKGROUND AND OBJECTIVES: Autistic children and children with attention-deficit/hyperactivity disorder (ADHD) may have more frequent visits to the emergency department (ED). We aim to identify the primary reasons for ED visits among autistic children and children with ADHD, compared to a random sample of visits.

METHODS: Using 2008 to 2017 Nationwide Emergency Department Sample data, we assessed the most frequent primary diagnoses for ED visits among children (ages 3-12 and 13-18 years, separately) (1) with an autism diagnosis, (2) with ADHD, and (3) a random sample (1000000 visits). We regressed primary reasons for visits on autism or ADHD diagnosis, controlling for individual characteristics, to assess the odds of presenting for these reasons.

RESULTS: Although the 10 most frequent diagnoses among the random sample were physical health conditions, autistic children and children with ADHD often presented for psychiatric conditions. Older children with autism and with ADHD more frequently presented for mood disorders (10%-15% of visits; odds ratios [ORs] = 5.2-8.5) and intentional self-harm (ORs = 3.2-5.0). Younger children with ADHD more commonly presented with mood disorders (6.6% of visits; OR = 18.3) and younger autistic children more often presented with attention-deficit, conduct, and disruptive behavior disorders (9.7% of visits; OR = 9.7).

CONCLUSIONS: Autistic children and children with ADHD have higher odds of presenting to the ED for psychiatric conditions than a random sample, including for self-harm. Clinicians should treat these populations sensitively, recognize and assess the risk for self-harm, and facilitate continuing psychiatric care

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Prostaglandins Leukotrienes Essent Fatty Acids. 2022;178.

PLASMA AND RED BLOOD CELL N3 FATTY ACIDS CORRELATE POSITIVELY WITH THE WISC-R VERBAL AND FULL-SCALE INTELLIGENCE QUOTIENTS AND INVERSELY WITH CONNER'S PARENT-RATED ADHD INDEX T-SCORES IN CHILDREN WITH HIGH FUNCTIONING AUTISM AND ASPERGER'S SYNDROME.

Oracka BJ, Min Y, Bhullar AS, et al.

Findings of the fatty acid status of people with autism spectrum disorders have been incongruent perhaps because of the diversity of the condition. A cross-sectional design study was used to investigated fatty acid levels and relationships between fatty acids, and cognition and behaviour in a homogenous group of children with autism spectrum disorder. Children with Asperger's syndrome (AS) /high functioning autism (n = 44) and healthy siblings (n = 17) were recruited from the Diagnostic and Therapeutic Centre for Children with Autism, Warsaw, Poland. In the AS group, plasma phosphatidylcholine 22:5n3 correlated positively with verbal (r = 0.357, p = 0.019) and full scale (r = 0.402, p = 0.008) IQs, red blood cell phosphatidylcholine 22:5n3 with verbal (r = 0.308, p = 0.044), performance (r = 0.304, p = 0.047) and full scale (r = 0.388, p = 0.011) IQs and red blood cell phosphatidylethanolamine 22:5n3 with verbal (r = 0.390, p = 0.010) and full scale (r = 0.370, p = 0.016) IQs. Whilst, plasma phosphatidycholine 20:5n3 (r = -0.395, p = 0.009), 22:6n3 (r = -0.402, p = 0.007) and total n3 fatty acids (r = -425, p = 0.005), red blood cell phosphatidlycholine 20:5n3 (r = -0.321, p = 0.036) and red blood cell phosphatidylethanolamine 20:5n3 (r = -0.317, p = 0.038), 22:6n3 (r = -0.297, p = 0.05) and total n3 fatty acids (r = -0.306, p = 0.046) correlated inversly with ADHD index. Similarly, inattention was negatively related with plasma phosphatidylcholine 22:6n3 (r = -0.335, p = 0.028), and total n3 fatty acids (r = -0.340, p = 0.026), oppositional with plasma phosphatidylcholine 18:3n3 (r = -0.333, p = 0.029), 20:5n3 (r = -0.365, p = 0.016), total n3 fatty acids (r = -0.293, p < 0.05), red blood cell phosphatidylcholine 18:3n3 (r = -0.337, p = 0.027) and red blood cell ethanolamine 18:3n3 (r = - 0.333, p = 0.029), 20:5n3 (r = -0.328, p = 0.032), 22:6n3 (r = 0.362, p = 0.017) and total n-3 fatty acids (r = -0.298, p < 0.05) and hyperactivity with plasma phosphatidylcholine 22:6n3 (r = -0.320, p = 0.039). In contrast, there were inverse correlations between red blood cell phosphatidylcholine 18:2n6 and performance (r = -0.358, p = 0.019) and full scale (r = -0.320, p = 0.039) IQs, and direct correlations between red blood cell phosphatidylcholine 22:4n6 (r = 0.339, p = 0.026) and 22:5n6 (r = 0.298, p < 0.05) and ADHD index, between red blood cell phosphatidylcholine 22:4n6 (r = 0.308, p = 0.044) and inattention, between plasma phosphatidylcholine 22:4n6 (r = 0.341, p = 0.025), red blood cell phosphatidylcholine 20:4n6 (r = 0.314, p = 0.041) and total n6 fatty acids (r = 0.336, p = 0.028) and oppositional and plasma phosphatidylcholine 20:3n6 (r = 0.362, p = 0.018) and red blood cell phosphatidylcholine 20:3n6 (r = 0.401, p = 0.009) and hyperactivity. The findings

of the ethnically homogenous children with Asperger's syndrome/high functioning autism study revealed positive associations between 22:5n3 and cognition, and negative relationships between 20:5n3 and 22:6n3 and behavioural problem. In contrast, cognitive ability and behavioural problems were negatively and positively associated with n6 fatty acids. Further investigation is required to establish whether there a cause and effect relationship. Regardless, it would be prudent to ensure that children with the conditions have optimum n3 PUFA intake

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Psychiatr Danub. 2021;33:1151-59.

CREATIVE PSYCHOPHARMACOTHERAPY IN CHILD AND ADOLESCENT PSYCHIATRY AND EXPERIENCES FROM BOSNIA AND HERZEGOVINA.

Kravia N, et al.

INTRODUCTION: Paediatric psychopharmacology involves the application of psychotropic agents to the treatment of children and adolescents with mental disorders and gathered knowledge from child and adolescent psychiatry (CAP), neurology, paediatrics and pharmacology. Defining elements of this discipline are: the metabolism of drugs is different in children than in adults (pharmacokinetics), the developing brain reacts specifically to the drug (pharmaco dynamics), and psychopathology itself is not differentiated yet. To make and overview of specifics in psychopharmacological use in CAP and emphasize some experiences from Bosnia and Herzegovina in that field.

METHODS: Through insight in current literature, we presented comprehensive findings and compare it with situation in Bosnia and Herzegovina.

RESULTS: The most common conditions in which psycho pharmaceuticals are used in CAP were attention deficit hyperactivity disorders (ADHD), depressive and bipolar disorder, obsessive compulsive disorder and the treatment of early psychosis. Psycho pharmaceuticals were also used to treat agitated conditions in various causes. We made an overview of psycho pharmaceuticals use in Bosnia and Herzegovina CAP and emphasized the fact that psycho stimulants are not approved for the use yet, although they are mostly prescribed medicament in CAP over the world. That limits us in the effectiveness of the treatment in ADHD and put us in the situations to use other medicaments instead (anxiolytics, antipsychotics, mood stabilizers) which are not approved for that condition.

CONCLUSION: The use of psycho pharmacotherapy in CAP is justified in cases where it is necessary to reduce the suffering of children and to improve their functionality at the time when cognitive, social and emotional advancement is most pronounced. Further research and clinical monitoring of efficacy and safety in the use of psycho pharmaceuticals in youngsters are necessary

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Psychiatry Res. 2022;311.

METHYLPHENIDATE SIGNIFICANTLY IMPROVES NEUROCOGNITIVE IMPAIRMENTS IN CHILDREN WITH ADHD .

Izmir SBI, Ipci M, Ercan ES.

This study aimed to investigate the effects of methylphenidate (MPH) on scores on a neurocognitive test battery for individuals with various presentations of attention deficit/hyperactivity disorder (ADHD) and the effect of comorbidities on executive function. This study included 861 children and adolescents aged 7ΓÇô17 years who were diagnosed with ADHD according to DSM-V criteria. The CNS Vital Signs Battery was utilized to compare the neuropsychological characteristics and MPH treatment responses of patients with predominantly inattentive (ADHD-I) and combined (ADHD-C) presentations of ADHD. Before MPH administration, a statistically significant difference was observed between groups only for complex attention. In addition, the overall prevalence rate of psychiatric comorbidities was 45.5%, and no statistically significant differences were found in the ADHD-I group pre- versus post-MPH administration. Prior to the administration of MPH, statistically significant differences were observed within the ADHD-C group between those with or without comorbidities. However, after MPH administration, these differences between the groups disappeared. The effects of MPH on improving scores on neuropsychological subtests were similar between the groups with different presentations of ADHD. Additionally, MPH treatment was effective despite the presence of comorbidities

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Psychol Med. 2022 Jan;52:352-61.

EVENT-RELATED BRAIN-OSCILLATORY AND EX-GAUSSIAN MARKERS OF REMISSION AND PERSISTENCE OF ADHD.

Vainieri I, Michelini G, Adamo N, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) often persists into adolescence and adulthood, but the processes underlying persistence and remission remain poorly understood. We previously found that reaction time variability and event-related potentials of preparation-vigilance processes were impaired in ADHD persisters and represented markers of remission, as ADHD remitters were indistinguishable from controls but differed from persisters. Here, we aimed to further clarify the nature of the cognitive-neurophysiological impairments in ADHD and of markers of remission by examining the finer-grained ex-Gaussian reaction-time distribution and electroencephalographic (EEG) brain-oscillatory measures in ADHD persisters, remitters and controls.

Methods: A total of 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 age-matched controls were compared on ex-Gaussian (mu, sigma, tau) indices and time-frequency EEG measures of power and phase consistency from a reaction-time task with slow-unrewarded baseline and fast-incentive conditions ('Fast task').

Results: Compared to controls, ADHD persisters showed significantly greater mu, sigma, tau, and lower theta power and phase consistency across conditions. Relative to ADHD persisters, remitters showed significantly lower tau and theta power and phase consistency across conditions, as well as lower mu in the fast-incentive condition, with no difference in the baseline condition. Remitters did not significantly differ from controls on any measure.

Conclusions: We found widespread impairments in ADHD persisters in reaction-time distribution and brain-oscillatory measures. Event-related theta power, theta phase consistency and tau across conditions, as well as mu in the more engaging fast-incentive condition, emerged as novel markers of ADHD remission, potentially representing compensatory mechanisms in individuals with remitted ADHD

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Public Health. 2021;196:101-06.

HOME PARTICIPATION, SUPPORT AND BARRIERS AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BEFORE AND DURING THE COVID-19 PANDEMIC.

Kaya Kara O, Tonak HA, Kara K, et al.

Objectives: Few studies have focused on the participation of children with attention-deficit/hyperactivity disorder (ADHD) in daily routine and leisure activities. This study aimed to compare the participation, support and barriers for children with ADHD at home pre-COVID-19 and during the COVID-19 outbreak.

Methods: The study included 55 children with ADHD aged 6-11 years. Participation frequency, involvement, desire for change, supports and barriers at home were assessed using the Participation and Environment Measure for Children and Youth (PEM-CY).

Results: During the COVID-19 pandemic compared with the pre-COVID-19 period, the mean frequency of participation of children with ADHD in computer and video games (5.8% vs 5%, respectively), socialising with other people (7% vs 6.2%) and household chores (5.5% vs 4.6%) was shown to be significantly higher ($p < 0.05$). Mothers of children with ADHD reported higher levels of involvement during the COVID-19 pandemic compared with the pre-COVID-19 period across four areas of home participation, including computer and video games (4.1% vs 3.2%, respectively), arts, crafts, music and hobbies (3.7% vs 3%), household chores (3.6% vs 2.8%) and personal care management (4.2% vs 3.5%) $p < 0.05$). Mothers of children with ADHD reported that during the pandemic the following two features of the environment made participation easier than pre-COVID-19 ($p < 0.05$): cognitive demands (36.4% vs 60%, respectively) and social demands (5.5% vs 34.5%). More mothers reported that services (92.7%), supplies (87.3%) and information (85.5%) were available and/or adequate in the COVID-19 period than pre-COVID-19 ($p < 0.05$).

Conclusions: Mothers of children with ADHD reported that their children were participating more frequently in some of the home-related activities during the COVID-19 pandemic compared to pre-COVID-19. Reduced cognitive and social demands, and more readily available resources in the home environment during the COVID-19 period resulted in increased home participation compared to pre-COVID-19

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Res Dev Disabil. 2022 May;124:104212.

ADOLESCENTS' EXECUTIVE FUNCTIONS: LINKS TO INATTENTION, HYPERACTIVITY-IMPULSIVITY, TRAIT MINDFULNESS, AND ATTACHMENT RELATIONSHIPS WITH FATHERS AND MOTHERS .

Al-Yagon M, Borenstein T.

BACKGROUND AND OBJECTIVES: Considering the important role of executive functions (EF) for adjustment across the lifespan, this study aimed to deepen understanding of protective/risk factors for EF in a potentially vulnerable population: adolescents with ADHD. This study compared adolescents with versus without ADHD for differences in EF, attachment relationships with fathers/mothers, and trait mindfulness and investigated these possible protective/risk factors' contributions to EF in both adolescent groups.

METHODS: Ninth graders (N = 91; 49 boys, 42 girls) ages 14-15 years (M = 14.50, SD = 0.50) comprised 45 with ADHD and 46 with typical development (TD). Adolescents completed three self-reports (trait mindfulness, attachment to mother/father). Mothers rated their adolescents' ADHD symptoms and EF.

RESULTS AND CONCLUSION: Significantly more maladaptive outcomes emerged for adolescents with ADHD than TD in their EF, attachment with mothers, and mindfulness. Regression analyses demonstrated the significant risk posed by ADHD symptoms and the protection offered by trait mindfulness and attachment with fathers in explaining EF. Discussion focused on understanding these protective/risk factors' possibly unique and complementary roles, suggesting interventions for adolescents with ADHD in family and school settings

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Res Autism Spectr Disord. 2022;93.

MELATONIN DISPENSING AND POLYPHARMACY RATES FOR NEW ZEALAND CHILDREN WITH AUTISM OR ATTENTION DEFICIT HYPERACTIVITY DISORDERS: A NATIONWIDE PHARMACOEPIDEMIOLOGICAL STUDY.

McLay LK, Bowden NJ, Eggleston MJF, et al.

Background: Chronic insomnia is common in children with autism and Attention Deficit Hyperactivity Disorder (ADHD). Melatonin is often used to treat childhood insomnia. However, it may interact with other medications being used to manage other symptoms. This pharmacoepidemiological study examined the rates of general and psychotropic polypharmacy among children with autism and/or ADHD, stratified by melatonin dispensing. The impact of sociodemographic and child characteristics on such dispensing was also examined.

Method: Linked national health and pharmaceutical administrative data for children aged 0-18 years in 2019 was utilized. Overall and melatonin dispensing stratified polypharmacy rates were calculated. Ordinal logistic regression models were employed to compare groups and adjust for confounders.

Results: Data were acquired for 10,209 children with autism (18.5% were dispensed melatonin), 5970 with ADHD (22.3% were dispensed melatonin), 2064 with autism and ADHD (29.9% were dispensed melatonin), and 1156,296 without a diagnosis of autism or ADHD (a control group; 0.5% dispensed melatonin). Relative to controls, rates of melatonin dispensing and polypharmacy were higher in children with autism and ADHD, and highest among those with both conditions. Children dispensed melatonin experienced the greatest rates of polypharmacy, especially if they had both autism and ADHD.

Conclusions: Children with autism and ADHD experience significant medication burden and potentially adverse interactions between psychotropic and sleep-related medication, raising important questions regarding their clinical care

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Res Dev Disabil. 2022;124.

ADOLESCENTS' EXECUTIVE FUNCTIONS: LINKS TO INATTENTION, HYPERACTIVITY-IMPULSIVITY, TRAIT MINDFULNESS, AND ATTACHMENT RELATIONSHIPS WITH FATHERS AND MOTHERS.

Al-Yagon M, Borenstein T.

Background and objectives: Considering the important role of executive functions (EF) for adjustment across the lifespan, this study aimed to deepen understanding of protective/risk factors for EF in a potentially vulnerable population: adolescents with ADHD. This study compared adolescents with versus without ADHD for differences in EF, attachment relationships with fathers/mothers, and trait mindfulness and investigated these possible protective/risk factors' contributions to EF in both adolescent groups.

Methods: Ninth graders (N = 91; 49 boys, 42 girls) ages 14-15 years (M = 14.50, SD = 0.50) comprised 45 with ADHD and 46 with typical development (TD). Adolescents completed three self-reports (trait mindfulness, attachment to mother/father). Mothers rated their adolescents ADHD symptoms and EF.
Results and conclusion: Significantly more maladaptive outcomes emerged for adolescents with ADHD than TD in their EF, attachment with mothers, and mindfulness. Regression analyses demonstrated the significant risk posed by ADHD symptoms and the protection offered by trait mindfulness and attachment with fathers in explaining EF. Discussion focused on understanding these protective/risk factors' possibly unique and complementary roles, suggesting interventions for adolescents with ADHD in family and school settings

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Research on Child and Adolescent Psychopathology. 2022 Feb;50:211-24.

MATERNAL EMOTION DYSREGULATION PREDICTS EMOTION SOCIALIZATION PRACTICES AND ADOLESCENT EMOTION LABILITY: CONDITIONAL EFFECTS OF YOUTH ADHD SYMPTOMS.

Oddo LE, Miller NV, Felton JW, et al.

Maternal emotional functioning and emotion socialization practices can facilitate or hinder children's emotional development, and youth with symptoms of attention-deficit/hyperactivity disorder (ADHD) are at increased risk for emotion lability. However, little is known about the independent and interactive effects of maternal emotion dysregulation and adolescent ADHD symptoms on maternal emotion socialization and adolescent emotion lability over time. Using secondary data analyses of a longitudinal community sample of youth and their mothers (Nbaseline = 247; 43.7% female), the current study examined direct and indirect effects of maternal emotion dysregulation on adolescent emotion lability via supportive and non-supportive emotion socialization practices as mediators, and the extent to which adolescent ADHD symptoms moderated these longitudinal pathways. Mothers reported on all study constructs. Results showed that non-supportive parenting responses to adolescents' negative emotional expressions partially mediated the association between maternal emotion dysregulation and adolescent emotion lability, and the effect was stronger at higher levels of youth ADHD symptom severity. Results suggest that parent- and youth-level characteristics interact to confer risk for non-supportive emotion socialization practices and adolescent emotion lability. This research contributes uniquely to theory and research on ADHD and emotional functioning across adolescence. Future research should extend this work by utilizing multi-modal assessment

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Research on Child and Adolescent Psychopathology. 2022 Mar;50:363-74.

TOO CONNECTED TO BEING CONNECTED? ADOLESCENTS' SOCIAL MEDIA EMOTIONAL INVESTMENT MODERATES THE ASSOCIATION BETWEEN CYBERVICTIMIZATION AND INTERNALIZING SYMPTOMS.

Marsh NP, Fogleman ND, Langberg JM, et al.

This study examined whether the association between cybervictimization and internalizing symptoms was moderated by adolescents' emotional connectedness to their social media. Participants were 288 adolescents (54.9% male participants) with (n = 151) and without (n = 137) attention-deficit/hyperactivity disorder (ADHD) between the ages of 13 and 15 years (M = 14.09, SD = 0.36). Adolescents reported on social integration and emotional connection (SIEC) to social media and parents reported on their impression of their adolescent's SIEC to social media. Adolescents also reported on cybervictimization experiences and internalizing symptoms. Adolescents with ADHD had higher cybervictimization scores than adolescents without ADHD and were also more likely to report multiple experiences of cybervictimization over the past month. Emotional investment in social media moderated the relations between cybervictimization and internalizing symptoms such that cybervictimization was associated with higher anxiety and depression symptoms at higher levels of emotional investment in social media. Results were consistent across both parent and adolescent report of social integration and emotional connection to social media. These findings indicate that cybervictimization may be associated with negative outcomes specifically among adolescents with a strong emotional connection to their social media use

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Rev Esp Salud Publica. 2022 Mar;96.

TREND IN MEDICINES USE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS (2010-2019).

Prieto AnB, et al.

OBJECTIVE: Attention deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder characterised primarily by three core symptoms: inattention, hyperactivity and impulsivity. It is one of the most commonly diagnosed childhood psychiatric disorders, with a worldwide prevalence of between 3% and 5%, and between 6% and 7% in the Spanish population. The aim of the study is to analyse the trend in the consumption of drugs used for the treatment of ADHD between 2010-2019 in Castilla y LeÃ³n.

METHODS: Epidemiological registry study of all dispensing in pharmacies in Castilla y LeÃ³n between 2010 and 2019 to patients under 19 years of age, of active substance N06BA04 (methylphenidate), N06BA09 (atomoxetine), N06BA12 (lisdexamfetamine), N06BA07 (modafinil) and C02AC02 (guanfacine). Data on drug use were obtained from the information system for the pharmaceutical provision of Castilla y LeÃ³n, CONCYLIA. Frequencies in absolute values and the corresponding percentages were calculated. Student's t-test was used to estimate differences between continuous variables and Pearson's Chi-square test for categorical variables, while the trend in consumption was analysed using the Cochran-Armitage test.

RESULTS: ADHD medication was dispensed annually to 1.77% of the population, with consumption being more than three times higher in boys than in girls (2.69% vs 0.81%; p=0.001). The age group with the highest peak use was 10-14 years with 3.42%. Methylphenidate was the drug used by the highest percentage of the population (2.44%) followed by lisdexamfetamine (0.37%).

CONCLUSIONS: Approximately 2 out of every 100 people aged 0-19 years were treated with some ADHD medication, mainly methylphenidate, in Castilla y LeÃ³n between 2010 and 2019

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Revista de la Facultad de Medicina Humana. 2021;22:193-96.

LIFESTYLE MEDICINE INTERVENTION in NEURODEVELOPMENTAL DISORDERS. CASE REPORT.

Toro JV.

Introduction: Neurodevelopmental disorders are conditions generated by dysfunction or interruption of brain development during childhood. In this group, attention deficit hyperactivity disorder and autism spectrum disorder stand out due to their prevalence and association between them. Studies suggest that these patients, due to their behavioral dysfunctions, develop unhealthy lifestyles, and that, in turn, these same habits could exacerbate these behaviors.

Clinical Case: We present a case of a 5 year old female with diagnoses of grade 1 autism spectrum disorder and attention deficit hyperactivity disorder, under pharmacological and non-pharmacological treatment without behavioral improvement. A lifestyle medicine approach was carried out with an emphasis on eating patterns, transitioning to a plant based diet, incorporating physical activity and sleep hygiene measures.

Conclusion: At four months there is evident improvement in hyperactivity, attention and socialization

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Schizophr Res. 2021;237:141-47.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN YOUTH WITH PSYCHOSIS SPECTRUM SYMPTOMS.

Fox V, Sheffield JM, Woodward ND.

Background: Childhood attention deficit-hyperactivity disorder (ADHD) is common in psychotic disorders. However, prevalence estimates vary widely and the impact of ADHD on the severity of psychotic symptoms and associated features is unclear. We used the Philadelphia Neurodevelopmental Cohort (PNC; n = 9498 youth age 8-21), which includes a comprehensive structured interview of clinical symptoms and the Penn Computerized Neurocognitive Battery (CNB), to clarify the prevalence of ADHD in psychosis spectrum (PS) youth and determine if comorbid ADHD is associated with severity of psychotic symptoms and cognitive impairment.

Methods: Prevalence of ADHD among PS youth was established by comparing PS youth to all other youth in the PNC cohort. Cognition was compared between four groups: typically developing (TD), ADHD, PS without ADHD (PS-ADHD), and PS with ADHD (PS+ADHD). To evaluate the impact of ADHD on psychosis

symptomatology, severity of positive and negative psychotic symptoms was compared between PS-ADHD and PS+ADHD groups.
Results: ADHD was more prevalent in PS youth compared to non-PS youth (45% vs. 20%). Cognition was significantly impaired in PS youth compared to TD youth, but the presence of ADHD in PS youth was not associated with greater cognitive impairment. Co-morbid ADHD was, however, associated with more severe psychosis symptoms in PS youth.
Conclusion: ADHD is more common among PS youth compared to youth without PS symptoms and is associated with more severe psychotic symptoms, but not severity of cognitive impairment. The association between ADHD and psychotic disorders may be mediated by psychosis symptoms in youth and may manifest a more stable cognitive impairment

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Sci Rep. 2022 Mar;12:5430.

THE GAP BETWEEN PERCEIVED MENTAL HEALTH NEEDS AND ACTUAL SERVICE UTILIZATION IN AUSTRALIAN ADOLESCENTS.

Islam MI, Yunus FM, Isha SN, et al.

Despite being highly prevalent, adolescent mental health problems are undertreated. To better understand the mental health treatment gap, we assessed the prevalence and correlates of help-seeking, including perceived need for care and access to that care. Data were drawn from Young Minds Matter (YMM) survey-the second Australian child and adolescents survey of mental health and wellbeing. Parent-reported data and self-reported child data were combined into one dataset to analyse 2464 Australian adolescents aged 13-17 years. We employed bivariate and multivariate logistic regression models to assess the correlation between independent variables (professionally assessed with mental disorders only, self-reported self-harm/suicidality only and both) and their distribution over outcome variables (perceived need and service use). Mental disorders include depression, anxiety, ADHD and conduct disorder. Our study revealed 15.0%, 4.6% and 7.7% had professionally assessed with mental disorders only, self-reported self-harm/suicidality only and both, respectively. Overall, 47.4% and 27.5% of adolescents respectively perceived need for care and used services in the past-12-months. While among those only who perceived the need, only 53% of adolescents used any services. Professionally assessed with mental disorders only, self-reported self-harm/suicidality only and both were associated with higher likelihood of perceived need and service use ($p<0.001$ for all). However, adolescents who self-reported self-harm/suicidality only were not found to be significantly associated with service use among those who perceived the need for care. Adolescents who perceived the need for mental health care but did not seek care represent a treatment gap. Our results suggest the importance of reducing the wide treatment gap that exists between need and care

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Sleep Med. 2022;90:230-37.

EVIDENCE OF A MATURATIONAL DISRUPTION IN NON-RAPID EYE MOVEMENT SLEEP SLOW WAVE ACTIVITY IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY, LEARNING AND INTERNALIZING DISORDERS.

Ricci A, He F, Calhoun SL, et al.

Background: Sleep slow wave activity (SWA) peaks during childhood and declines in the transition to adolescence during typical development (TD). It remains unknown whether this trajectory differs in youth with neuropsychiatric disorders.
Methods: We analyzed sleep EEGs of 664 subjects 6 to 21 y (449 TD, 123 unmedicated, 92 medicated) and 114 subjects 7-12 y (median 10.5 y) followed-up at 18-22 y (median 19 y). SWA (0.4-4 Hz) power was calculated during non-rapid eye movement sleep.
Results: TD and unmedicated youth showed cubic central and frontal SWA trajectories from 6 to 21 y (p-cubic<0.05), with TD youth showing peaks in central SWA at 6.8 y and frontal at 8.2 y. Unmedicated attention-deficit/hyperactivity (ADHD) and/or learning disorders (LD) showed peak central SWA 2 y later (at 9.6 y, coinciding with peak frontal SWA) than TD, followed by a 67% steeper slope by 19 y. Frontal SWA peak and slope in unmedicated ADHD/LD, and that of central and frontal in internalizing disorders (ID), were similar to TD. Unmedicated ADHD/LD did not differ in the longitudinal SWA percent change by 18-22 y; unmedicated

ID showed a lower longitudinal change in frontal SWA than TD. Medicated youth showed a linear decline in central and frontal SWA from 6 to 21 y (p-linear<0.05).
Conclusions: ADHD/LD youth show a maturational delay and potential topographical disruption in SWA during childhood and steeper decline throughout adolescence, suggesting faster synaptic pruning. Youth with ID experience less changes in frontal SWA by late adolescence. Psychotropic medications may impact the maturational trajectory of SWA, but not the magnitude of developmental decline by late adolescence

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Soc Neurosci. 2022 Feb;17:86-93.
INTERPERSONAL NEGOTIATION SKILLS IN ADHD.
Figueiredo T, Sudo F, Serra-Pinheiro MA, et al.
Social interaction difficulties are amongst the most prevalent and pervasive adverse outcomes for children and adolescents with ADHD. Problem-solving strategies are impaired in affected individuals, according to the literature. This study aimed to investigate the social problem-solving skills of children and adolescents with and without ADHD, using objective quantitative measures provided by the Interpersonal Negotiation Strategies Interview (INSI). Since verbal communication skills and working memory may be impaired in ADHD, we investigated their contribution to the performance. Forty-three children and adolescents with ADHD and 27 clinical controls with clinical diagnoses other than ADHD completed the INSI along with measures of verbal communication skills (Verbal Comprehension Index [VCI]): Similarities, Vocabulary and Comprehension subtests from the Wechsler Battery, visual (Corsi Blocks) and verbal (Digit Span) working memory tasks. Groups performed similarly on measures of intellectual functioning, working memory, and verbal communication. For the entire sample, VCI scores were positively correlated with INSI performance scores. The ADHD group performed worse on the INSI than the clinical control group. Linear regression analysis showed that inattention and hyperactivity/impulsivity levels and Similarities predicted INSI's performance. Our findings indicate that interpersonal negotiation difficulties in ADHD are related to DSM-5 defining symptoms of the disorder

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The Clinical Neuropsychologist. 2022 Feb;36:264-86.
WHAT'S RACE GOT TO DO WITH IT? INFORMANT RATING DISCREPANCIES IN NEUROPSYCHOLOGICAL EVALUATIONS FOR CHILDREN WITH ADHD.
Wexler D, Salgado R, Gornik A, et al.
Objective: To evaluate race-based discrepancies in informant ratings and in rates of Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosis among a clinically referred sample of Black and White children.
Method: Demographic information and ratings of inattention, hyperactivity/impulsivity, and conduct were collected from caregivers and teachers as part of neuropsychological evaluations at an outpatient clinic. The final sample included 3,943 children (6-18 years), of which 70% were White and 30% were Black.
Results: Teachers, but not caregivers, endorsed more inattentive symptoms and conduct problems for Black than for White children, irrespective of ADHD diagnostic status and socioeconomic status (SES), and after controlling for child sex, child age, and learning difficulties. Teachers endorsed more hyperactive/impulsive symptoms for Black children with ADHD of lower SES than for White children with these characteristics. Caregivers of Black children of higher SES reported fewer hyperactive/impulsive symptoms than caregivers of White children of higher SES. Despite differences in teachers' ratings by race, diagnostic rates of ADHD in the context of neuropsychological evaluations were comparable for Black and White children.
Conclusions: Consistent with previous literature, teachers endorsed more ADHD and conduct problems in Black children. Within our clinically referred sample, this may reflect teacher bias rather than actual prevalence differences by rafce, given that Black caregivers endorsed fewer or similar numbers of symptoms relative to White caregivers. This lack of racial disparities in rates of ADHD diagnosis is inconsistent with findings in community- and population-based samples, and reflects possible benefit of the use of neuropsychological evaluations in diagnostic decision-making for ADHD

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Transl Psychiatry. 2022 Apr;12:148.

MATERNAL LEVELS OF ACUTE PHASE PROTEINS IN EARLY PREGNANCY AND RISK OF AUTISM SPECTRUM DISORDERS IN OFFSPRING.

Brynge M, Gardner R, SjÃ¶qvist H, et al.

Previous research supports a contribution of early-life immune disturbances in the etiology of autism spectrum disorders (ASD). Biomarker studies of the maternal innate (non-adaptive) immune status related to ASD risk have focused on one of the acute phase proteins (APP), C-reactive protein (CRP), with conflicting results. We evaluated levels of eight different APP in first-trimester maternal serum samples, from 318 mothers to ASD cases and 429 mothers to ASD-unaffected controls, nested within the register-based Stockholm Youth Cohort. While no overall associations between high levels of APP and ASD were observed, associations varied across diagnostic sub-groups based on co-occurring conditions. Maternal levels of CRP in the lowest compared to the middle tertile were associated with increased risk of ASD without ID or ADHD in offspring (OR=1.92, 95% CI 1.08-3.42). Further, levels of maternal ferritin in the lowest (OR=1.78, 95% CI 1.18-2.69) and highest (OR=1.64, 95% CI 1.11-2.43) tertiles were associated with increased risk of any ASD diagnosis in offspring, with stronger associations still between the lowest (OR=3.81, 95% CI 1.91-7.58) and highest (OR=3.36, 95% CI 1.73-6.53) tertiles of ferritin and risk of ASD with ID. The biological interpretation of lower CRP levels among mothers to ASD cases is not clear but might be related to the function of the maternal innate immune system. The finding of aberrant levels of ferritin conferring risk of ASD-phenotypes indicates a plausibly important role of iron during neurodevelopment

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Transl Psychiatry. 2022 Mar;12:112.

PARENTAL AUTOIMMUNE AND AUTOINFLAMMATORY DISORDERS AS MULTIPLE RISK FACTORS FOR COMMON NEURODEVELOPMENTAL DISORDERS IN OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Ellul P, Acquaviva E, Peyre H, et al.

Epidemiological studies have raised concerns about the risk of neurodevelopmental disorders (NDD) in children of patients with autoimmune or inflammatory disorders (AID). The pathophysiological pathways underlying this association are still unknown and little is known about the specific and distinct risk of each AID. To explore these questions, we investigated the association between the occurrences of several NDD in the offspring of mothers or fathers with different IDA. We conducted a meta-analysis-PROSPERO (CRD42020159250)-examining the risk of NDD in the offspring of mothers or fathers with AID. We performed specific analyses separately in fathers or mothers of NDD patients as well as subgroup analyses for each NDD and AID. We searched MEDLINE, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, and Web of Science Core Collection published until December 2021. From an initial pool of 2074 potentially relevant references, 14 studies were included, involving more than 1,400,000 AID and 10,000,000 control parents, 180,000 children with NDD and more than 14,000,000 control children. We found AID in mothers (Adjusted OR 1.27 [95% CI 1.03; 1.57] p = 0.02, [I2 = 65%, Tau2 = 0.03 p = 0.01] and adjusted OR 1.31 [95% CI 1.11; 1.55] p = 0.001, [I2 = 93%, Tau2 = 0.13 p = 0.001] and, although in a lesser extent, in fathers (adjusted OR 1.18 [95% CI 1.07; 1.30] p = 0.01, [I2 = 15.5%, Tau2 = 0.002 p = 0.47]) and adjusted OR 1.14 [95% CI 1.10; 1.17] p < 0.0001, [I2 = 0%, Tau2 = 0 p = 0.29]) to be associated with ASD and ADHD in the offspring. This difference in the strength of the association was found in the AID-specific analyses, suggesting that AID increase the risk of NDD by a shared mechanism but that a specific maternal route appears to represent an additional excess risk. Inflammatory bowel disease were not associated with an additional risk (neither in fathers nor in mothers) of NDD in offspring. Our results suggest that complex and multiple AID-specific pathophysiological mechanisms may underlie the association of AID and NDD in offspring. Further, comprehensive studies of the different AID and NDD are needed to draw definitive conclusions about the pathophysiological links between parental AID and NDD in children

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World Journal of Pediatrics. 2022.

PRENATAL RISK FACTORS AND GENETIC CAUSES OF ADHD IN CHILDREN.

Kian N, Samieefar N, Rezaei N.

Background: Attention deficit/hyperactivity disorder (ADHD) is a common disease among children; it affected 5-7% of the population in 2015. ADHD is a multifactorial disease, and its etiology is still not clearly understood.

Data Sources: This narrative review has been done by searching the PubMed and Embase databases using attention deficit/hyperactivity disorder, ADHD, risk factors; genetics; pediatrics; psychiatrics as keywords.

Results: ADHD is considered to be a hereditary disorder in which genes play the fundamental role in the pathogenesis; however, findings from genetic-environmental studies support the hypothesis that genetic factors can exert effects on an individual's condition by determining his/her responses to environmental exposures, especially those during the prenatal stage.

Conclusion: ADHD is considered as a hereditary disorder in which genes and prenatal risk factors play fundamental roles in the pathogenesis

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Zhongguo Dang Dai Er Ke Za Zhi. 2022 Mar;24:255-60.

A PROSPECTIVE STUDY OF THE DECISION TREE PREDICTION MODEL FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PRESCHOOL CHILDREN.

Huang XX, Ou P, Qian QF, et al.

OBJECTIVES: To study the clinical value of attention time combined with behavior scale in the screening of attention deficit hyperactivity disorder (ADHD) in preschool children.

METHODS: A total of 200 preschool children with ADHD diagnosed in Fujian Maternal and Child Health Hospital from February 2019 to March 2020 were enrolled as the ADHD group. A total of 200 children who underwent physical examination in the hospital or kindergartens during the same period were enrolled as the control group. Attention time was recorded. Chinese Version of Swanson Nolan and Pelham, Version IV Scale-Parent Form (SNAP-IV) scale was used to evaluate symptoms. With clinical diagnosis as the gold standard, the decision tree analysis was used to evaluate the clinical value of attention time combined with behavior scale in the screening of ADHD.

RESULTS: Compared with the control group, the ADHD group had significantly higher scores of SNAP-IV items 1, 4, 7, 8, 10, 11, 14, 15, 16, 18, 20, 21, and 22 ($P<0.05$) and a significantly shorter attention time ($P<0.05$). The variables with statistically significant differences between the two groups in univariate analysis were used as independent variables to establish a decision tree model. The accuracy of the model in predicting ADHD was 81%, that in predicting non-ADHD was 69%, and the overall accuracy was 75%, with an area under the ROC curve of 0.816 (95% CI: 0.774-0.857, $P<0.001$).

CONCLUSIONS: The decision tree model for screening ADHD in preschool children based on attention time and assessment results of behavior scale has a high accuracy and can be used for rapid screening of ADHD among children in clinical practice

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ID: 146 Maximum Downward Slopes Of Sleep Slow Waves As A Potential Marker Of Attention Deficit Hyperactivity Disorder Clinical Phenotypes

Alessio Fasano[1], Carlo Biancardi[2], Gabriele Masi[3], Paolo Frumento[4], Egidio Falotico[1], Ugo Faraguna[3,4], Federico Sicca[3]

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Sleep problems are common in children with Attention Deficit Hyperactivity Disorder (ADHD) [Cortese, 2015], possibly due to shared pathophysiology. However, few differences in the macrostructure of the sleep EEG have emerged between ADHD and healthy children [Díaz-Román et al., 2016]. We wanted to verify that the slope of Slow Waves (SW) was a potential predictive parameter of psychiatric comorbidities and neuropsychological dimensions in ADHD. 70 children (8.76 ± 2.77 y) with ADHD, with no epilepsy and no intellectual disabilities, underwent psychiatric and neurologic evaluation and were assessed through the CBCL 6-18, the CPRS-R, the WISC-IV rating scales, and a standard 10-20 EEG during naps. We grouped the extracted SW in bins of equal amplitude and then measured associations, through generalized linear regression, between their maximum downward slopes (MDS) and the clinical scores. Sorted by degree of significance: negative association between the Processing Speed Index and the MDS (0–30μV) in anterior and temporal right areas; positive association between the Processing Speed Index and the MDS (20–50μV) in temporal and posterior left areas; positive association between autistic traits and the MDS (50–90μV) in anterior and temporal left areas; negative association between internalizing symptoms (CBCL 6-18) and the MDS (0–40μV) in temporal and posterior left areas; positive association between comorbid multiple anxiety disorder and the MDS (50–60μV) in posterior and temporal left areas. Consistency of clusters' localization suggests that alterations in local cortical synchronization, revealed by MDS, could underlie specific neurodevelopmental trajectories resulting in different ADHD clinical phenotypes.

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ORIGINAL PAPER

Clinical characteristics of children and adolescents with ADHD with or without methylphenidate prescription at their first diagnostic assessment

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Abstract
Attention Deficit/Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder diagnosed in the scholar age. It is associated with significant impairment in global functioning, and in moderate/severe presentations the outcome is critically dependent on pharmacological optimization of the multi-modal treatment. Methylphenidate (MPH) is the first-choice pharmacological treatment in children and adolescents with ADHD, with substantial evidence of significant efficacy and effectiveness on global functioning and symptoms' severity. There is some evidence supporting a few clinical and socio-demographic variables as predictors of pharmacological treatment prescription in children with ADHD independently of ADHD symptoms severity. However, it is warranted to investigate clinical and general psychopathological characteristics potentially associated with negative outcomes and the need for pharmacological treatment to inform appropriate prescription strategies. In this context, we compared 268 children and adolescents who were prescribed MPH (ADHD/MPH) for the first time after their first diagnostic assessment at our center, and 444 children and adolescents with ADHD (ADHD/noMPH) who were recommended non-pharmacological evidence-based interventions alone. ADHD/MPH group had higher severity of non-ADHD psychopathological symptoms compared to the ADHD/noMPH group, as documented by higher scores on the Child Behavior Checklist (CBCL) subscales, higher severity of ADHD symptoms, lower average IQ and lower adaptive levels independently of IQ. More specifically, beside externalizing symptoms, also internalizing symptoms were significantly higher in the ADHD/MPH group. The presence of significant non-ADHD psychopathology should be considered as a clinical factor associated with the need for MPH prescription in children and adolescents with ADHD.

Keywords ADHD · Methylphenidate · Early intervention · Psychopathology · Treatment predictors

Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder in scholar age, with a worldwide estimated prevalence of approximately 5% [1, 2], and severe cases displaying a prevalence of 1.3% within the general population [3].

Outcome studies of ADHD, especially in severe or moderate cases not sufficiently responding to cognitive behavioral therapy/parent training, is critically dependent on pharmacological optimization of the multi-modal treatment [4].

There is no doubt that methylphenidate (MPH) is the first-line pharmacological treatment for ADHD in developmental age [5], with an effect size on core symptoms of ADHD and emotional dysregulation which is among the largest in medicine [6].

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Although this has been rapidly changing over the last 10 years [7], in Italy only 1% of the severe cases are treated with MPH according to data gathered between 2007 and 2016 within the national registry [8].

In this context, pharmacological undertreatment is often associated with nonsufficient awareness of the non-ADHD psychopathological complexity, which rapidly evolves across developmental stages and significantly affects global functioning and quality of life of children, adolescents and their families.

Recent data from the Millennium Cohort Study on child ADHD showed that male gender and conduct problems are the best predictors of pharmacological treatment in children with ADHD independently of ADHD symptoms severity [9].

However, non-ADHD psychopathological characteristics potentially associated with negative outcomes and the need for pharmacological treatment have not been sufficiently investigated in large groups.

To better characterize clinical factors influencing drug prescription, we carried out an observational, naturalistic, retrospective, cross-sectional case–control study on 715 consecutive children and adolescents with ADHD assessed for a first clinical diagnosis over the last three years at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital (Rome, Italy).

The aim of our study was to describe psychopathological characteristics peculiar to children and adolescent with ADHD to whom MPH treatment was proposed, to provide clinicians with factors potentially informing treatment prescription beyond the mere severity of ADHD core symptoms, thus favoring appropriate treatment prescription strategies and preventing the development of non-ADHD psychopathological comorbidity.

Participants

In this retrospective study, 712 children and adolescents with ADHD who attended the Child and Adolescents Neuropsychiatry Unit of the Bambino Gesù Children's Hospital (Rome, Italy) for a first diagnosis were recruited over the course of 3 years (from January 2018 to December 2020).

Children and adolescents (mean age = 9.4, SD = 2.9; 107 females/605 males) received their first diagnosis of ADHD by experienced developmental psychiatrists and neuropsychologists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria [10].

Only patients with combined hyperactive/impulsive and inattentive presentation of ADHD (ADHD/C) were recruited. This choice was made to increase homogeneity in results, focusing on the most prevalent presentation of the disorder.

The diagnosis of ADHD was based on the developmental history, an extensive clinical examination, and a semi-structured interview, Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version, K-SADS-PL DSM-5 [11], which diagnoses current and past episodes of psychopathology in children and adolescents according to DSM-5 criteria [10].

Participants who were included in the study met the following criteria: (a) a primary diagnosis of ADHD, according to the criteria of DSM-5 [10]; (b) the absence of neurological and neurosensory deficit; (c) the absence of autism spectrum disorder; (d) the absence of past drug treatment.

The study was performed in accordance with the Declaration of Helsinki and all participants and their parents gave written informed consent for the possible use of their data in future studies.

According to the severity of ADHD symptoms [12], 268 children and adolescents were prescribed pharmacological treatment with MPH (ADHD/MPH) for the first time while 444 children and adolescents with ADHD (ADHD/noMPH) were recommended group-based parent training/education programs and group-based psychological treatments (as cognitive-behavioral therapy and social skills training).

Medication

MPH is the first-line medication for children and adolescents with ADHD in line with the National Institute for Health and Care Excellence (NICE) and Agenzia Italiana del Farmaco (AIFA) guidelines. Before the single-dose MPH challenge, all the patients who were eligible to receive MPH treatment underwent an electrocardiogram (ECG) with the calculation of the corrected QT interval, and blood tests to exclude any other medical condition associated with ADHD or potentially mimicking ADHD symptoms (e.g. thyroiditis). All children and adolescents of ADHD/MPH group received the administration of 0.3 mg/kg of the short-acting MPH preparation Ritalin©.

Instruments

Global functioning was assessed with the Children's Global Assessment Scale (C-GAS) [13].

The C-GAS estimates the overall severity of disturbance (range = 0–100). Scores over 90 indicate superior functioning, whereas scores under 70 suggest impaired global functioning.

Non-verbal Intelligence Quotient was assessed with the Perceptual Reasoning Index of the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV, Italian edition)

[14] or Colored Progressive Matrices or Standard Progressive Matrices (CPM/SPM) [15].

The adaptive skills were evaluated by means of The Adaptive Behavior Assessment System–Second Edition (ABAS–II, Italian edition) [16] or the Vineland Adaptive Behavior Scales-Second Edition (Vineland-II, Italian edition) [17]. ABAS-II provides a comprehensive norm-referenced assessment of adaptive skills. The norm-referenced standard scores of ABAS-II of the General Adaptive Composite (GAC) were considered in the analysis (M = 100, SD = 15). The Vineland II, also, measures personal and social skills needed in an individual's everyday life. The Adaptive Behavior Composite was considered in the analysis (M = 100, SD = 15).

Conners' Parent Rating Scales Long Version Revised (CPRS-R:L, Italian edition) [18] was used to assess behaviors that are related to ADHD. It is completed by parents to obtain a measure of hyperactivity and inattention symptoms for ADHD and it comprises 14 subscales. We analysed the two DSM-IV Symptoms Scales: Inattentive (CPRS L) and Hyperactive-Impulsive (CPRS M). Raw scores were converted into T-scores. According to the cut-off thresholds T-scores > 70 were classified as very elevated and T-scores from 60 to 70 were classified as high average or elevated.

The Child Behavior Checklist for Ages 6–18 (CBCL 6–18, Italian edition) [19] is completed by parents and is a questionnaire of child and adolescent behaviors and emotions. Parents are required to evaluate behaviours and emotions during the preceding 6 months on a 3-point Likert scale for each item (0 = Not True; 1 = Somewhat or Sometimes True; 2 = Very True or Often True). The hierarchical structure of the CBCL encompasses 113 items and several scales, as follows: (1) Syndrome Scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behaviour, and Aggressive Behaviour); (2) Broad Band Scales (Internalizing Problems which incorporates Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints; Externalizing Problems which incorporates Rule-Breaking Behav-iour, and Aggressive Behaviour; Total Problems); (3) DSM-Oriented Scales (Affective Problems, Anxiety Problems, Somatic Problems, ADHD Problems, Oppositional Defiant Problems, Conduct Problems); and (4) 2007-Other Scales (Sluggish Cognitive Tempo, Obsessive-Compulsive Problems, Post-traumatic Stress Problems). According to the cut-off thresholds of Achenbach and Rescorla (2001), *t*-scores > 69 are classified as clinically relevant, t-scores of 65–69 as borderline, and t-scores < 65 as non-clinical symptoms. We analysed only *t*-scores of 7 Syndrome Scales (Anxious/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-breaking Behaviour, Aggressive Behaviour. because there were no overlapping items across the subscales.

Statistical analyses

The Shapiro–Wilk test and skewness–kurtosis test were used to verify the normality of the data and Levene's test for the homogeneity of variances. Parametric tests were computed when data were normally distributed, and the assumption of homogeneity was not violated. When one assumption was not met, corrections were developed to produce a more valid critical value.

Since the MANCOVA assumption of homogeneity of variance was violated, Pillai's Trace test was considered as the best option for its robustness.

Student's t-tests were used to compare the ADHD/MPH vs ADHD/noMPH groups and Boys vs Girls groups on age, IQ, and ABAS. To correct for multiple testing, Bonferroni's correction was used (*p*-value 0. 05/6 < 0.008, after Bonferroni's correction).

Multivariate Analysis of Variance (MANOVA) was used to compare the ADHD/MPH vs ADHD/noMPH groups on CBCL Scales and on CPRS-R:L Scales. Considering that group ADHD/MPH differed from group ADHD/noMPH for age and IQ, MANCOVA on CBCL Scales and on CPRS-R:L scales were conducted also controlling for those variables.

Box's M test was used to check the equality of multiple variance–covariance matrices.

In our retrospective study data has been retrieved from clinical files of patients assessed for clinical purposes during the last three years. For this reason, some psychometric scales' scores were not always available for all participants. Therefore, the number of patients included in every single analysis will be specified in the Results section accordingly.

The statistical software SPSS Version 22 (IBM Corporation, 2017) was used for analyses.

Results

The ADHD/MPH group differed from the ADHD/noMPH group for age ($t_{710} = 4.32$, $p < 0.0001$, Cohen's d = 0.33; respectively, ADHD/MPH (268): M = 9.97, SD = 2.78, Median = 9.46, IQV = 4.20; ADHD/noMPH (444): M = 9.03, SD = 2.81, Median = 8.5, IQV = 3.62), for IQ ($t_{546} = -3.38$, p = 0.0008, Cohen's d = 0.29; respectively, ADHD/MPH (196): M = 101.19, SD = 19.29, Median = 102, IQV = 26.8; ADHD/noMPH (352):M = 106.7, SD = 17.72, Median = 110, IQV = 25) and for adaptive skills ($t_{670} = -6.53$, $p < 0.0001$, Cohen's d = 0.52; respectively, ADHD/MPH (243): M = 66.44, SD = 14.72, Median = 65, IQV = 21; ADHD/noMPH (427): M = 74.51, SD = 16, Median = 73, IQV = 22).

The two groups differed for gender ($\chi^2_1 = 10.93$, $p = 0.001$), specifically ADHD/MPH was composed by 243 Boys and 25 Girls while ADHD/noMPH by 362 Boys and 82 Girls.

Considering gender, Boys and Girls did not differ after Bonferroni's correction (p-value 0. 05/6 < 0.008) on age ($t_{710} = 2.17$, $p = 0.03$, Cohen's d = 0.23; respectively, Boys (605): M = 9.48, SD = 2.9, Median = 8.9, IQV = 4.10; Girls (107): M = 8.83, SD = 2.65, Median = 8.51, IQV = 3.53), IQ ($t_{546} = 2.12$, p = 0.035, Cohen's d = 0.24; respectively, Boys: M (468) = 105.36, SD = 18.04, Median = 110, IQV = 27; Girls (80): M = 100.7, SD = 20.36, Median = 102, IQV = 35) and for adaptive skills ($t_{670} = 0.43$, $p = 0.66$, Cohen's d = 0.05; Boys (589): M = 71.78, SD = 16.12, Median = 69, IQV = 22; Girls (101): M = 70.98, SD = 15.58, Median = 70, IQV = 18).

Group with ADHD/MPH differed from a group with ADHD/noMPH for C-GAS scores (ANOVA: $F_{(1, 457)} = 54.95$, p < 0.00001), even when IQ-score and age were controlled for (ANCOVA: $F_{(1, 366)} = 36.63$, p < 0.0001). Specifically, the global functioning of children with ADHD/MPH was found more impaired than that of children with ADHD/noMPH (respectively, ADHD/MPH (179): M = 50.16, SD = 5.94; ADHD/noMPH (281): M = 54.91, SD = 7.12).

A MANCOVA on ADHD symptoms, as derived from CPRS-R:L, was conducted with 2 CPRS-R:L subscales as within factor and Group (ADHD/MPH vs ADHD) as between factor, controlling for IQ and age.

Box's M test ($F_{(10)} = 6.29$, $p = 001$) was found significant. A Group effect was found ($F_{(1, 523)} = 50.01$, $p < 0.0001$, $\eta^2_p = 0.08$) with mean scores of the group with ADHD/MPH higher than those of the group with ADHD/noMPH (respectively, ADHD/MPH (189): M = 77.34, SE = 0.93; ADHD/noMPH (339): M = 69.55, SE = 0.69). A significant CPRS-R:L subscale effect (Pillai's Trace $F_{(21, 441)} = 21.44$, $p < 0.00001$, $\eta^2_p = 0.03$) was found. No interaction Group X CPRS-R:L (Pillai's Trace $F_{(13, 6799)} = 0.09$, $p = 0.75$, $\eta^2_p = 0.00$) was found (Table 1).

Differences between the group with ADHD/MPH and group with ADHD/noMPH in behavioral and emotional symptoms, as measured by CBCL 6–18 questionnaire, were investigated. A MANCOVA was conducted with 7 CBCL 6–18 subscales as within factor and Group (ADHD/MPH vs ADHD) as between factor, controlling for IQ and age.

Table 1 Comparisons between ADHD/noMPH and ADHD/MPH Group on the severity of ADHD symptom

CPRS-R:L subscale	ADHD/noMPH Mean SD	ADHD/MPH Mean SD
Global index restless/impulsive	71.30 15.02	79.57 11.25
Global index emotional liability	67.69 14.87	75.31 13.07

Table 2 Comparisons between ADHD/noMPH and ADHD/MPH Group on behavioral and emotional symptoms

CBCL 6–18 subscale	ADHD/noMPH Mean SD	ADHD/MPH Mean SD
Anxious/depressed	61.97 8.78	65.26 9.17
Somatic complaints	58.30 7.64	60.07 7.78
Social problems	62.78 8.27	66.63 8.44
Thought problems	62.15 9.33	65.73 8.84
Attention problems	66.79 9.17	71.41 9.19
Rule-breaking behaviour	61.08 8.24	64.16 8.03
Aggressive behaviour	64.01 10.07	69.01 10.37

Box's M test ($F_{(28)} = 1.42$, $p = 0.06$) was found not significant. A Group effect was found ($F_{(1, 483)} = 28.27$, $p < 0.0001$, $\eta^2_p = 0.05$) with mean scores of the group with ADHD/MPH higher than those of the group with ADHD/noMPH (respectively, ADHD/MPH (181): M = 66.04, SE = 0.47; ADHD/noMPH (306): M = 62.44, SE = 0.37). A significant CBCL 6–18 subscale effect, (Pillai's Trace $F_{(6, 478)} = 18.61$, $p < 0.0001$, $\eta^2_p = 0.04$) was found. No interaction Group x CBCL 6–18, (Pillai's Trace $F_{(6, 478)} = 2.01$, $p = 0.06$, $\eta^2_p = 0.006$) was found (Table 2).

Discussion

In this retrospective study, we investigated non-ADHD psychopathological symptoms of 712 consecutive children and adolescents at their first diagnostic evaluation for ADHD in a naturalistic clinical setting.

Our results showed that non-ADHD psychopathological symptoms were higher in the ADHD/MPH group compared to the ADHD/noMPH group, as documented by higher scores on CBCL 6–18 subscales. Therefore, our patients with ADHD, for whom an ADHD-specific pharmacological treatment is warranted, display not only more severe ADHD symptoms but also a complex psychopathological picture of symptoms even at the first clinical evaluation. Specifically, besides externalizing symptoms, also internalizing symptoms were significantly higher in treated patients. This is consistent with previous research findings showing that the overlap between internalizing and externalizing problems in ADHD may be mediated by emotional dysregulation and associated with neurobiological bases [20].

Furthermore, since the best evidence-based treatment for ADHD in terms of long-term outcome is pharmacological treatment plus cognitive behavioural treatment [4], identification of internalizing symptoms along with externalizing symptoms at the first diagnosis is crucial for an adequate tailored-to-patient cognitive behavioural strategy.

Our results showed that girls are still underdiagnosed and undertreated than boys. Traditionally boys are more likely to be referred, diagnosed and treated for ADHD symptoms than girls. This seemed to depend on gender differences in symptomatology: for example, males would have more disruptive/externalizing symptoms which would alert diagnostic evaluations earlier and more frequently than females [9].

The slight difference found for age between the two groups (ADHD/MPH on average one year older than ADHD/noMPH) might be explained by the fact that most of the severe patients present for assessment at a third level clinical center after a first non-effective trial of non-pharmacological treatment that usually requires several months.

As confirmation that the children who received the drug had more severe symptoms of ADHD, the scores of CPRS-R:L subscales were significantly higher in the group with ADHD/MPH even after controlling for IQ and age.

The group with ADHD/MPH displayed also a lower average IQ compared to the group with ADHD/noMPH. This is consistent with existing literature showing that the severity of ADHD is generally associated with lower IQ scores in pediatric populations [21].

Moreover, also adaptive level (i.e. ABAS–II and Vineland-II scores) and global functioning (i.e. C-GAS score) were lower in the group with ADHD/MPH even after controlling for IQ, suggesting that the degree of impairment is related to symptom's severity independently of IQ scores, and confirming the need for ADHD-specific drug treatment with MPH.

In fact, there is considerable evidence that higher IQ can be a compensation factor in ADHD but ADHD symptoms significantly worsen functioning within the same IQ level: for example children with high IQ and ADHD perform worse than high IQ children without ADHD, but they perform better than children with ADHD and standard IQ [22–24].

Taken together, our results support the strong need to consider MPH treatment beyond the severity of ADHD symptoms, thus favoring appropriate treatment prescription strategies and preventing the development of further psychopathology.

In fact, there is evidence that a proper ADHD-specific pharmacological treatment and an adequate treatment timing are significantly linked to better symptomatologic and functional outcomes in adolescence and adulthood including prevention/attenuation of comorbidities [4, 25–27].

Another aspect that needs to be discussed is that our sample has a proportion of treated children and adolescents (approximately 38% of the entire group) that is higher than generally reported in our country [7], this may be associated with a referral bias as a third level center usually sees more severe/complex cases compared to community-based facilities. However, it should be also considered that in our country there is an overall significantly lower rate of drug treatment in severe ADHD as compared to other countries according to the latest report of the official Italian ADHD treatment registry [8].

A thorough discussion of the multiple aspects impacting this prescription pattern is not possible here, but a good description of the socio-cultural context and medical habits that shaped MPH prescription in Italy can be found elsewhere [28].

Our study has some limitations. First, the study is cross-sectional and this does not allow the authors to draw any conclusions about the actual therapeutic potential impact of MPH treatment on non-ADHD clinical dimensions. In this regard, our considerations can only be speculative. Second, it can be argued that more sophisticated tools can be used to assess general psychopathology as compared to the CBCL that we use here. However, it should be noted that CBCL still represents a cost-effective tool that has been shown to be valid at characterizing the types of psychopathologic conditions driving child psychiatry referrals [29]. Finally, our study does not focus on potential presentation-related differences in pharmacological treatment predictors. As previously stated this choice was made to maximize homogeneity in results. However, future studies specifically addressing the existence of pharmacological treatment predictors by disorder's presentation are warranted.

Further longitudinal follow-up studies on the same sample are ongoing and will help understand the impact of treatment in several clinical outcomes after 3 and 6 months of MPH treatment. Nonetheless, we believe that our data can contribute to raise the awareness of ADHD-related psychopathological burden among clinicians and promote appropriate treatment prescription strategies to improve functioning levels and quality of life of children, adolescents and their families, and prevent the development of further psychopathology.

Author contributions DM performed the statistical analyses. PDR wrote the first draft of the manuscript. IP, SDV and BDA assisted in the literature search and preparation of the manuscript. SV supervised research activities and provided the final revision of the manuscript. All the authors approved the final version of the manuscript.

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Declarations

Conflicts of interest Not applicable.

Ethics approval See methods' section.

Consent to participate See methods' section.

Consent for publication See methods' section.

References

1. Polanczyk G, de Lima MS, Horta BL et al (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942–948
2. Polanczyk GV, Willcutt EG, Salum GA et al (2014) ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. Int J Epidemiol 43:434–442
3. Donfrancesco R, Marano A, Calderoni D et al (2015) Prevalence of severe ADHD: an epidemiological study in the Italian regions of Tuscany and Latium. Epidemiol Psychiatr Sci 24:525–533
4. Arnold LE, Hodgkins P, Caci H et al (2015) Effect of treatment modality on long-term outcomes in attention-deficit/hyperactivity disorder: A systematic review. PLoS ONE 10(2):e0116407
5. Cortese S, Adamo N, Del Giovane C et al (2018) Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5(9):727–738
6. Leucht S, Helfer B, Gartlehner G, Davis JM (2015) How effective are common medications: a perspective based on meta-analyses of major drugs. BMC Med 13:253
7. Casadei G, Cartabia M, Reale L et al (2017) Italian regional health service costs for diagnosis and 1-year treatment of ADHD in children and adolescents. Int J Ment Health Syst 11:33
8. Germinario AEP, Arcieri R, Marzi M, et al (2016) ADHD (Attention-Deficit/Hyperactivity Disorder) National Register (Italy): data 2007–2016. 34 p. Rapporti ISTISAN 16/37 (in Italian)
9. Russell AE, Ford T, Russell G (2019) Barriers and predictors of medication use for childhood ADHD: findings from a UK population-representative cohort. Soc Psychiatry Psychiatr Epidemiol 54:1555–1564
10. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.) https://doi.org/10.1176/appi.books.9780890425596
11. Kaufman J, Birmaher B, Brent D et al (1997) Schedule for affective disorders and schizophrenia for school-age children present and lifetime version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988
12. National Institute for Health and Care Excellence (2018) Attention deficit hyperactivity disorder: diagnosis and management. https://www.nice.org.uk/guidance/ng87
13. Shaffer D, Gould MS, Brasic J et al (1983) A children's global assessment scale (CGAS). Arch Gen Psychiatry 40:1228–1231
14. Grizzle R (2011) Wechsler Intelligence Scale for Children, Fourth Edition. In: Goldstein S, Naglieri JA (eds) Encyclopedia of Child Behavior and Development. Springer, US, Boston, MA, pp 1553–1555
15. Raven J (1981) Manual for Raven's Progressive Matrices and Vocabulary Scales. Research Supplement No.1: The 1979 British Standardisation of the Standard Progressive Matrices and Mill Hill Vocabulary Scales, Together With Comparative Data From Earlier Studies in the UK, San Antonio, Texas
16. Oakland T (2011) Adaptive Behavior Assessment System – Second Edition BT - Encyclopedia of Clinical Neuropsychology. In: Kreutzer JS, DeLuca J, Caplan B (eds) Springer. New York, NY, New York, pp 37–39
17. Sparrow SS (2011) Vineland Adaptive Behavior Scales BT - Encyclopedia of Clinical Neuropsychology. In: Kreutzer JS, DeLuca J, Caplan B (eds) Springer. New York, NY, New York, pp 2618–2621
18. Conners CK, Sitarenios G, Parker JDA, Epstein JN (1998) the revised conners' parent rating scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 26:257–268
19. Volkmar FR (2013) Child Behavior Checklist for Ages 6–18 BT - Encyclopedia of Autism Spectrum Disorders. Springer New York, New York, NY, p 581
20. Katsuki D, Yamashita H, Yamane K et al (2020) Clinical subtypes in children with attention-deficit hyperactivity disorder according to their child behavior checklist profile. Child Psychiatry Hum Dev 51(6):969–977
21. Frazier TW, Demaree HA, Youngstrom EA (2004) Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology 18(3):543–555
22. Katusic MZ, Voigt RG, Colligan RC et al (2011) Attention-deficit hyperactivity disorder in children with high intelligence quotient: Results from a population-based study. J Dev Behav Pediatr 32(2):103–109
23. Mahone EM, Hagelthorn KM, Cutting LE et al (2002) Effects of IQ on executive function measures in children with ADHD. Child Neuropsychol 8(1):52–65
24. He XX, Qian Y, Wang YF (2013) Practical executive function performance in high intelligence quotient children and adolescents with attention-deficit/hyperactivity disorder. Natl Med J China 93(3):172–176
25. Daviss WB (2008) A review of co-morbid depression in pediatric ADHD: Etiology, phenomenology, and treatment. J Child Adolesc Psychopharmacol 18(6):565–571
26. Mannuzza S, Klein RG, Moulton JL 3rd (2008) Lifetime criminality among boys with attention deficit hyperactivity disorder: a prospective follow-up study into adulthood using official arrest records. Psychiatry Res 160:237–246
27. Shaw M, Hodgkins P, Caci H et al (2012) A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: Effects of treatment and non-treatment. BMC Med 10:99
28. Frazzetto G, Keenan S, Singh I (2007) 'I Bambini e le Droghe': The Right to Ritalin vs the Right to Childhood in Italy. BioSocieties 2(4):393–412
29. Biederman J, DiSalvo M, Vaudreuil C et al (2020) Can the Child Behavior Checklist (CBCL) help characterize the types of psychopathologic conditions driving child psychiatry referrals? Scand J Child Adolesc Psychiatry Psychol 8:157–165

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RESEARCH

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ADHD symptoms and school impairment history in parents of ADHD children are a fundamental diagnostic and therapeutic clue

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Abstract

Background: Attention Deficit and Hyperactivity Disorder (ADHD) is a multi-factorial condition, with inheritance playing a major role. Recognizing parents' ADHD represents a clue not only for an earlier diagnosis of the disease in their children, but also to optimize psycho-educational therapy outcomes, by addressing the impairment of parenting related to untreated ADHD. This study aimed to assess the frequency of features suggestive of ADHD during childhood among parents of affected children, and the presence of school and emotional impairment.

Methods: We administered the Wender Utah Rating Scale-25, a self-assessment tool for the retrospective identification of symptoms consistent with ADHD during childhood, to a cohort of 120 parents of 60 children with ADHD, and to a consistent number of "controls".

Results: The WURS-25 proved positive in 49.1% of fathers and 30.0% of mothers of ADHD patients, compared to 1.7% of fathers and 1.7% of mothers of non-ADHD patients ($p < 0.0001$).

The questions addressing learning and emotional impairment provided significantly higher scores in parents with an overall positive test compared to those with negative test ($p < 0.0001$).

Conclusions: This study demonstrates a remarkably high rate of symptoms consistent with ADHD during childhood in parents of affected children. Physicians should be aware that this is a relevant anamnestic clue and, given the relevance of parents' role in the management of children with ADHD, an important issue to address in order to optimize patients' treatment.

Keywords: Attention Deficit Hyperactivity Disorder, Familiarity, Wender Utah Rating Scale-25, School impairment, Emotional lability

Background

Attention Deficit and Hyperactivity Disorder (ADHD) is a condition characterized by marked, persistent, maladaptive levels of inattention, impulsiveness, and hyperactivity, which has a negative impact on social, educational, and professional performances. Its estimated prevalence worldwide is 5% in children and 2.5% in adults [1], with studies showing that in half the cases, the disorder persists during adulthood [2, 3]. According to a survey [4], 40% of children diagnosed with ADHD undergo remission during adulthood, in 40% of cases symptoms persist in an attenuated form with related emotional deregulation, social and professional difficulties, while 20% continue to show features consistent with the typical form of the disease.

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Although not yet fully understood, ADHD aetiology is probably multi-factorial. Several factors have been demonstrated to be involved, including low birth weight, smoking, drug and alcohol exposure during pregnancy, among biological factors [5], and maternal psychiatric disorders, family dysfunction and lower socioeconomic status among environmental modifiers [6]. The identification of specific causative genes is still hampered by the significant phenotypic heterogeneity of the disorder [7]. Nevertheless, the role of inheritance has been well clarified [8]: twins concordance amounts to 70–76% [9–11] and the presence of an affected first-degree relative has been demonstrated to give to any child a four times higher risk to develop the disorder [12].

This study aimed to assess the frequency of features suggestive of ADHD during childhood among parents of affected children, and the presence of school difficulties and emotional lability.

Methods

A prospective case–control study was performed at the Child Neurology and Psychiatry Unit of the University teaching, tertiary children's hospital, Institute for Maternal and Child Health "Burlo Garofolo", in Trieste, Italy, from April 2019 to October 2019. The study was approved by the Institutional Review Board and all participants gave their written consent to take part in it.

We considered as "cases" the parents of children who had received a diagnosis of ADHD (of any of the following types: impulsive/hyperactive, inattentive and distractible, combined) between January 2005 and June 2019. The control group consisted of parents of children with various neuropsychiatric conditions, summarized in Fig. 1, and did not include those of patients who presented other conditions leading to attention or behavioural deficits, potentially acting as confounding factors. Furthermore, since all ADHD patients had an intellective quotient (IQ) over 70, we selected comparable controls, thus excluding also parents of children with IQ $\leq$ 70.

The Wender Utah Rating Scale-25 (WURS-25) [13, 14] in the Italian language (Fig. 2) was administered online to all participating parents. The WURS-25 is a self-assessment tool for the retrospective identification of the presence and severity of symptoms consistent with ADHD during childhood (age 6–10 years). It consists of 25 items, of which 21 address ADHD (inattention, hyperactivity,

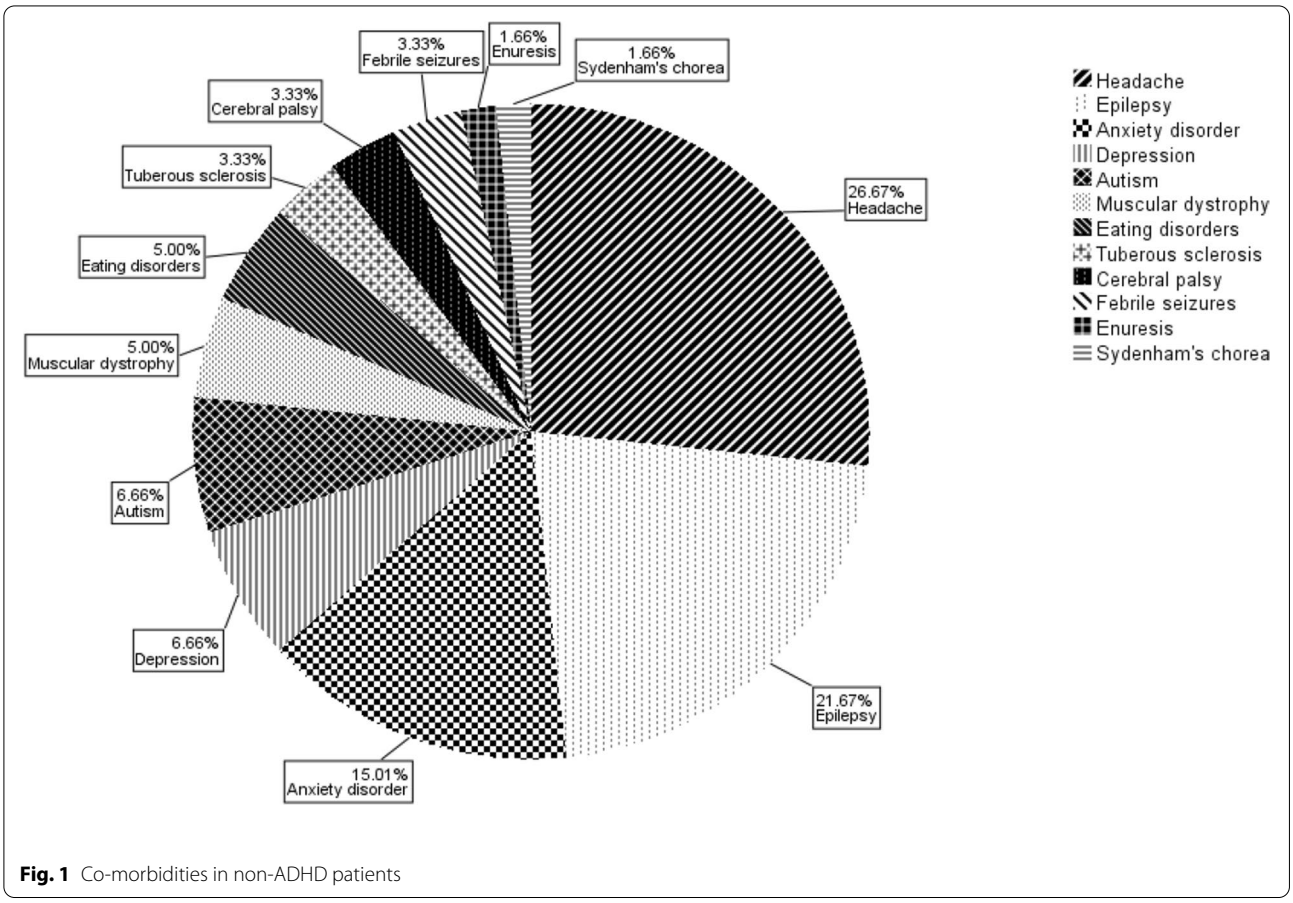

Fig. 1 Co-morbidities in non-ADHD patients

- As a child I was (or had):

		0	1	2	3	4
1	Easily distracted					
2	Anxious worrying					
3	Nervous fidgety					
4	Inattentive daydreaming					
5	Hot- or short-tempered					
6	Temper outbursts tantrums					
7	Trouble not finishing things					
8	Stubborn strong-willed					
9	Sad or blue depressed					
10	Disobedient with parents					
11	Low opinion of myself					
12	Irritable					
13	Moody ups and downs					
14	Angry					
15	Impulsive, acting without thinking					
16	Tendency to be immature					
17	Guilty feelings regretful					
18	Losing control of myself					
19	Tendency to be or act irrationally					
20	Unpopular, not very friendly					
21	Trouble seeing someone else`s view					
22	Trouble with authorities					
23	Overall a poor student					
24	Troubles with math or numbers					
25	Not achieving up to potential					

Where: 0 = Not at all or slightly; 1 = Mildly; 2 = Moderately; 3 = Quite a bit; 4 = Very much

- Has you repeated classes? (indicate which)

Fig. 2 The Wender Utah Rating Scale (WURS) 25

impulsivity, affective, emotional, and functional dysfunction), and 4 serve as control items. This tool has shown good psychometric properties and satisfactory internal and temporal reliability, and it is considered a screening tool for the retrospective assessment of ADHD in childhood. As ADHD symptoms undergo remission through adulthood in a relevant percentage of cases,when assessing the presence of symptoms suggestive of ADHD in the adult population there is a substantial risk of underestimating the real prevalence of the disorder during their childhood: hence, the WURS represented a suitable tool for this study, providing an accurate picture of the period in which the disorder may have been more expressed.

We instructed the subjects to recall their behaviour and mood during primary school (age 6 to 10), rating every item from 0 to 4 (not at all or very slightly (score = 0), mildly (score = 1), moderately (score = 2), quite a bit

(score = 3), or very much (score = 4)). The total score ranges from 0 to 100: we considered 46 as the cut-off score suggestive for previous ADHD 13.

Four questions (number 22–25) aimed to evaluate scholastic impairment and provided an overall score ranging from 0 to 16 points. Seven questions (number 2, 3, 9, 11–13, 17) investigated the presence of emotional lability, providing an overall score ranging from 0 to 28 points.

We used the Chi-Square Test for the dichotomous variables and the Fisher exact test in case of frequencies below 5. For continuous variables, we used the Wilcoxon-Mann Whitney test (for all distributions, the Kolmogorov–Smirnov test for normality had a p-value < 0.05).

Results with p-value ≤ 0.05 were considered statistically significant.

Results

Two hundred and two patients were considered for participation in the study; 142 were not included due to the presence of exclusion criteria or to the impossibility to contact their families. Sixty ADHD children (56 males) were therefore finally considered, along with 120 parents (60 mothers and 60 fathers): the latter were considered as "cases" and were matched to 60 mothers and 60 fathers of non-ADHD children as a control group.

Regarding the disease subtypes, 2/60 (3.3%) children had predominant hyperactivity, 14/60 (23.3%) predominant inattention, and 44/60 (74.3%) a combined disorder. Forty-four out of 60 (73%) children had at least one co-morbidity: 35/60 (58%) patients displayed Oppositional Defiant Disorder, 11/60 (23%) Specific Learning Disorder, 10/60 (17%) Mood or Anxiety Disorder, and 7/60 (12%) other disorders, such as mixed learning disorder, language disorder, autism, epilepsy or obsessive–compulsive disorder. Seventeen out of 60 (28%) enrolled patients had more than one co-morbidity. Finally, 46/60 (77%) children with ADHD were on ongoing drug therapy with methylphenidate, in 15/60 (25%) in association with an antipsychotic drug, with 1 patient taking risperidone as a single drug. Thirteen out of 60 (22%) children were not receiving any drug therapy.

Among parents of ADHD children, 60/60 (100%) mothers and 57/60 (95%) fathers answered the questionnaire, versus 60/60 (100%) and 60/60 (100%) mothers and fathers of non-ADHD children, respectively.

The test proved positive (score ≥ 46) in 46/117 (39.3%) parents of children with ADHD and 2/120 (1.7%) parents of non-ADHD children ($\chi^2 = 51.99$, $p < 0.0001$) (Fig. 3).

Among parents of ADHD children, we detected a higher rate of positivity in fathers (28/57, 49.1%) compared to mothers (18/60, 30.0%) ($\chi^2 = 4.48$, $p = 0.034$), while this difference was not observed among controls (1/60, 1.7% fathers and 1/60, 1.7% mothers; $\chi^2 = 0.000$, $p = 1.000$).

As for mothers, 94.7% of the positive tests belonged to"the case group", which meant that they had a child with ADHD ($\chi^2 = 17.01$, $p < 0.0001$). Similar results were observed in fathers, with a slightly higher correlation (96.6% vs. 3.4%, $\chi^2 = 29.43$, $p < 0.0001$).

In parents tested positive, a concomitant compromise of school and emotional functioning was sought.

The median score of the questions investigating school impairment was 8 (IQR 7–10) among the 48 parents with overall positive WURS test, versus 3 (IQR 1–4) among the 189 parents testing negative (Table 1, Fig. 3). Of interest, the 28.3% of parents with overall positive WURS test, repeated at least one school year. Through the Wilcoxon-Mann–Whitney test, we compared the school impairment scores of parents with an overall positive and negative WURS test, finding significantly higher scores among parents with a positive test ($p < 0.0001$). The median score was 9 (IQR 7–12) among the 19 mothers who tested positive, versus 3 (IQR 1–4) among the 101 testing negative. A statistically significant difference was found between the two groups ($p < 0.0001$). Besides, 26.3% of mothers with positive test reported having repeated at least one school year. The median score of fathers was 8 (IQR 7–9) among the 29 who tested positive, versus 3 (IQR 2–5) among the 88 testing negative. Even in this case, there was a statistically significant difference between the two groups ($p < 0.0001$), and again, the 27.6% of fathers with positive test reported having repeated at least one school year.

The median score of the questions assessing emotional lability was 14 (IQR 11.5–15) among the 48 parents with positive WURS test, versus 5 (IQR 3–7) among the 189 who tested negative. The difference was statistically significant ($p < 0.0001$) (Table 2, Fig. 3). The median score of mothers was 14 (IQR 14–15) among the 19 who tested positive, versus 5 (IQR 3–7) among the 101 testing negative ($p < 0.0001$). Among fathers, the median score was 13 (IQR 10–15) among the 29 who tested positive, versus 5 (IQR 3–7) among the 88, testing negative ($p < 0.0001$).

Discussion

This study shows a high rate of symptoms consistent with ADHD during childhood in parents of children affected by this disorder.

Several aspects are involved in the multi-factorial pathogenesis of ADHD, including genetic, neurobiological and environmental elements. Inheritance likely plays a fundamental role in pathogenesis: the assessment of its weight would allow not only a better understanding of the disease but also an early diagnosis in the children of affected parents, along with timely treatment and

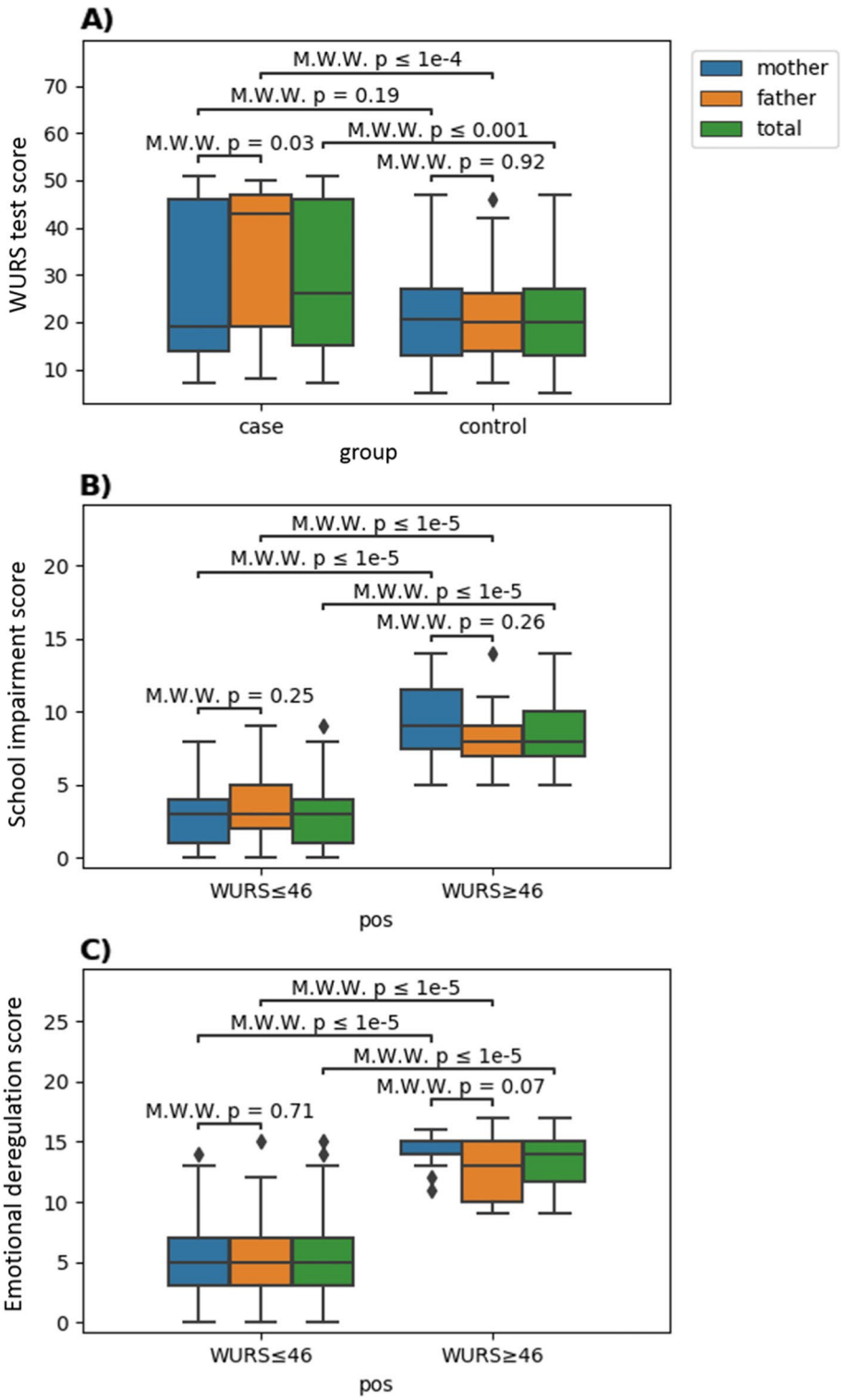

Fig. 3 Scores distribution of the WURS-25 test comparing cases and controls, and on questions investigating school impairment and emotional deregulation comparing subjects with an overall positive or negative test

Table 1 Parents stratified by study group and WURS-25 test result (positive/negative)

	Parents of ADHD children			Parents of non-ADHD children			
	N	Negative test	Positive test	N	Negative test	Positive test	*p*-value
Total	117	71 (60.7%)	46 (39.3%)	120	118 (98.3%)	2 (1.7%)	< 0.0001
Mothers	60	42 (70%)	18 (30%)	60	59 (98.3%)	1 (1.7%)	< 0.0001
Fathers	57	29 (50.9%)	28 (49.1%)	60	59 (98.3%)	1 (1.7%)	< 0.0001

Table 2 Median and interquartile range (in parenthesis) score of questions assessing school difficulties and emotional functioning stratified by sex with Wilcoxon-Mann–Whitney test *p*-values

		Positive		Negative		
		N	Median	N	Median	*p*-value
School difficulties	**Mothers**	19	9.0 (9)	101	3.0 (8)	< 0.0001
	Fathers	29	8.00 (9)	88	3.00 (9)	< 0.0001
	Total	48	8.0 (9)	189	3.0 (9)	< 0.0001
Emotional deregulation	**Mothers**	19	14.0 (5)	101	5.0 (14)	< 0.0001
	Fathers	29	13.0 (8)	88	5.0 (15)	< 0.0001
	Total	48	14.0 (8)	189	5.0 (15)	< 0.0001

prevention of detrimental consequences. Remarkably, a positive family history may be a relevant diagnostic clue, which physicians should specifically address. On the other hand, parent training is a cornerstone of treatment for children with mild-to-moderate ADHD [15]. Since parental ADHD may particularly impair parenting and family functioning, hindering the ability to deal with affected children, identifying affected parents could be a clue to optimize patients' outcomes [16, 17].

In this study we found a significant association between kinship and parents' WURS test positivity: in particular, 49.1% of fathers and 30.0% of mothers of ADHD patients, compared to 1.7% of fathers and 1.7% of mothers of non-ADHD patients, had a positive test, reporting features consistent with ADHD during their childhood. Remarkably none of the surveyed parents had ever been diagnosed with ADHD, underlying a lack of standardized diagnostic criteria to detect this condition in the past. However, the WURS test does not allow the retrospective diagnosis of ADHD: indeed, its aim is to highlight the presence of emotional and behavioural traits consistent with the disorder.

These results are in line with the previous literature. The role of genetic factors has been assessed over time [8] , and it has been confirmed by the high concordance between twins [3, 9, 11]. Bidwell demonstrated a four-time higher risk of developing ADHD in children with affected parents or first-degree relatives, compared to the general population [12]. Previous studies relied on the WURS test to assess symptoms suggestive of ADHD during childhood in parents of affected children. Starck and colleagues found a WURS test positivity in 49.1% of fathers and 27.3% of mothers of ADHD patients [18]: compared to the above mentioned survey, our study was powered by the analysis of data from a control group and by the comparable number of enrolled fathers and mothers, which allowed us to stratify the weight of familiarity by the sex of affected parents. Moreover, to our knowledge, this is the first study that separately examined the school and emotional impairment of parents during their childhood, through a specific sub-analysis of the scores obtained in the specific test questions addressing these issues.

Regarding school performances, we found an association between reported parents' school difficulties and WURS test positivity, confirming the pivotal role of undiagnosed and untreated ADHD in learning difficulties. The latter, as underlined by Marzocchi and colleagues [7], can be explained in the light of a vicious circle between the deficit of self-regulation cognitive processes and the inability to adopt effective organizational and executive strategies appropriate to the task. This profile negatively affects the performance in the comprehension of written texts, studying, and resolution of arithmetic problems [19, 20]. In this study, we found that mothers with positive tests showed higher scores in the questions investigating school impairment, compared to fathers testing positive. This issue could further demonstrate that in females with ADHD, inattention is usually preponderant compared to hyperactivity, negatively affecting academic performances.

Similar results were found about emotional deregulation. Parents with an overall positive WURS test demonstrated higher scores in the questions assessing emotional lability, compared to parents with negative tests.

Tabassam and Grainger widely described the emotional dysfunction in ADHD children, characterized by sudden emotional changes, dysphoria, irritability, low tolerance to frustration, emotional hyper-reactivity, and emotions-recognition deficits [21]. The concurrent effect of the critical judgment of families, teachers, and peers, easily led to low self-esteem, sense of social rejection and loneliness, which in turn can promote the development of further psychopathologies, such as mood disorders. By stratifying data by gender, we found that the mothers tested positive displayed a higher median score compared to positive testing fathers, underlying the central role of emotional lability within the disorder in females. In a longitudinal study involving 140 children diagnosed with ADHD, Hinshaw found that female subjects had more severe anxiety, depressive symptoms, and more significant difficulties in daily functioning compared to males [22]: at ten years follow-up, girls with ADHD were more likely to display self-injuring behaviours and suicide attempts compared to boys.

This study, not only confirms these data but also highlights a high occurrence of school and emotional impairment in parents of affected children during their childhood, strengthening the suitability of the WURS test for the retrospective assessment of symptoms suggestive of ADHD, considering the crucial role of these two aspects in the diagnosis of the disorder.

The main limits of this study consist of the relatively small sample size and the lack of a correlation analysis between patients and parents, due to the choice to collect and investigate the results in a completely anonymous way. For the same reason, we assessed every parent independently; therefore, it was not possible to compare the association with an affected child with a single positive parent and both parents' positivity. On the other hand, the guarantee of anonymity provided a parental participation rate of almost 100%, which in turn, represents the strength of this study. A further point of strength was the case–control design, which allowed additional comparative results.

Conclusions

This study demonstrated a high rate of symptoms consistent with ADHD during childhood in parents of children affected by this disorder. Physicians should actively investigate parents' history when evaluating children with suspected ADHD. A proper assessment of the parents of these patients would also be crucial to optimize psycho-educational outcomes.

Abbreviations

ADHD: Attention Deficit and Hyperactivity Disorder; IQ: Intellective Quotient; WURS-25: Wender Utah Rating Scale-25; IQR: Interquartile Range.

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Authors' contributions

AS designed the study, GP collected the data; VR performed the statistical analysis; LCW and FR drafted the work, and EB edited the manuscript; all the authors approved the final version of the manuscript and take full responsibility for its contents.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Institute for Maternal and Child Health – IRRCCS "Burlo Garofolo", where it was conducted, and all participants gave their written consent to take part in it.

Consent for publication

Patients and/or their caregivers gave written consent for data publication.

Competing interests

The authors declare that they have no competing interests.

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References

1. American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
2. Barkley RA, Fischer M, Edelbrock C, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria–III. Mother-child interactions, family conflicts and maternal psychopathology. J Child Psychol Psychiatry. 1991 Jan;32(2):233–55.
3. Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustün TB, Zaslavsky AM. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry. 2005;57(11):1442–51.
4. Ianes D, Marzocchi GM, Sanna G. (2009). L'iperattività. Aspetti clinici e interventi psicoeducativi, Erickson, Trento.
5. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000;157(5):816–8.
6. Scahill L, Schwab-Stone M, Merikangas KR, Leckman JF, Zhang H, Kasl S. Psychosocial and clinical correlates of ADHD in a community sample of school-age children. J Am Acad Child Adolesc Psychiatry. 1999;38(8):976–84.
7. Marzocchi GM, Sclafani M, Rinaldi R, Giangiacomo A. 2012. ADHD in pediatria. Guida operativa, Erickson, Trento.
8. Gizer IR, Ficks C, Waldman ID. Candidate genes studies of ADHD: a meta-analytic review. Hum Genet. 2009;126(1):51–90.
9. Burt SA. Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. Psychol Bull. 2009;135(4):608–37.

10. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005;57(11):1313–23.
11. Wood AC, Neale MC. Twin studies and their implications for molecular genetic studies: endophenotypes integrate quantitative and molecular genetics in ADHD research. J Am Acad Child Adolesc Psychiatry. 2010;49(9):874–83.
12. Bidwell LC, Willcutt EG, McQueen MB, DeFries JC, Olson RK, Smith SD, Pennington BF. A family based association study of DRD4, DAT1, and 5HTT and continuous traits of attention-deficit hyperactivity disorder. Behav Genet. 2011;41(1):165–74.
13. Ward MF, Wender PH, Reimherr FW. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry. 1993;150(6):885–90.
14. McCann BS, Scheele L, Ward N, Roy-Byrne P. Discriminant validity of the Wender Utah Rating Scale for attention-deficit/hyperactivity disorder in adults. J Neuropsychiatry Clin Neurosci. 2000;12(2):240–5.
15. National Collaborating Centre for Mental Health. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people, and adults. Clinical Guideline 27. London: National Institute for Health and Clinical Excellence; 2008.
16. Weiss M, Hechtman L, Weiss G. ADHD in parents. J Am Acad Child Adolesc Psychiatry. 2000;39(8):1059–61.
17. Sonuga-Barke EJS, Daley D, Thompson M. Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD? J Am Acad Child Adolesc Psychiatry. 2002;41(6):696–702.
18. Starck M, Grünwald J, Schlarb AA. Occurrence of ADHD in parents of ADHD children in a clinical sample. Neuropsychiatr Dis Treat. 2016;3(12):581–8.
19. Friedman LM, Rapport MD, Raiker JS, Orban SA, Eckrich SJ. Reading Comprehension in Boys with ADHD: The Mediating Roles of Working Memory and Orthographic Conversion. J Abnorm Child Psychol. 2017;45(2):273–87.
20. Iglesias-Sarmiento V, Deaño M, Alfonso S, Conde Á. Mathematical learning disabilities and attention deficit and/or hyperactivity disorder: A study of the cognitive processes involved in arithmetic problem solving. Res Dev Disabil. 2017;61:44–54.
21. Tabassam W, Grainger J. Self-concept, attributional Style and Self-efficacy Belief of Student with learning disabilities with and without Attention Deficit Hyperactivity Disorder. "Learning Disability Quarterly." 2002;25(2):141–51.
22. Hinshaw SP, Carte ET, Sami N, Treuting JJ, Zupan BA. Preadolescent girls with attention-deficit/hyperactivity disorder: II Neuropsychological performance in relation to subtypes and individual classification. J Consult Clin Psychol. 2002 Oct;70(5):1099–111.

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MINIREVIEW

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Clinical characteristics, neuroimaging findings, and neuropsychological functioning in attention-deficit hyperactivity disorder: Sex differences

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Abstract

Recent clinical studies, in both children/adolescents and adults, have shown the extreme neuropsychological heterogeneity of attention-deficit hyperactivity disorder (ADHD): specific neuropsychological deficits have been found only in a minority of individuals, with no direct correlation between discrete cognitive performances and the trajectory of clinical symptoms. Deficits in specific neuropsychological functions may be common in ADHD, but nevertheless no cognitive or neuropsychological profile may fully explain the disorder. Sex differences in the ADHD presentation, both at a neuropsychological and clinical level, also contribute to this clinical and neuropsychological heterogeneity. At a neuropsychological level, females with ADHD may show greater working memory problems, poorer vocabulary skills and worse visual spatial reasoning. Structural and functional imaging study also show discrete differences across sex; however, the great majority of clinical studies mainly or exclusively include male participants with insufficient data to draw firm conclusions on sex differences within the disorder. Here, we report the recent literature data, discussing still open research questions about the clinical presentation, neuroimaging findings, and neuropsychological functioning in ADHD with a focus on the impact of sex differences—a deeper insight in these unresolved issues may have relevant clinical and therapeutic implications for tailored, effective, and long-lasting interventions.

KEYWORDS
attention-deficit hyperactivity disorder, executive function, girls, neuroimaging, sex differences

1 | INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity/impulsivity, or a combination of these symptoms (American Psychiatric Association, 2013). It is one of the most common and costly conditions, affecting approximately 6% of children (Polanczyk et al., 2007), associated with functional impairment, poor health-related quality of life (Coghill et al., 2017), and significantly increased mortality rates (Dalsgaard et al., 2015). The management of the disorder is based on a multimodal approach combining behavioral and pharmacological interventions (Zuddas & Carucci, 2020).

ADHD is an example of a valid clinical neuropsychiatric syndrome with marked heterogeneity across multiple levels of analysis,

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although, at the moment, its etiology and pathophysiology are incompletely understood. A growing body of evidence supports a model in which several genetic and environmental factors interact each other during prenatal and early postnatal periods, increasing the neurobiological predisposition to the disorder (Cortese & Coghill, 2018; Faraone & Larsson, 2019; Walton et al., 2017). This, in turn, leads to subtle alterations within several brain systems that result in different deficits in multiple neuropsychological domains. This model recognizes a high degree of pathogenetic heterogeneity in the ADHD population, with significant individual differences in the extent to which genetic, environmental, and neuro-pathophysiological processes are involved in the disorder (Cortese & Coghill, 2018).

Sex differences in the ADHD presentation, both at a neuropsychological and clinical level, also contribute to the clinical and neuropsychological heterogeneity of the disorder. The majority of the clinical studies, however, mainly or exclusively includes males, and clinicians rarely take into account sex influence on ADHD core features' presentation. Here, we discuss the recent literature data on the neuropsychological functioning of ADHD individuals focusing the impact of sex differences both at a clinical and a neuropsychological level. For a more in-depth analysis of the topic, we also considered sex differences in the results of the neuroimaging studies.

1.1 | Method

This narrative minireview has been conducted by search and "research" of the most relevant literature in the topic area, via keyword searches on relevant electronic databases (PubMed and Google Scholar). The single and combining keywords used for literature searching have been: "ADHD" (or "attention deficit/hyperactivity disorder"), "gender" (or "sex"), "clinical characteristics" (or "presentation"), "neuroimaging" (or "MRI"), "neuropsychological functioning" (or "executive functioning"). We included clinical studies, meta-analyses, and systematic reviews of the last 20 years (we included older papers if they had a historical value on the topic). We mostly selected articles dealing with developmental age.

The results of our search are divided into three sections: (1) ADHD clinical presentation; (2) neuroimaging; and (3) neuropsychological functioning. We briefly discuss each topic in ADHD individuals and then focus on sex differences. The main results are reported in Table 1.

2 | ADHD CLINICAL PRESENTATION

As other neurodevelopmental disorders, ADHD clinical presentation varies with age, with the associated functional impairment also varying from patient to patient. ADHD children are highly impaired in their social relationships, have more experiences of rejection by peers and a more pessimistic view of their social world (Grygiel et al., 2018); they are also at a significant risk for more behavioral, familial, and academic failures (Coghill et al., 2017). ADHD adolescents present earlier sexual activity, especially those with high levels of comorbid conduct disorder symptoms (Galera et al., 2010). In adulthood, ADHD is associated with worse educational, occupational, economic, and social outcomes, more divorces, and higher probability to be incarcerated (Ebejer et al., 2012; Klein et al., 2012).

Significance

Neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), are more frequently diagnosed in males, but the underlying reasons are not completely understood. Sex-specific characteristics may help to better understand different aspects of the disorder and may provide useful insights into the different neuropsychological functioning between the two sexes. Here we review sex differences in ADHD at different levels of analysis (clinical, neuropsychological, and neurofunctional) in order to improve clinicians' alertness, diagnostic accuracy, and therapeutic specificity for tailored, effective, and long-lasting interventions in both sexes.

ADHD comorbidities are also heterogeneous and they vary over the life-course: In childhood, oppositional defiant disorder and conduct disorder are more common, while in adolescence and adulthood, anxiety disorders, affective disorders, antisocial personality disorders, and substance abuse disorders are more frequent (Charach et al., 2011; Franke et al., 2018; Harstad et al., 2014). Adults with ADHD, especially when a psychiatric comorbidity is present, may also show more intense suicidal behavior than normally developed adults (Fitzgerald et al., 2019).

2.1 | Biological models for sex differences in ADHD

In most studies, clinical samples consist mainly of male participants: The DSM-5 diagnostic criteria have been developed and validated using mostly male samples. A "*male prototype of ADHD*" might have been therefore structured, making ADHD in girls underdiagnosed in clinical practice (Mowlem et al., 2019; Nussbaum, 2012).

Male to female sex ratio ranges from 2:1 to 10:1 (averages 4:1), with higher ratio in clinical samples; this difference results attenuated with age and, in adulthood, male to female ratio is nearly 1:1 (Faraone et al., 2015; Mowlem et al., 2019).

Interestingly, male to female prevalence ratio has not been accurately reported for subthreshold ADHD (presence of ADHD symptoms that do not fully meet all criteria) that appears equally prevalent in boys and girls in a large-scale community study (Hong et al., 2014).

The so called "*female protective effect model*" may explain the differences in prevalence by sex: According to this model, females would need greater exposure to genetic and environmental ADHD risk factors to develop full ADHD symptoms. In fact, one hypothesis is that females with ADHD are more likely to inherit few high-impact

TABLE 1 Main sex differences

	Males	Females	Experimental groups	Most relevant studies on the topic
Clinical presentation				
	More hyperactivity, externalizing problems, physical aggression, tic disorders, and motor coordination disorders	More inattention, internalizing problems, verbal aggression, poorer coping skills, language disorder, and lower IQ	Children, adolescents, and adults	Gaub and Carlson (1997)[a], Rucklidge (2010)[a], Nussbaum (2012)[a], Ottosen et al. (2019) Mowlem et al. (2019)
Neuroimaging	Males	Females		
Structural anomalies	SA reduction of right ACC and left medial PFC	SA reduction in PFC (dlPFC bilaterally, left latero-inferior PFC, right medial PFC, right OFC) and left ACC[b]	Children	Dirlikov et al. (2015)
Cortical	SA reduction in PMC[b]			
	WM abnormalities in motor regions (primary motor M1)[b]	WM abnormalities in prefrontal regions (medial OFC)[b]	Children	Jacobson et al. (2015)
Subcortical	Volumetric reductions in basal ganglia and amygdala	No volume or shape difference[b]	Children	Qiu et al. (2009), Seymour et al. (2017), Tang et al. (2019)
	Shape-localized abnormalities in the caudate, putamen, and globus pallidus[b]			
	Volume reduction in the caudate, globus pallidus, and thalamus[b]	Greater relative volume reduction in the caudate, globus pallidus, and thalamus[c]	Preschoolers	Rosch, Crocetti, et al. (2018)
	No ADHD-related sex differences		Children, adolescents, and adults	Hoogman et al. (2017)
Functional anomalies	Underactivation in networks involving frontal, temporal, cerebellar, occipital, and subcortical regions during *working memory* task		Adults	Valera et al. (2010)
	Negative correlation between *working memory* neural activity and *hyperactivity symptoms*[b]	Negative correlation between *working memory* neural activity and *inattentive symptoms*[b]		
	Underactivation of bilateral frontal and parietal areas	Underactivation of right inferior frontal and postcentral gyri, right cerebellum, right middle temporal gyrus, and left basal ganglia, during *forethought* task[b]	Adolescents	Poissant et al. (2016)
	Hyperactivation of amygdala and superior temporal gyrus, during *forethought* task[b]			
	Hypoactivation of fronto-striatal and frontoparietal networks, during *response inhibition* task *(SST)*[b]	Hypoactivation of fronto-striatal and frontoparietal networks, during *response inhibition* task *(SST)* similar to males	Adolescents	van Rooij et al. (2015)
	Anomalies in FC, between vmPFC, striatum, and amygdala[b]	Greater diagnostic effects of anomalies in FC, between vmPFC and striatum, and amygdala[c]	Children	Rosch, Mostofsky, et al. (2018)
		Atypical intrinsic FC between striatum and dlPFC: stronger positive FC with the ACC and negative FC with the dlPFC		

(Continues)

TABLE 1 (Continued)

	Males	Females	Experimental groups	Most relevant studies on the topic
Neuropsychological functioning	Males	Females		
Processing speed, working memory, and visual special reasoning	Poorer processing speed, and deficits in motor functioning[c]	Working memory weakness, poorer vocabulary skills, worse visual spatial reasoning[c]	Children, adolescents and adults	Rucklidge (2010), Nussbaum (2012)[a]
Sustained attention	More commission errors (impulsivity) during *CPT*[c]	No differences on omission errors (attention) during *CPT*[c]	Children	Hasson and Fine (2012)[a]
Inhibition	Greater impairment in inhibition skills[c]		Adolescents	Rucklidge (2006)
		Impaired response control on tasks with higher cognitive load[b]	Children	Seymour et al. (2016)
	Higher impairment during conscious, effortful response inhibition[b]		Children	O'Brien et al. (2010)
		Greater response inhibition deficits in adolescence[b]	Children and adolescents	DeRonda et al. (2021)
	Greater behavioral disinhibition (impaired inhibitory control on the *SST* and *GNG task)*[b,c]		Children	Patros et al. (2018)
Planning		Higher impairment in planning[c]	Children	O'Brien et al. (2010)
Working memory		Greater working memory deficits[b]	Adults	Schweitzer et al. (2006)
Delay discounting		Increased delay discounting[b,c]	Children	Rosch and Mostofsky (2016), Patros et al. (2018)
	No sex differences on delay gratification and temporal discounting tasks	Tend to prefer smaller immediate rewards[c]	Children and adults	Doidge et al. (2021)[a]
Motor overflow	More mirror overflow[b]		Children	MacNeil et al. (2011), Cole et al. (2008)
		Similar levels of excessive mirror overflow, but more variable tap times[b]	Children	Chen et al. (2021)

Abbreviations: ACC, anterior cingulate cortex; CPT, continuous performance test; dlPFC, dorso-lateral prefrontal cortex; FC, functional connectivity; GNG, go/no-go task; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PMC, primary motor cortex; SA, surface area; SST, Stop Signal Task; vmPFC, ventromedial prefrontal cortex; WM, white matter.

[a]Meta-analyses or reviews.

[b]Compared their sex-matched controls.

[c]Compared to opposite-sex subjects.

genes which are rare and therefore less frequently manifest ADHD. It is also possible that females with ADHD inherit the same genes but require greater exposure to environmental factors than males to clinically manifest the disorder (Taylor et al., 2016).

Molecular genetic research suggests an important role for sex chromosome genes: In the male brain, the sex determining region on the Y-chromosome seems to regulate dopamine biochemistry and function. In addition, this region plays a key role in regulating the function of specific genes expressed in the brain areas involved in motor control, reward, and attention, closely related to ADHD pathophysiology. Furthermore, females with only one X chromosome (Turner syndrome) are more susceptible to ADHD (Liedmeier et al., 2020; Loke et al., 2015). This may suggest that the additional X chromosome could protect female from developing ADHD (Greven et al., 2018). Klinefelter syndrome, in which males have an extra X chromosome (XXY), is associated with ADHD too, but, interestingly, such patients show mainly ADHD-inattentive symptoms, similar to that is observed in women with idiopathic ADHD. These results seem to suggest that the number of X chromosome may influence sexual dimorphism in the ADHD profile (Green et al., 2019).

Endocrine factors are also involved in the sex differences in ADHD prevalence. Androgenic hormones determine the dimorphic characteristics of the brain and regulate the distribution, receptor density, and activity of the dopaminergic, gabaergic, glutamatergic, and serotoninergic systems (Gillies et al., 2014; Waddell & McCarthy, 2012).

According to the "*evolutionary theory of sexual selection*" (Geary, 2010), males and females have a predisposition, determined by an evolutionary advantage, to develop different psychopathological features. This predisposition has not been fully understood but appears to have a genetic, epigenetic, and hormonal basis. Males appear to have a window of vulnerability in early developmental stages and therefore to be at an increased risk of earlier onset disorders such as ADHD; females seem more likely to develop psychopathological manifestations with prevalent onset in adolescence, such as internalizing disorders. Hormones play a crucial role in this trend: Prenatal exposure to high testosterone levels, as largely documented later in life in individuals with externalizing disorders, may modulate the dopaminergic transmission pathway, predisposing the subject to traits such as disinhibition and sensation seeking, which are often associated with externalizing spectrum psychopathologies (Martel, 2013). In fact, the exposure to higher levels of testosterone in utero may be related to a lower D2:D4 ratio, which, in turn, has been reported to correlate with more ADHD symptoms (Breedlove, 2010; Stevenson et al., 2007). In females, on the other hand, an increase in estrogen levels during puberty seems to interfere with serotonergic transmission and to predispose to traits such as negative emotionality and rumination, which, in the case of hormonal dysregulation, can be associated with internalizing disorders (Martel, 2013).

Interestingly, a correlation between estrogen hormones and dopamine D2 receptors in the striatum has been also investigated. In female puberty, the increase in estrogen levels correlates with an increase in these receptors. This may partly explain the narrowing of the gap in the male:female ratio in the transition from childhood to adulthood (Nussbaum, 2012).

Finally, stress hormones may also contribute to the sex differences in ADHD. Men, compared to women, seem to have a stronger activation of the adrenocorticotropic hormone and cortisol response to stress, suggesting a different, sex-dependent, HPA axis functioning: Stress hormones have downstream effects on the activity and sensitivity of the dopaminergic neurons in the prefrontal cortex and ventral striatum, two brain areas typically involved in ADHD (Gillies et al., 2014; Stephens et al., 2016).

2.2 | Sex differences in ADHD clinical presentation

Girls receiving a diagnosis of ADHD are more likely to be diagnosed with the predominantly inattentive presentation and are usually less hyperactive (Gaub & Carlson, 1997; Mowlem et al., 2019; Rucklidge, 2010). Contrary to ADHD males, who are prone to disruptive and aggressive behaviors (Gaub & Carlson, 1997; Mowlem et al., 2019; Rucklidge, 2010) and show more frequently comorbidity with tic disorders and motor coordination disorders (Ottosen et al., 2019), ADHD girls show poorer coping skills, less self-esteem, and more frequent comorbidities with language disorders and intellectual disability (Gaub & Carlson, 1997; Rucklidge, 2010). Moreover, females usually have higher ratings of internalizing problems, as anxiety and mood disorders, personality and eating disorders; they also have more self-reported self-harm and suicidal ideation (Gaub & Carlson, 1997; Mowlem et al., 2019; Nussbaum, 2012; Rucklidge, 2010). Criminality, violent crimes, and prison sentences have been found to be higher in men compared with women with ADHD, as well as psychopathic traits in non-incarcerated adults (Rucklidge, 2010). Some authors show that alcohol and drug abuse are also higher in ADHD men than in women (Rucklidge, 2010). However, in a large population study, when compared to males, ADHD females showed a stronger association with several comorbid disorders including oppositional defiant/conduct disorders (ratio of the hazard ratio HRR 1.97), autism spectrum disorders (HRR, 1.86), intellectual disability (HRR 1.79), personality disorders (HRR 1.23), suicidal behaviors (HRR 1.28), schizophrenia (HRR 1.21), and substance use disorders (HRR 1.21), thus identifying a more vulnerable group of patients and evidencing that females can be equally or even more impaired than males (Ottosen et al., 2019).

In terms of social functioning, differences have been found across sexes. Males behave more aggressively than girls, resulting in exclusion by peers. Girls are usually less physically, but more verbally aggressive; if compared with girls without ADHD, they are also more inclined to relational aggression, that is, to ruin or disrupt the victim's social relationships (Rucklidge, 2010). When compared to males, females also seem less aware of their dysfunctional behavior and tend to be bullied rather than bully (Novik et al., 2006).

Considering the different clinical presentation and comorbidities in males compared to females, it is likely that the behavior of ADHD females may be perceived as less problematic or disruptive

and therefore that their symptoms are more tolerated by teachers and parents. As a result, females may be diagnosed only when they show significantly more severe forms of ADHD or when they have a clinical presentation like males. Alternatively, they may come to clinical attention only when they transit into other diagnoses such as anxiety disorder or depression.

A recent population-based study has shown sex differences in parental perceptions of ADHD behaviors and impairment. In a sample of 283 children aged 7–12 years, ADHD females, when compared with ADHD males by the Parental Account of Childhood Symptoms (PACS), showed more emotional problems, lower scores on parental stress indicators, fewer conduct problems, fewer complaints at school due to hyperactivity, and higher prosocial scores. Interestingly, females are perceived by parents to be more socially adequate and less compromised, being able to mask the core ADHD symptoms. It is yet to be understood whether prosocial behavior may be a way of compensating for the cardinal clinical features of ADHD (Mowlem et al., 2019).

3 | NEUROIMAGING

3.1 | Neuroimaging data in ADHD individuals

Abnormalities in the prefrontal cortex and the interconnected subcortical structures including the caudate, putamen, globus pallidus, and cerebellum have been largely described in ADHD (Castellanos et al., 2002; Nakao et al., 2011; Valera et al., 2007).

Structural magnetic resonance imaging (MRI) studies show that individuals with ADHD have significantly smaller global gray matter volumes compared to healthy ones, smaller gray matter volumes in the caudate nucleus and in the right lentiform nucleus, and larger gray matter volumes in the left posterior cingulate cortex/precuneus, a crucial portion of the default mode network (DMN) (Nakao et al., 2011; Sonuga-Barke et al., 2016). Smaller volumes in the frontal regions and the striatum represents one of the central features of ADHD; interestingly, caudate, putamen, and globus pallidus are part of the fronto-striato-thalamo-cortical circuits essential for higher executive functions (Nakao et al., 2011).

Recently, the enhancing neuro imaging genetics through meta-analysis (ENIGMA)-ADHD working group analyzed brain imaging data from 1,713 participants with ADHD and 1,529 healthy controls from 23 sites (age range: 4–63 years; 66% males). Through a precise mega and meta-analysis, significantly smaller volumes of the amygdala, accumbens, caudate, hippocampus, putamen, and of the whole intracranial volume were found in the ADHD population. Compared to previous studies mainly indicating a unilateral caudate and putamen volumes reduction (Ellison-Wright et al., 2008), these alterations resulted bilateral rather than unilateral; furthermore, authors explored possible confounders related to clinical measures and found that the structural brain volume differences were not related to any comorbid disorders, medication effect, or ADHD symptoms severity, but could be exclusively inferred to the condition of ADHD itself (Hoogman et al., 2017).

Several studies also examined the morphology of different areas of the cerebral cortex evidencing a predominantly thinner cortex with reduced surface area. In ADHD children, a widespread reduction of cortical dimensions in the PFC, superior parietal cortex, and medial and anterior temporal regions have been reported, thus with less agreement on the precise location of change (Batty et al., 2010; Narr et al., 2009; Shaw et al., 2006; Sowell et al., 2003).

Furthermore, the same ENIGMA-ADHD working group, recently confirmed that children with ADHD showed a smaller surface area, mainly in frontal, temporal, and cingulate regions. Differences in the cortical thickness (i.e., thinner in ADHD children) were limited to the temporal pole and the fusiform gyrus (Hoogman et al., 2019). Compared to previous researches showing a greater cortical thinning in the regions implicated in attention and executive functioning in adult (Makris et al., 2007), in this study neither surface area nor thickness differences were found in the adolescent or adult population; furthermore no significant correlations were found between cortical alterations and either stimulant treatment or intelligence quotient (IQ) (Hoogman et al., 2019).

Results from functional MRI (fMRI) studies seem to delineate specific pattern in ADHD children and they further suggest specific neural correlates for ADHD subtypes: Compared to typically developing children (TDC), ADHD-inattentive (ADHD-I) children show connectivity differences in the prefrontal dorsolateral cortex and cerebellum, while ADHD-combined type (ADHD-C) children differ from TDC mainly in the medial prefrontal cortex, posterior parietal nodes of the default network, and also sensorimotor, visual, and cingulo-opercular systems (Fair et al., 2012).

In a recent meta-analysis of fMRI studies, when compared to control subjects, ADHD participants showed abnormal activation in the brain areas involved in motor control, interference inhibition, switching, attention, and timing, during different emotional and cognitive tasks (Rubia, 2018). ADHD children also showed an hypoactivation in the systems involved in executive functions (frontoparietal network) and attention (ventral attentional network). A significant hyperactivation in ADHD compared to control group was instead observed in the DMN. Reciprocal interrelation between DMN and brain areas involved in attentional processes and executive functions appears to be also functionally impaired (Cortese et al., 2012; Rubia, 2018).

In addition to impaired integrity and connectivity in the DMN, which lead to consequent lack of attention and mind wandering, ADHD individuals also show fronto-striatal and frontoparietal connections' deficits, with consequent impaired decision-making speed and efficiency; ventro-striatal connections' deficits, with consequent delay aversion; and impaired orbitofrontal connectivity, with consequent learning deficits (Sonuga-Barke et al., 2016).

3.2 | ADHD-related sex differences in neuroimaging data

As evidenced by Hoogman et al. (2017) within the ENIGMA study, a main effect of sex can be evidenced in the volumes of most of the

subcortical structures, apart from accumbens and caudate volumes, independently from the ADHD diagnosis. Longitudinal studies also show that brain development has different trajectories in girls and boys. Gray matter increase rate in the frontal lobe peaks at about 10.5 years in girls versus 11.5 years in boys, with males showing a more rapid increase during adolescence. A similar increase has been observed in parietal and temporal lobe volumes and in the caudate nucleus; total cerebral gray matter volume is 10% larger in males, but peaks much earlier in girls than boys (10.5 years vs. 14 years) (Mahone & Wodka, 2008; Nussbaum, 2012).

Alongside the well-known sex differences in brain structure and development (Kaczkurkin et al., 2019) and a large number of neuroimaging studies in those with ADHD, there is a growing literature investigating sex differences in cortical and subcortical morphology and in functional connectivity in children with ADHD.

In studies examining the *cortical morphology*, girls, but not boys, show an overall surface area (SA) reduction in the prefontal cortex (PFC), in particular in the dorsolateral PFC bilaterally, in the left latero-inferior PFC, in right medial PFC, in right orbitofrontal cortex (OFC), and in left anterior cingulate cortex (ACC). Boys, unlike girls, have a SA reduction only at the right ACC level and in the left medial PFC. Moreover boys, differently to girls, show an overall SA reduction in premotor cortex (PMC) (Dirlikov et al., 2015).

Similar results have been also found by Jacobson et al. (2015) who examined sex differences in motor/premotor and prefrontal white matter (WM) microstructure applying diffusion tensor imaging (DTI) in children (8–12 years) with ADHD. Boys showed WM abnormalities in the motor regions (specifically primary motor M1), which are crucial to the more basic aspects of motor response control, while girls showed WM abnormalities in the prefrontal regions (specifically medial OFC), which are responsible for top-down regulation of high-order emotional and behavioral responses.

Sex-related differences of *subcortical structures* have also been investigated. In a sample of 47 ADHD children (27 boys and 20 girls) and 66 controls (35 boy and, 31 girls) aged 8–12 years, the large deformation diffeomorphic metric mapping (LDDMM) was used to examine the effects of ADHD, sex, and their relationship with basal ganglia volume and shape. Boys with ADHD showed considerably smaller basal ganglia volumes compared to typically developing (TD) boys. Volume compression was seen bilaterally in the caudate head and body and in the anterior putamen as well as in the right ventral putamen and in the left anterior globus pallidus; conversely, posterior putamen was more pronounced in boys with ADHD than in TD ones. No volume or shape differences were evidenced in girls with ADHD (Qiu et al., 2009).

Also, in a study conducted in school-age children with and without ADHD, sexually dimorphic volumetric reductions and shape compressions in the bilateral globus pallidus and amygdala have been reported in boys with ADHD compared to TD boys, whereas no differences were found in any structure between ADHD and TD girls. Further correlational analyses showed that in ADHD boys, a localized expansion in the globus pallidus, putamen, and amygdala correlated with greater emotional dysregulation (Seymour et al., 2017).

Consistent with these findings, another study that examined basal ganglia morphology confirmed a reduced volume and shape abnormalities of the globus pallidus and putamen (within subregions of the putamen receiving projections from limbic, executive, and motor cortices) in boys, but not in girls, with ADHD. These basal ganglia anomalies appear to correlate with poorer response control, regardless of cognitive demand, exclusively among boys (Tang et al., 2019).

In contrast to the previous study (Tang et al., 2019) showing subcortical differences in ADHD boys, but not girls, only one study in *preschoolers* (4–5 years old), naïve to stimulant medication, showed a reduced volume of the caudate, globus pallidus, and thalamus among girls with ADHD compared to TD girls, whereas no significant differences were observed among boys (Rosch, Crocetti, et al., 2018).

Few neuroimaging studies have investigated sex differences in *functional connectivity* (FC) of fronto-striatal networks in children with ADHD.

A functional imaging study in adults with ADHD revealed significantly altered patterns of neural activity during a verbal working memory task for males but not for females: 23 ADHD males showed a significant underactivation in widespread networks involving frontal, temporal, cerebellar, occipital, and subcortical regions during working memory task; 21 ADHD females showed no impairment compared to same sex control subjects. Within the same study, a negative correlation between neural activity during the working memory task and the number of hyperactive symptoms was found in men, while in women, a similar correlation was found with the number of inattentive symptoms (Valera et al., 2010). These findings are in line with another study including only female ADHD adolescents evidencing no differences in working memory-related brain activation (Sheridan et al., 2007).

Similarly, a study comparing 23 ADHD adolescents with 21 healthy controls during the assessment of congruent or incongruent stories found that ADHD males had a bilateral frontoparietal (including premotor cortex and supplementary motor) area underactivation compared to controls with an hyperactivation of the amygdala and superior temporal gyrus. ADHD females had a more widespread underactivation pattern in right inferior frontal and postcentral gyri, right cerebellum (a region activated in response to temporally unexpected stimuli), right middle temporal gyrus, and left basal ganglia. This could be a potential explanation of several difficulties on female ability to predict "when" events are going to occur (Poissant et al., 2016). By contrast, an fMRI study examining the neural correlates of response inhibition in a large cohort of 185 adolescents with ADHD using the *Stop Task* found a hypoactivation in both frontal-striatal and frontal–parietal networks in ADHD participants and also in their unaffected siblings when compared to controls, with no sex differences (van Rooij et al., 2015). Furthermore, a large fMRI meta-analysis including a range of cool, hot EF and emotion processing tasks also found no sex differences in activation deficits (Cortese et al., 2012).

Another seminal study evidenced an association between a greater PFC SA and a greater reduction in ISV during a motivational

go/no-go (GNG) task (motivational contingencies present) in ADHD participants. This association was particularly evident, among boys with ADHD, at the right OFC level, and among the overall group of ADHD children, at the right medial PFC level, delineating a noticeable effect of sex (Rosch et al., 2015).

Finally, a recent study (Rosch, Mostofsky, et al., 2018) examined ADHD-related sex differences in fronto-subcortical FC and association with delay discounting and demonstrated, for the first time, fronto-subcortical functional networks anomalies in girls with ADHD. Children with ADHD showed, in fact, atypical FC between the ventromedial PFC and subcortical regions, including the striatum and amygdala, and the greatest diagnostic effect was found among girls. Furthermore, girls, but not boys, showed heightened delay discounting.

4 | NEUROPSYCHOLOGICAL FUNCTIONING

4.1 | ADHD and executive functions

In the past, causal models of ADHD tended to posit a single-core dysfunction and focused on a single aspect of functioning—a behavioral inhibition deficit. Barkley et al. conceptualized a theoretical model that linked inhibition to four executive neuropsychological functions (working memory, behavioral inhibition, regulation of motivation, and motor control) that appeared to depend on it for their effective execution (Barkley, 1997). Later, Willcutt et al. (2005) evidenced that ADHD is associated with weaknesses in several key EF domains; however, although EF weaknesses are significantly associated with ADHD, EF deficits appear per se not to be sufficient to cause ADHD in all subjects with the disorder. In fact, less than half of ADHD children exhibit significant impairment on a specific EF task (Nigg & Casey, 2005). According to a reconceptualization model of EF, between 16% and 51% of children with ADHD were classified as impaired in an individual measure, but only 10% of them showed deficits across all five domains of EF and 21% did not show impairment on any of the five measures (Castellanos et al., 2006).

ADHD is characterized by quite independent cognitive domains deficits with a significant heterogeneity from patient to patient: In a study including 83 ADHD boys compared with 66 healthy boys on a broad battery of six neuropsychological tasks, the ADHD group performed worse across all six domains, with larger effect size for delay aversion (0.82) and working memory (0.95); medium for impulsivity (0.61), decision-making (0.55), and timing (0.71); and small for response variability (0.37). The proportion of ADHD boys with a deficit on each factor was indeed moderate, ranging from 18% to 36%. A quarter of ADHD boys did not exhibit a deficit on any of the six factors, with almost all who did have at least one deficit showed it in no more than three factors (Coghill et al., 2014). Another study showed that ADHD children significantly differed from controls also on emotion regulation and recognition (Sjowall et al., 2013).

Aside from the classical "cold" EF (i.e., motor response inhibition, working memory, sustained attention, response variability, and cognitive switching), other mechanisms including the so called "hot" EF (i.e., motivational dysfunction, delay aversion, sensitivity to reward and punishment, and emotional processing) and response variability and cognitive processing speed (and alerting) have been increasingly investigated as they have been shown to play a significant role in the disorder (Willcutt et al., 2008). The importance of reinforcements and reward perception is in fact a key point in the ADHD pathophysiology (Castellanos et al., 2006). ADHD children are hypersensitive to the lengthening of the time intervals between action and reinforcement, finding it difficult waiting for reward (Kuntsi et al., 2001). This is consistent with the "delay aversion" model developed by Sonuga-Barke, which suggests that ADHD symptoms are a functional expression of a motivational style rather than the result of an altered regulatory system (the so called "*dual-pathway hypothesis*") (Karalunas & Huang-Pollock, 2011; Sonuga-Barke, 2003).

In 2010, the two-pathway model has been extended and revised into the "*three-way" model:* Deficit in temporal processing, mediated by cortico-cerebellar loop disturbance, constitutes a third important component of ADHD, along with cognitive and motivational deficits. ADHD individuals appear consistently compromised in three main temporal processing domains—motor timing, perceptual timing, and temporal prediction. Main deficits in ADHD have been found in the tasks of sensory-motor synchronization, duration discrimination, reproduction, and postponement (Sonuga-Barke et al., 2010).

It is also worth noting that individuals with ADHD have been reported to be greatly inconsistent in their performance on neurocognitive tasks (Klein et al., 2006), and increased response-time intrasubject variability (RT-ISV) has been consistently documented as a critical etiological feature of ADHD (Kofler et al., 2013). A meta-analytic review of 319 studies performed in children, adolescents, and adults confirmed a greater RT variability in ADHD compared to their TD control group (Hedges' $g = 0.76$ in children/adolescents; Kofler et al., 2013). In a later study including a sample of 53 TDC and 70 children with ADHD (6.8 to13.6 years of age), RT-ISV measured by Eriksen flanker task (EFT) and sustained attention to response task (SART) was statistically significantly higher in ADHD compared to TDC ($p < 0.001$). Moreover, average amplitude of each frequency was measured for the ADHD-impaired, ADHD-unimpaired, and TDC groups: RT fluctuations seemed to be specifically driven by the ADHD-impaired subset (Adamo et al., 2014).

4.2 | ADHD and executive functions: Sex differences

Problems in neurocognitive functioning have been reported both in males and females with ADHD (Nussbaum, 2012). Several studies in ADHD found more impulsive errors, poorer processing speed, and deficits in motor functioning in males compared to females (Hasson & Fine, 2012; Nussbaum, 2012; Rucklidge, 2010). In contrast, females with ADHD were found to show more working memory problems,

poorer vocabulary skills, less intellectual abilities, and worse visual spatial reasoning (Gaub & Carlson, 1997; Nussbaum, 2012; Rucklidge, 2010). However, the literature on the topic remains inconclusive with many studies evidencing no sex difference in executive functioning (Rucklidge, 2010; Sjowall et al., 2013).

Studies using the *continuous performance test (CPT)* in ADHD children evidenced that boys were more likely to commit commission errors compared to their female counterpart, while no omission differences were found between the two sexes (Hasson & Fine, 2012; Newcorn et al., 2001). It could indicate that inhibitory control, but not inattention, can be mediated by sex and that the relationship between sex and impulsivity is stronger than the one between sex and inattention. Similarly, adolescent males with ADHD appeared to be more impaired in inhibition skills than females (Rucklidge, 2006).

In adults, attentional skills appear also to be potentially influenced by sex. In a meta-analysis, including 25 neuropsychological studies comparing adults with ADHD and healthy controls, a strong linear association between the male sex and a poorer functioning on the *Stroop Color-Word Test* (a measure of focused attention and interference control) was found. Thus, adult females with ADHD seem to perform better than males on attention tasks (Balint et al., 2009).

Conversely, working memory has been found to be more impaired in adult ADHD women compared to their male counterpart. Across all examined groups (ADHD-combined or inattentive types and normal controls), adult males performed significantly better than females on specific working memory tasks, such as *letter-number sequencing* and *digit span* of the Wechsler scales and Paced Auditory Serial Addition Task (PASAT) *number correct* and *omissions errors* (Schweitzer et al., 2006).

In a sample of 56 ADHD children (26 females and 30 males) and 90 controls (42 females and 48 males) aged 8–13 years, girls and boys with ADHD showed *similar* patterns of deficit on tasks involving both working memory and response preparation; however, they showed *different* patterns of executive dysfunction on tasks related to planning and response inhibition, and girls, but not boys with ADHD, showed higher impairment in planning (O'Brien et al., 2010).

ADHD girls, compared to TD children, also show an impaired response control (higher commission error rate and higher tau RT-ISV) during a complex GNG task, suggesting that cognitive load influences response control in children with ADHD in a sexually dimorphic manner in a context of possible different neural maturational processes timing (Seymour et al., 2016). The expansion of this study, including 8- to 17-year-old children with ADHD ($n = 353$, 104 girls) and TD controls ($n = 241$, 86 girls) revealed less improvement in response inhibition with age resulting in greater deficits in adolescence in girls, consistently with the developmental lag model of ADHD (DeRonda et al., 2021).

During a motivational GNG task a lower ISV has been found in boys, but not in girls with ADHD, suggesting a motivational contingencies' influence on cognitive task performance, with consequent ISV improvement in boys (Rosch et al., 2015).

Boys with ADHD tend to manifest atypical motor development earlier and longer than do girls with ADHD (Mahone & Wodka, 2008). Not surprisingly, cognitive tasks that require speed represent an area of weakness for boys, but not necessarily for girls. This may be related to differences in basal ganglia development (Mahone & Wodka, 2008). Thus, in the classroom setting, boys with ADHD may have difficulties in graphomotor control and speed. In contrast, young girls with ADHD may not be as at risk under academic demand such as handwriting, or when are strictly guided by teachers to maintain their optimal level of alertness and attention. However, girls with ADHD may have more difficulties than control girls when involved in tasks requiring independent planning, particularly when the planning must be done mentally, for example without an immediate feedback (Mahone & Wodka, 2008).

Regarding the impact of sex on impairment in motor control, some studies have been consistent in highlighting that boys show more mirror overflow movements (i.e., synkinetic movements occurring symmetrically opposite of intentional movements) than girls across diagnosis (Cole et al., 2008; MacNeil et al., 2011) as well as in the ADHD population (Mostofsky et al., 2003). However, a recent study revealed similar levels of excessive mirror overflow in boys and girls with ADHD, with boys exhibiting more variable tap times compared to TD boys, while no diagnostic effect was observed in girls (Chen et al., 2021). These contrasting results are interpreted by the same authors due to a possibly age effect considering the broader age range (5–12 years) in this last study compared to the previous ones (about 8–12 years). Further research on motor abilities also suggest that motor overflow tend significantly to reduce through adolescence in ADHD boys, while dysrhythmia and slow speed may tend to persist, reflecting possible distinct underlying neurologic processes in the developmental trajectories (Crasta et al., 2021).

Elucidating sex differences in reward-based decision-making in ADHD, a study by Rosch and Mostofsky (2016) examined for the first time sex differences in delay discounting among children with ADHD-C, compared to TD controls, using two tasks—a classic "real-reward" discounting task and a novel "real-time" discounting task, during which participants experienced the delays and rewards associated with their choices in real time. The results confirmed that ADHD children show greater delay discounting. Further, in the latter task, only ADHD girls, but not boys, showed greater delay discounting compared to TD controls. The preference for immediate reward, according to the authors, may be explained by a possible diminished response to reward and a greater aversion to delay in girls with ADHD.

A recent study confirmed poorer performance on delay discounting (classic *delay discounting task* and *real-time discounting task*) and cognitive control tasks (*GNG task*, *spatial span task*, *Stop Signal Task*) in ADHD participants, compared to TD samples, and revealed ADHD-related sex differences. Specifically, girls and boys showed impaired inhibitory control on the *Stop Signal Task*, but only ADHD boys showed impaired inhibitory control on the *GNG task*. As noted by the authors, considering that these two tasks are respectively influenced by working memory and behavioral inhibition, boys with ADHD, compared to girls, exhibit greater behavioral disinhibition.

In addition, girls, but not boys, exhibited increased delay discounting (Patros et al., 2018).

Finally, a very recent meta-analysis by Doidge et al. (2021), on sex differences on delay gratification and temporal discounting tasks in both TD and ADHD samples, confirmed that females with ADHD were more likely to prefer smaller immediate rewards than males with ADHD. The authors argued that this difference could be explained by ADHD symptom severity differences; the presence of comorbid conditions; worse outcomes in coping abilities; internalizing distress, speech, and language; and difficulties with organization and social skills issues, at a greater rate than ADHD males.

5 | CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The data reported in this minireview indicate that ADHD is not a single pathophysiological entity. Growing evidence suggest the existence of different clinical presentations, variable functional impairment and different psychopathological and cognitive profiles. Sex differences appear to be a substantial contributor to the ADHD heterogeneity in clinical presentation and in the underlying neuropsychological substrates. At a neuropsychological level, differences between children with and without ADHD mainly occur in several domains such as EF, motivation, and time perception (Coghill et al., 2018; O'Neil et al., 2018); however no specific impairment is a necessary or sufficient cause of the disorder: Different clusters of neuropsychological weaknesses among individuals can lead to a large clinical heterogeneity.

Although in childhood and adolescence ADHD appears to affect mainly boys (Greven et al., 2018; Mowlem et al., 2019), this finding may be not realistic since a possible diagnostic bias due to the structuring of a "*male prototype of ADHD*" may lead to a diagnostic selection on the basis of the clinical presentation described in the DSMs for males (Mowlen et al., 2019; Nussbaum, 2012). Females with ADHD are more often inattentive rather than hyperactive and, generally, have more internalizing comorbidities. This leads girls to be perceived as less impaired by parents and teachers, and therefore they reach the attention of clinicians less frequently and at older age, although significant comorbidities may be more strongly associated with ADHD in females than in males: The presence of ADHD seems to be associated with a higher relative risk of having comorbid autism spectrum disorders, oppositional defiant/conduct disorders, intellectual disability, personality disorders, schizophrenia, substance abuse disorders, and suicidal behaviors in females than in males (Ottosen et al., 2019).

Sex-specific variance in brain neuroanatomy, circuits and neurocognition, have been identified within ADHD females presenting different trajectories in brain development, probably related to more working memory problems, poorer vocabulary skills, less intellectual abilities, worse visual spatial reasoning, and higher impairment in planning (Greven et al., 2018; Mahone & Wodka, 2008; Nussbaum, 2012; O'Brien et al., 2010; Rucklidge, 2010; Schweitzer et al., 2006). It should be considered, however, that only few studies have involved sufficiently large samples of females: Further studies are indeed needed to better characterize ADHD in females, in order to reduce the health gap between sexes (Mowlem et al., 2019; Nussbaum, 2012; Young et al., 2020).

The integration of a sex-sensitive perspective in all aspects of ADHD research is urgently needed also considering that efficacy and the adverse events of many therapeutic compounds can vary according to sex: This difference appears to be related to pharmacokinetic and pharmacodynamic properties, immunological and hormonal factors, and a general lower lean body mass in women (Rademaker, 2001; Yu et al., 2016; Zucker & Prendergast, 2020).

Based on the false hypothesis that men and women are identical, currently, medications are studied mainly in men and the data obtained about the clinical efficacy and the potential side effects are then extrapolated to women. A recent systematic review (Kok et al., 2020) examining the efficacy/effectiveness and adverse events of ADHD medications (stimulants and nonstimulants) in an ADHD population revealed a MPH stronger effect earlier in the day but also an earlier decline after a single administration, and therefore less improvement in the ADHD core symptoms during the day, in girls compared to boys. Girls and women also appeared to be more responsive to nonstimulants; data on adverse events were not conclusive due to limited findings (Kok et al., 2020).

In summary, from a precision medicine perspective, we should consider ADHD as not as a single neurobiological entity: A better characterization of ADHD children and adolescents' neuropsychological profile should allow to identify different subgroups that could receive a more specific clinical assessment and, therefore, more effective therapies. Greater efforts should be made to better investigate ADHD clinical presentation in females, and to better understand their underlying neuropsychological functioning. This aim should be achieved in order to develop tailored diagnostic protocols as well as personalized and effective therapeutic strategies and to improve the quality of care of girls with ADHD.

6 | STRENGTHS AND LIMITATIONS

This narrative minireview aims to review the state of art for sex differences in child and adolescent ADHD presentation at clinical, neuroimaging, and neuropsychological levels. We discussed with a combined, concise, and accessible way, the clinical, neurobiological (i.e., neuroimaging), and neuropsychological interplay in the disorder, which are usually considered separately: This unified approach may contribute to a better understanding of the sex difference observed in this disorder and in turn to design more effective, comprehensive sex-specific therapeutic strategies.

Our work also has some limitations. This paper was designed as comprehensive narrative minireview since a more systematic approach would probably need a separate paper for each section. Further efforts should be made in order to carry out a *series* of systematic reviews of these topics and clinical trials aimed at accurately exploring sex differences in developmental clinical samples finalized to the advance of this field of research.

CONFLICT OF INTEREST

SC had collaborations within projects from the European Union (7th Framework Program: PERS, ADDUCE, MATRICS) and as subinvestigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen Cilag, and Angelini. Travel support from Fidia Farmaceutici. CB had collaborations within projects from the European Union (7th Framework Program: PERS, MATRICS) and as subinvestigator in sponsored clinical trials by Lundbeck, Otsuka, Janssen Cilag, and Angelini. FD had collaborations as subinvestigator in clinical trial sponsored by Lundbeck and as independent rater in clinical trials sponsored by Servier. AG was in the advisory boards for Eli Lilly and Shire. She has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen, and Otsuka. She has been speaker for Novartis, Eli Lilly and Shire. AZ served in an advisory or consultancy role for Angelini, EduPharma, Servier, and Takeda. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier, and Shire. He received royalties from Giunti OS, Oxford University Press. The present work is unrelated to the above grants and relationships. CN and MB do not have any conflict of interests to declare.

AUTHOR CONTRIBUTIONS

Conceptualization, S.C. and A.Z.; *Writing – Original Draft*, S.C., C.N., and M.B.; *Writing – Review & Editing*, C.B., F.D., and A.G.; *Supervision*, A.G. and A.Z. All authors take responsibility for the final manuscript.

PEER REVIEW

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REFERENCES

Adamo, N., di Martino, A., Esu, L., Petkova, E., Johnson, K., Kelly, S., Castellanos, F. X., & Zuddas, A. (2014). Increased response-time variability across different cognitive tasks in children with ADHD. *Journal of Attention Disorders*, *18*(5), 434–446. https://doi.org/10.1177/1087054712439419

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Author.

Balint, S., Czobor, P., Komlosi, S., Meszaros, A., Simon, V., & Bitter, I. (2009). Attention deficit hyperactivity disorder (ADHD): Gender- and age-related differences in neurocognition. *Psychological Medicine*, *39*(8), 1337–1345. https://doi.org/10.1017/S0033291708004236

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65–94. https://doi.org/10.1037/0033-2909.121.1.65

Batty, M. J., Liddle, E. B., Pitiot, A., Toro, R., Groom, M. J., Scerif, G., Liotti, M., Liddle, P. F., Paus, T., & Hollis, C. (2010). Cortical gray matter in attention-deficit/hyperactivity disorder: A structural magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(3), 229–238. https://doi.org/10.1016/j.jaac.2009.11.008

Breedlove, S. M. (2010). Minireview: Organizational hypothesis: Instances of the fingerpost. *Endocrinology*, *151*(9), 4116–4122. https://doi.org/10.1210/en.2010-0041

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., Blumenthal, J. D., James, R. S., Ebens, C. L., Walter, J. M., Zijdenbos, A., Evans, A. C., Giedd, J. N., & Rapoport, J. L. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*, *288*(14), 1740–1748. https://doi.org/10.1001/jama.288.14.1740

Castellanos, F. X., Sonuga-Barke, E. J., Milham, M. P., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends in Cognitive Sciences*, *10*(3), 117–123. https://doi.org/10.1016/j.tics.2006.01.011

Charach, A., Yeung, E., Climans, T., & Lillie, E. (2011). Childhood attention-deficit/hyperactivity disorder and future substance use disorders: Comparative meta-analyses. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*(1), 9–21. https://doi.org/10.1016/j.jaac.2010.09.019

Chen, C., Rosch, K. S., Seymour, K. E., Crocetti, D., Mahone, E. M., & Mostofsky, S. H. (2021). Sex effects on Mirror overflow during finger tapping in children with ADHD. *Journal of the International Neuropsychological Society*, *17*, 1–11. https://doi.org/10.1017/S1355617721000576

Coghill, D. R., Banaschewski, T., Soutullo, C., Cottingham, M. G., & Zuddas, A. (2017). Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. *European Child & Adolescent Psychiatry*, *26*(11), 1283–1307. https://doi.org/10.1007/s00787-017-0986-y

Coghill, D. R., Seth, S., & Matthews, K. (2014). A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: Advancing beyond the three-pathway models. *Psychological Medicine*, *44*(9), 1989–2001. https://doi.org/10.1017/S0033291713002547

Coghill, D. R., Toplak, M., Rhodes, S., & Adamo, N. (2018). Cognitive functioning in ADHD: Inhibition, memory, temporal discounting, decision-making, timing and reaction time variability. In T. Banaschewski, D. Coghill, & A. Zuddas (Eds.), *Oxford textbook of attention deficit hyperactivity disorder* (pp. 94–102). Oxford University Press.

Cole, W. R., Mostofsky, S. H., Larson, J. C., Denckla, M. B., & Mahone, E. M. (2008). Age-related changes in motor subtle signs among girls and boys with ADHD. *Neurology*, *71*(19), 1514–1520. https://doi.org/10.1212/01.wnl.0000334275.57734.5f

Cortese, S., & Coghill, D. (2018). Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): Looking back, looking forward. *Evidence-Based Mental Health*, *21*(4), 173–176. https://doi.org/10.1136/ebmental-2018-300050

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*, *169*(10), 1038–1055. https://doi.org/10.1176/appi.ajp.2012.11101521

Crasta, J. E., Zhao, Y., Seymour, K. E., Suskauer, S. J., Mostofsky, S. H., & Rosch, K. S. (2021). Developmental trajectory of subtle motor signs in attention-deficit/hyperactivity disorder: A longitudinal study from childhood to adolescence. *Child Neuropsychology*, *27*(3), 317–332. https://doi.org/10.1080/09297049.2020.1847265

Dalsgaard, S., Ostergaard, S. D., Leckman, J. F., Mortensen, P. B., & Pedersen, M. G. (2015). Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: A nationwide cohort study. *Lancet*, *385*(9983), 2190–2196. https://doi.org/10.1016/S0140-6736(14)61684-6

DeRonda, A., Zhao, Y., Seymour, K. E., Mostofsky, S. H., & Rosch, K. S. (2021). Distinct patterns of impaired cognitive control among boys and girls with ADHD across development. *Research on Child and Adolescent Psychopathology*, *49*(7), 835–848. https://doi.org/10.1007/s10802-021-00792-2

Dirlikov, B., Shiels Rosch, K., Crocetti, D., Denckla, M. B., Mahone, E. M., & Mostofsky, S. H. (2015). Distinct frontal lobe morphology in girls and boys with ADHD. *Neuroimage Clinical*, *7*, 222–229. https://doi.org/10.1016/j.nicl.2014.12.010

Doidge, J. L., Flora, D. B., & Toplak, M. E. (2021). A meta-analytic review of sex differences on delay of gratification and temporal discounting tasks in ADHD and typically developing samples. *Journal of Attention Disorders*, *25*(4), 540–561. https://doi.org/10.1177/1087054718815588

Ebejer, J. L., Medland, S. E., van der Werf, J., Gondro, C., Henders, A. K., Lynskey, M., Martin, N. G., & Duffy, D. L. (2012). Attention deficit hyperactivity disorder in Australian adults: Prevalence, persistence, conduct problems and disadvantage. *PLoS ONE*, *7*(10), e47404. https://doi.org/10.1371/journal.pone.0047404

Ellison-Wright, I., Ellison-Wright, Z., & Bullmore, E. (2008). Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry*, *8*, 51. https://doi.org/10.1186/1471-244X-8-51

Fair, D. A., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U., Schlaggar, B. L., Mennes, M., Gutman, D., Bangaru, S., Buitelaar, J. K., Dickstein, D. P., di Martino, A., Kennedy, D. N., Kelly, C., Luna, B., Schweitzer, J. B., Velanova, K., Wang, Y. F., … Milham, M. P. (2012). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*, 80. https://doi.org/10.3389/fnsys.2012.00080

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., Rohde, L. A., Sonuga-Barke, E. J. S., Tannock, R., & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, *1*, 15020. https://doi.org/10.1038/nrdp.2015.20

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562–575. https://doi.org/10.1038/s41380-018-0070-0

Fitzgerald, C., Dalsgaard, S., Nordentoft, M., & Erlangsen, A. (2019). Suicidal behaviour among persons with attention-deficit hyperactivity disorder. *British Journal of Psychiatry*, *7*, 1–6. https://doi.org/10.1192/bjp.2019.128

Franke, B., Michelini, G., Asherson, P., Banaschewski, T., Bilbow, A., Buitelaar, J. K., Cormand, B., Faraone, S. V., Ginsberg, Y., Haavik, J., Kuntsi, J., Larsson, H., Lesch, K. P., Ramos-Quiroga, J. A., Réthelyi, J. M., Ribases, M., & Reif, A. (2018). Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *European Neuropsychopharmacology*, *28*(10), 1059–1088. https://doi.org/10.1016/j.euroneuro.2018.08.001

Galéra, C., Messiah, A., Melchior, M., Chastang, J. F., Encrenaz, G., Lagarde, E., Michel, G., Bouvard, M. P., & Fombonne, E. (2010). Disruptive behaviors and early sexual intercourse: The GAZEL youth study. *Psychiatry Research*, *177*(3), 361–363. https://doi.org/10.1016/j.psychres.2010.03.009

Gaub, M., & Carlson, C. L. (1997). Gender differences in ADHD: A meta-analysis and critical review. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(8), 1036–1045. https://doi.org/10.1097/00004583-199708000-00011

Geary, D. C. (2010). *Male, female: The evolution of human sex differences* (2nd ed.). American Psychological Association.

Gillies, G. E., Virdee, K., McArthur, S., & Dalley, J. W. (2014). Sex-dependent diversity in ventral tegmental dopaminergic neurons and developmental programing: A molecular, cellular and behavioral analysis. *Neuroscience*, *282*, 69–85. https://doi.org/10.1016/j.neuroscience.2014.05.033

Green, T., Flash, S., & Reiss, A. L. (2019). Sex differences in psychiatric disorders: What we can learn from sex chromosome aneuploidies. *Neuropsychopharmacology*, *44*(1), 9–21. https://doi.org/10.1038/s41386-018-0153-2

Greven, C. U., Richards, J. S., & Buitelaar, J. K. (2018). Sex differences in ADHD. In T. Banaschewski, D. Coghill, & A. Zuddas (Eds.), *Oxford textbook of attention deficit hyperactivity disorder* (pp. 154–160). Oxford University Press.

Grygiel, P., Humenny, G., Rębisz, S., Bajcar, E., & Świtaj, P. (2018). Peer rejection and perceived quality of relations with schoolmates among children with ADHD. *Journal of Attention Disorders*, *22*(8), 738–751. https://doi.org/10.1177/1087054714563791

Harstad, E., Levy, S., & Committee on Substance Abuse. (2014). Attention-deficit/hyperactivity disorder and substance abuse. *Pediatrics*, *134*(1), e293–e301. https://doi.org/10.1542/peds.2014-0992

Hasson, R., & Fine, J. G. (2012). Gender differences among children with ADHD on continuous performance tests: A meta-analytic review. *Journal of Attention Disorders*, *16*(3), 190–198. https://doi.org/10.1177/1087054711427398

Hong, S. B., Dwyer, D., Kim, J. W., Park, E. J., Shin, M. S., Kim, B. N., Yoo, H. J., Cho, I. H., Bhang, S. Y., Hong, Y. C., Pantelis, C., & Cho, S. C. (2014). Subthreshold attention-deficit/hyperactivity disorder is associated with functional impairments across domains: A comprehensive analysis in a large-scale community study. *European Child & Adolescent Psychiatry*, *23*(8), 627–636. https://doi.org/10.1007/s00787-013-0501-z

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S. J., van Hulzen, K., Medland, S. E., Shumskaya, E., Jahanshad, N., Zeeuw, P., Szekely, E., Sudre, G., Wolfers, T., Onnink, A. M. H., Dammers, J. T., Mostert, J. C., Vives-Gilabert, Y., Kohls, G., … Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *Lancet Psychiatry*, *4*(4), 310–319. https://doi.org/10.1016/S2215-0366(17)30049-4

Hoogman, M., Muetzel, R., Guimaraes, J. P., Shumskaya, E., Mennes, M., Zwiers, M. P., Jahanshad, N., Sudre, G., Wolfers, T., Earl, E. A., Soliva Vila, J. C., Vives-Gilabert, Y., Khadka, S., Novotny, S. E., Hartman, C. A., Heslenfeld, D. J., Schweren, L. J. S., Ambrosino, S., Oranje, B., … Franke, B. (2019). Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry*, *176*(7), 531–542. https://doi.org/10.1176/appi.ajp.2019.18091033

Jacobson, L. A., Peterson, D. J., Rosch, K. S., Crocetti, D., Mori, S., & Mostofsky, S. H. (2015). Sex-based dissociation of white matter microstructure in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(11), 938–946. https://doi.org/10.1016/j.jaac.2015.08.014

Kaczkurkin, A. N., Raznahan, A., & Satterthwaite, T. D. (2019). Sex differences in the developing brain: Insights from multimodal neuroimaging. *Neuropsychopharmacology*, *44*(1), 71–85. https://doi.org/10.1038/s41386-018-0111-z

Karalunas, S. L., & Huang-Pollock, C. L. (2011). Examining relationships between executive functioning and delay aversion in attention deficit hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology*, *40*(6), 837–847. https://doi.org/10.1080/15374416.2011.614578

Klein, C., Wendling, K., Huettner, P., Ruder, H., & Peper, M. (2006). Intra-subject variability in attention-deficit hyperactivity disorder. *Biological Psychiatry*, *15*(10), 1088–1097. https://doi.org/10.1016/j.biopsych.2006.04.003

Klein, R. G., Mannuzza, S., Olazagasti, M. A., Roizen, E., Hutchison, J. A., Lashua, E. C., & Castellanos, F. X. (2012). Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*, *69*(12), 1295–1303. https://doi.org/10.1001/archgenpsychiatry.2012.271

Kofler, M. J., Rapport, M. D., Sarver, D. E., Raiker, J. S., Orban, S. A., Friedman, L. M., & Kolomeyer, E. G. (2013). Reaction time variability in ADHD: A meta-analytic review of 319 studies. *Clinical Psychology Review*, *33*(6), 795–811. https://doi.org/10.1016/j.cpr.2013.06.001

Kok, F. M., Groen, Y., Fuermaier, A. B. M., & Tucha, O. (2020). The female side of pharmacotherapy for ADHD—A systematic literature

review. *PLoS ONE*, *15*(9), e0239257. https://doi.org/10.1371/journal.pone.0239257

Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I. response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry*, *42*(2), 199–210.

Liedmeier, A., Jendryczko, D., van der Grinten, H. C., Rapp, M., Thyen, U., Pienkowski, C., Hinz, A., & Reisch, N. (2020). Psychosocial well-being and quality of life in women with turner syndrome. *Psychoneuroendocrinology*, *113*, 104548. https://doi.org/10.1016/j.psyneuen.2019.104548

Loke, H., Harley, V., & Lee, J. (2015). Biological factors underlying sex differences in neurological disorders. *International Journal of Biochemistry & Cell Biology*, *65*, 139–150. https://doi.org/10.1016/j.biocel.2015.05.024

MacNeil, L. K., Xavier, P., Garvey, M. A., Gilbert, D. L., Ranta, M. E., Denckla, M. B., & Mostofsky, S. H. (2011). Quantifying excessive mirror overflow in children with attention-deficit/hyperactivity disorder. *Neurology*, *76*(7), 622–628. https://doi.org/10.1212/WNL.0b013e31820c3052

Mahone, E. M., & Wodka, E. L. (2008). The neurobiological profile of girls with ADHD. *Developmental Disabilities Research Reviews*, *14*(4), 276–284. https://doi.org/10.1002/ddrr.41

Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N., Caviness, V. S., Faraone, S. V., & Seidman, L. J. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral Cortex*, *17*(6), 1364–1375. https://doi.org/10.1093/cercor/bhl047

Martel, M. M. (2013). Sexual selection and sex differences in the prevalence of childhood externalizing and adolescent internalizing disorders. *Psychological Bulletin*, *139*(6), 1221–1259. https://doi.org/10.1037/a0032247

Mostofsky, S. H., Newschaffer, C. J., & Denckla, M. B. (2003). Overflow movements predict impaired response inhibition in children with ADHD. *Perceptual and Motor Skills*, *97*(3 Pt 2), 1315–1331. https://doi.org/10.2466/pms.2003.97.3f.1315

Mowlem, F., Agnew-Blais, J., Taylor, E., & Asherson, P. (2019). Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms. *Psychiatry Research*, *272*, 765–773. https://doi.org/10.1016/j.psychres.2018.12.128

Nakao, T., Radua, J., Rubia, K., & Mataix-Cols, D. (2011). Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*, *168*(11), 1154–1163. https://doi.org/10.1176/appi.ajp.2011.11020281

Narr, K. L., Woods, R. P., Lin, J., Kim, J., Phillips, O. R., del'Homme, M., Caplan, R., Toga, A. W., McCracken, J., & Levitt, J. G. (2009). Widespread cortical thinning is a robust anatomical marker for attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(10), 1014–1022. https://doi.org/10.1097/CHI.0b013e3181b395c0

Newcorn, J. H., Halperin, J. M., Jensen, P. S., Abikoff, H. B., Arnold, L. E., Cantwell, D. P., Conners, C. K., Elliott, G. R., Epstein, J. N., Greenhill, L. L., Hechtman, L., Hinshaw, S. P., Hoza, B., Kraemer, H. C., Pelham, W. E., Severe, J. B., Swanson, J. M., Wells, K. C., Wigal, T., & Vitiello, B. (2001). Symptom profiles in children with ADHD: Effects of comorbidity and gender. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(2), 137–146. https://doi.org/10.1097/00004583-200102000-00008

Nigg, J. T., & Casey, B. J. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Development and Psychopathology*, *17*(3), 785–806. https://doi.org/10.1017/S0954579405050376

Novik, T. S., Hervas, A., Ralston, S. J., Dalsgaard, S., Rodrigues Pereira, R., Lorenzo, M. J., & ADORE Study Group. (2006). Influence of gender on attention-deficit/hyperactivity disorder in Europe—ADORE. *European Child & Adolescent Psychiatry*, *15*(Suppl. 1), I15–I24. https://doi.org/10.1007/s00787-006-1003-z

Nussbaum, N. L. (2012). ADHD and female specific concerns: A review of the literature and clinical implications. *Journal of Attention Disorders*, *16*(2), 87–100. https://doi.org/10.1177/1087054711416909

O'Brien, J. W., Dowell, L. R., Mostofsky, S. H., Denckla, M. B., & Mahone, E. M. (2010). Neuropsychological profile of executive function in girls with attention-deficit/hyperactivity disorder. *Archives of Clinical Neuropsychology*, *25*(7), 656–670. https://doi.org/10.1093/arclin/acq050

O'Neil, S., Halperin, J. M., & Coghill, D. R. (2018). Neuropsychological functioning and ADHD: A developmental perspective. In T. Banaschewski, D. Coghill, & A. Zuddas (Eds.), *Oxford textbook of attention deficit hyperactivity disorder* (pp. 118–130). Oxford University Press.

Ottosen, C., Larsen, J. T., Faraone, S. V., Chen, Q., Hartman, C., Larsson, H., Petersen, L., & Dalsgaard, S. (2019). Sex differences in comorbidity patterns of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(4), 412–422.e3. https://doi.org/10.1016/j.jaac.2018.07.910

Patros, C. H. G., Sweeney, L. K., Mahone, E. M., Mostofsky, S. H., & Rosch, K. S. (2018). Greater delay discounting among girls, but not boys, with ADHD correlates with cognitive control. *Child Neuropsychology*, *24*(8), 1026–1046. https://doi.org/10.1080/09297049.2017.1359525

Poissant, H., Rapin, L., Chenail, S., & Mendrek, A. (2016). Forethought in youth with attention deficit/hyperactivity disorder: An fMRI study of sex-specific differences. *Psychiatry Journal*, *2016*, 6810215. https://doi.org/10.1155/2016/6810215

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*(6), 942–948. https://doi.org/10.1176/ajp.2007.164.6.942

Qiu, A., Crocetti, D., Adler, M., Mahone, E. M., Denckla, M. B., Miller, M. I., & Mostofsky, S. H. (2009). Basal ganglia volume and shape in children with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *166*(1), 74–82. https://doi.org/10.1176/appi.ajp.2008.08030426

Rademaker, M. (2001). Do women have more adverse drug reactions? *American Journal of Clinical Dermatology*, *2*(6), 349–351. https://doi.org/10.2165/00128071-200102060-00001

Rosch, K. S., Crocetti, D., Hirabayashi, K., Denckla, M. B., Mostofsky, S. H., & Mahone, E. M. (2018). Reduced subcortical volumes among preschool-age girls and boys with ADHD. *Psychiatry Research: Neuroimaging*, *271*, 67–74. https://doi.org/10.1016/j.pscychresns.2017.10.013

Rosch, K. S., Dirlikov, B., & Mostofsky, S. H. (2015). Reduced intrasubject variability with reinforcement in boys, but not girls, with ADHD: Associations with prefrontal anatomy. *Biological Psychology*, *110*, 12–23. https://doi.org/10.1016/j.biopsycho.2015.06.010

Rosch, K. S., & Mostofsky, S. H. (2016). Increased delay discounting on a novel real-time task among girls, but not boys, with ADHD. *Journal of the International Neuropsychological Society*, *22*(1), 12–23. https://doi.org/10.1017/S1355617715001071

Rosch, K. S., Mostofsky, S. H., & Nebel, M. B. (2018). ADHD-related sex differences in fronto-subcortical intrinsic functional connectivity and associations with delay discounting. *Journal of Neurodevelopmental Disorders*, *10*(1), 34. https://doi.org/10.1186/s11689-018-9254-9

Rubia, K. (2018). Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. *Frontiers in Human Neuroscience*, *12*, 100. https://doi.org/10.3389/fnhum.2018.00100

Rucklidge, J. J. (2006). Gender differences in neuropsychological functioning of New Zealand adolescents with and without attention deficit disorder. *International Journal of Disability, Development and Education*, *53*(1), 47–66.

Rucklidge, J. J. (2010). Gender differences in attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America*, *33*(2), 357–373. https://doi.org/10.1016/j.psc.2010.01.006

Schweitzer, J., Hanford, R. B., & Medoff, D. R. (2006). Working memory deficits in adults with ADHD: Is there evidence for subtype differences? *Behavioral and Brain Function*, *2*, 43. https://doi.org/10.1186/1744-9081-2-43

Shaw, P., Lerch, J., Greenstein, D., Sharp, W., Clasen, L., Evans, A., Giedd, J., Castellanos, F. X., & Rapoport, J. (2006). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *63*(5), 540–549. https://doi.org/10.1001/archpsyc.63.5.540

Seymour, K. E., Mostofsky, S. H., & Rosch, K. S. (2016). Cognitive load differentially impacts response control in girls and boys with ADHD. *Journal of Abnormal Child Psychology*, *44*(1), 141–154. https://doi.org/10.1007/s10802-015-9976-z

Seymour, K. E., Tang, X., Crocetti, D., Mostofsky, S. H., Miller, M. I., & Rosch, K. S. (2017). Anomalous subcortical morphology in boys, but not girls, with ADHD compared to typically developing controls and correlates with emotion dysregulation. *Psychiatry Research: Neuroimaging*, *261*, 20–28. https://doi.org/10.1016/j.pscychresns.2017.01.002

Sheridan, M. A., Hinshaw, S., & D'Esposito, M. (2007). Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(10), 1357–1366. https://doi.org/10.1097/chi.0b013e31812eecf7

Sjowall, D., Roth, L., Lindqvist, S., & Thorell, L. B. (2013). Multiple deficits in ADHD: Executive dysfunction, delay aversion, reaction time variability, and emotional deficits. *Journal of Child Psychology and Psychiatry*, *54*(6), 619–627. https://doi.org/10.1111/jcpp.12006

Sonuga-Barke, E. J. (2003). The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neuroscience and Biobehavioral Reviews*, *27*(7), 593–604. https://doi.org/10.1016/j.neubiorev.2003.08.005

Sonuga-Barke, E. J., Bitsakou, P., & Thompson, M. (2010). Beyond the dual pathway model: Evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(4), 345–355. https://doi.org/10.1016/j.jaac.2009.12.018

Sonuga-Barke, E. J., Cortese, S., Fairchild, G., & Stringaris, A. (2016). Annual research review: Transdiagnostic neuroscience of child and adolescent mental disorders—Differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety. *Journal of Child Psychology and Psychiatry*, *57*(3), 321–349. https://doi.org/10.1111/jcpp.12496

Sowell, E. R., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., & Peterson, B. S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet*, *362*(9397), 1699–1707. https://doi.org/10.1016/S0140-6736(03)14842-8

Stephens, M. A., Mahon, P. B., McCaul, M. E., & Wand, G. S. (2016). Hypothalamic-pituitary-adrenal axis response to acute psychosocial stress: Effects of biological sex and circulating sex hormones. *Psychoneuroendocrinology*, *66*, 47–55. https://doi.org/10.1016/j.psyneuen.2015.12.021

Stevenson, J. C., Everson, P. M., Williams, D. C., Hipskind, G., Grimes, M., & Mahoney, E. R. (2007). Attention deficit/hyperactivity disorder (ADHD) symptoms and digit ratios in a college sample. *American Journal of Human Biology*, *19*(1), 41–50. https://doi.org/10.1002/ajhb.20571

Tang, X., Seymour, K. E., Crocetti, D., Miller, M. I., Mostofsky, S. H., & Rosch, K. S. (2019). Response control correlates of anomalous basal ganglia morphology in boys, but not girls, with attention-deficit/hyperactivity disorder. *Behavioural Brain Research*, *367*, 117–127. https://doi.org/10.1016/j.bbr.2019.03.036

Taylor, M. J., Lichtenstein, P., Larsson, H., Anckarsater, H., Greven, C. U., & Ronald, A. (2016). Is there a female protective effect against attention-deficit/hyperactivity disorder? Evidence from two representative twin samples. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(6), 504–512.e502. https://doi.org/10.1016/j.jaac.2016.04.004

Valera, E. M., Brown, A., Biederman, J., Faraone, S. V., Makris, N., Monuteaux, M. C., Whitfield-Gabrieli, S., Vitulano, M., Schiller, M., & Seidman, L. J. (2010). Sex differences in the functional neuroanatomy of working memory in adults with ADHD. *American Journal of Psychiatry*, *167*(1), 86–94. https://doi.org/10.1176/appi.ajp.2009.09020249

Valera, E. M., Faraone, S. V., Murray, K. E., & Seidman, L. J. (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *61*(12), 1361–1369. https://doi.org/10.1016/j.biopsych.2006.06.011

van Rooij, D., Hoekstra, P. J., Mennes, M., von Rhein, D., Thissen, A. J., Heslenfeld, D., Zwiers, M. P., Faraone, S. V., Oosterlaan, J., Franke, B., Rommelse, N., Buitelaar, J. K., & Hartman, C. A. (2015). Distinguishing adolescents with ADHD from their unaffected siblings and healthy comparison subjects by neural activation patterns during response inhibition. *American Journal of Psychiatry*, *172*(7), 674–683. https://doi.org/10.1176/appi.ajp.2014.13121635

Waddell, J., & McCarthy, M. M. (2012). Sexual differentiation of the brain and ADHD: What is a sex difference in prevalence telling us? *Current Topics in Behavioral Neurosciences*, *9*, 341–360. https://doi.org/10.1007/7854_2010_114

Walton, E., Pingault, J. B., Cecil, C. A., Gaunt, T. R., Relton, C. L., Mill, J., & Barker, E. D. (2017). Epigenetic profiling of ADHD symptoms trajectories: A prospective, methylome-wide study. *Molecular Psychiatry*, *22*(2), 250–256. https://doi.org/10.1038/mp.2016.85

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry*, *57*(11), 1336–1346. https://doi.org/10.1016/j.biopsych.2005.02.006

Willcutt, E. G., Sonuga-Barke, E. J. S., Nigg, J. T., & Sergeant, J. A. (2008). Recent developments in neuropsychological models of childhood psychiatric disorders. *Advances in Biological Psychiatry*, *24*, 195–226.

Young, S., Adamo, N., Ásgeirsdóttir, B. B., Branney, P., Beckett, M., Colley, W., Cubbin, S., Deeley, Q., Farrag, E., Gudjonsson, G., Hill, P., Hollingdale, J., Kilic, O., Lloyd, T., Mason, P., Paliokosta, E., Perecherla, S., Sedgwick, J., Skirrow, C., … Woodhouse, E. (2020). Females with ADHD: An expert consensus statement taking a lifespan approach providing guidance for the identification and treatment of attention-deficit/hyperactivity disorder in girls and women. *BMC Psychiatry*, *20*(1), 404. https://doi.org/10.1186/s12888-020-02707-9

Yu, Y., Chen, J., Li, D., Wang, L., Wang, W., & Liu, H. (2016). Systematic analysis of adverse event reports for sex differences in adverse drug events. *Scientific Reports*, *6*, 24955. https://doi.org/10.1038/srep24955

Zucker, I., & Prendergast, B. J. (2020). Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of Sex Differences*, *11*(1), 32. https://doi.org/10.1186/s13293-020-00308-5

Zuddas, A., & Carucci, S. (2020). Management and treatment of attention-deficit/hyperactivity disorder. In J. R. Geddes, N. C. Andreasen, & G. M. Goodwin (Eds.), *New Oxford textbook of psychiatry* (3rd ed., pp. 344–355). Oxford University Press.

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