NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD OTTOBRE 2019

ADHD Atten Deficit Hyperact Disord. 2019.

THE INTERPLAY OF DELAY AVERSION, TIMING SKILLS, AND IMPULSIVITY IN CHILDREN EXPERIENCING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS.

Blume F, Kuehnhausen J, Reinelt T, et al.

Impulsive behaviours occurring as a central deficit in connection with attention-deficit/hyperactivity disorder (ADHD) are associated with social and academic impairment in children. Whereas impulsivity was shown to be related to both delay aversion and deficient timing skills, the mutual relation between the latter two has hardly been investigated. The present study therefore examined the interplay of delay aversion, timing skills, and impulsivity in a sample of eighty-eight children aged between seven and fourteen, twenty-one of them diagnosed with ADHD. Children participated in a delay aversion and a tapping task, while parents reported about their impulsiveness. The results showed that both delay aversion and deficient timing skills were related to impulsivity. Contrasting prior assumptions, delay aversion and timing skills were also shown to be related, even when controlling for impulsivity. Implications for interventions aiming to reduce childrenΓÇÖs impulsivity as well as methodological considerations regarding whether to view ADHD as a category or a continuum are discussed

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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.

ADHD Atten Deficit Hyperact Disord. 2019.

STIGMA AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: NEGATIVE PERCEPTIONS AND ANGER EMOTIONAL REACTIONS MEDIATE THE LINK BETWEEN ACTIVE SYMPTOMS AND SOCIAL DISTANCE.

Meza JI, Monroy M, Ma R, et al.

This study aimed to understand the contributions of active ADHD symptoms and the diagnostic label of ADHD in yielding negative attitudes and social distance ratings. Using AmazonΓÇÖs Mechanical Turk (n = 305), respondents were assigned to read a vignette about: (a) a typically developing child, (b) a child with active ADHD symptoms and (c) a child with active ADHD symptoms + diagnostic label. Participants were then asked to answer questions about their beliefs and feelings about the child in the vignette. The active ADHD symptom condition predicted higher levels of social distance, and this link was mediated by negative and animalistic adjective ratings, and by angry emotions felt by the participants after reading the vignettes. Our findings suggest that ADHD symptoms drive negative views and social distance and that an ADHD label may serve as a protective factor to help people overcome biases related to childhood ADHD. ADHD symptom literacy and contact with children with varying levels of ADHD symptoms may be an important target to help reduce negative attitudes

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Alzheimer's and Dementia. 2019;15:1480.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND FALLS IN OLDER ADULTRS.

Fernandez MC, Campora N, Berrios W, et al.

Background: Falls are a known health problem in the older adult. The prevalence increases with age, female gender and people living alone. Falls have also been associated with cognitive dysfunction. The mechanisms involved in increasing the risk of falls in cognitive impairment are not yet known. Attention Deficit Hyperactivity Disorder (ADHD) is a syndrome that occurs in childhood and can persist in adulthood, very often underdiagnosed. The objective was to evaluate whether adult ADHD influences the risk of falls in elderly patients with cognitive impairment.

Methods: This was a retrospective observational longitudinal study. We included consecutive patients who consulted between January 2009 and December 2010 with diagnosis of mild cognitive impairment (MCI) according to Petersen criteria. A comprehensive neurocognitive evaluation, anamnesis, physical examination and brain MRI were performed. Univariate statistical analysis (Chi2 for qualitative variables and T-test for cuntitative variables) and multivariate analysis (logistic regression) were performed using SPSS 20.0.

Results: We included 130 patients with a diagnosis of MCI, 65 with a history of falls and 75 without this history. In the univariate analysis, there was a statistically significant difference in age, female gender and antecedent of ADHD. Of these, only the last two remained significant in the multivariate analysis of logistic regression (female gender OR 9.24, antecedent of ADHD OR 7.3).

Conclusions: ADHD is a very important risk factor for falls in older adults that until now had not been considered. Future studies should characterize this risk and develop preventive strategies for this group of patients. References Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri, E. (2010). Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology. 2010;21(5): 658-68. Petersen RC, Smith GE, Waring SC, Ivnik R J, Tangalos EG, Kokmen, E. Mild cognitive impairment: clinical characterization and outcome. Archives of neurology. 1999;56(3): 303-8. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. Mov Disord. 2008;23(3): 329-42

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Alzheimer's and Dementia. 2019;15:975-76.

ATTENTION IS PREDICTED BY ALZHEIMER'S DISEASES POLYGENIC RISK SCORE IN TYPICALLY DEVELOPING CHILDREN MORE THAN CHILDREN WITH ATTENTION/DEFICIT-HYPERACTIVITY DISORDER.

Yoon W, Zayats T, Kim H-W, et al.

Background: ADHD has been conceptualized to neuropsychiatric deficits including attention, working memory, response inhibition, response time variability, and executive function2,3. The association of

polygenic risk for AD and general cognitive ability, memory in general population remains controversial 8-10. The aim of this study is to investigate polygenic risk for AD affects cognitive performance in children with ADHD and typically developing children.
Methods: Subjects were recruited 2012 - 2017 at the Asan Medical Center. All participants were 6-12 years. The Korean Wechsler Intelligence Scales for Children-Fourth Edition14 and a neurocognitive battery consisting of the Advanced Test of Attention, the ChildrenΓÇÖs Color Trails Test (CCTT), the Stroop ColorΓÇôWord Test, and the Rey-Kim Memory Test for Children were administered. Genomic DNA was extracted from whole blood. The genotyping of both subsets was performed according to the standard Affymetrix protocol at DNA Link. The quality control and imputation procedures were performed. We obtained summary statistic GWAS data from the International Genomics of Alzheimer's Project (IGAP) Study. The PRS derived based on the IGAP-stage 1 was tested for association with the cognitive performances. The best fitting model was chosen based on the r2 value. Permutation was applied and empirical p-value (pemp) was derived.
Results: The Working Memory Index was explained by AD polygenic risk in healthy controls by 39.3 percent. It remained significant after permutation tests (R2 = 39.3%, Pemp = 0.007). The visual (R2= 6.4%, Pemp=0.040) and auditory (R2=17.2%, Pemp=0.019) Commission Errors in visual CPT and the visual response time variability (R2=14.5%, Pemp=0.024) were significantly explained by AD polygenic risk in the control group, but not in ADHD. The AD polygenic risk score explained 25.6% of the variance of the auditory omission errors in the ADHD group (R2=25.6%, Pemp=0.031), but not in the control group. The Copy score in the K-CFT was significantly affected by AD polygenic risk in ADHD (R2=31.2%, Pemp=0.028). Difference inference index in the CCTT was predicted significantly in the healthy controls, but not in ADHD (R2=11.1%, Pemp=0.044).
Conclusions: Attention is predicted by AD's polygenic risk in healthy controls more than children with ADHD

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Anadolu Psikiyatr Derg. 2019;20:539-47.

ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH ADHD BY COMPARISON WITH TYPE 1 DIABETES AND HEALTHY CONTROL GROUPS.

Yurteri N, Pekcanlar AA, Elldokuz H.

Objective: The purpose of this study is to compare health related quality of life of children and adolescents with attention deficit hyperactivity disorder (ADHD) both with health related quality of life of type 1 diabetes mellitus (T1DM) and healthy control groups.
Methods: Sixty ADHD newly diagnosed cases with no treatment, age and gender matched two control groups; 60 T1DM and 60 healthy control groups aged between 8 and 16 years were enrolled in this study. The diagnostic assessments and exclusion criteria of psychiatric disorders of all subjects were made according to the DSM-IV criteria and the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and the Lifetime (K-SADS PL). Sociodemographic Form, Pediatric Quality of Life Scale for Children (PedsQL 4.0 TM) were applied to all of participants and their parents. DSM-IV based Turgay ADHD and Distruptive Behavior Disorders Screening Scale, ADHD Rating Scale-IV and Clinical Global Impression Scale were additionally administered to ADHD group. HbA1c levels were used in terms of T1DM disease severity.
Results: Children and adolescents diagnosed ADHD reported lower self-concept in emotional functioning and psychosocial health summary scores than children and adolescents with T1DM. Compared with healthy controls, children and adolescents diagnosed ADHD reported lower self-concept in all subscales and total scores of PedsQL except physical health summary. Parent of ADHD children reported lower concept in all scores of quality of life than parents of healthy controls.
Conclusions: Life quality in terms of psychosocial health were found to be impaired in newly diagnosed ADHD subjects more than T1DM and healthy controls. Evaluation of quality of life during diagnosis and treatment stages of ADHD may help to identify and manage the overall impact of the disorder

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Anadolu Psikiyatr Derg. 2019;20:442-48.

AN EVALUATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SPECIFIC LEARNING DISORDER IN CHILDREN BORN TO DIABETIC GRAVIDAS: A CASE CONTROL STUDY.

Akaltun, et al.

Objective: Children born after risky pregnancies are known to have an increased disposition to neurodevelopmental disorders. The purpose of our study was to investigate the relationship between diabetic pregnancy and attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD).

Methods: One hundred thirty-seven children of mothers with diabetic pregnancies and 128 children of mothers without a history of diabetic pregnancy were enrolled. Forty-nine of the case group had a history of insulin-dependent diabetes mellitus (IDDM) and 88 of gestational diabetes mellitus (GDM). All participants were evaluated using The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (6-18) (K-SADS PL), the Wechsler Intelligence Scale for Children-Revised (WISC-R), and the SLD Battery. The results were then subjected to statistical analysis.

Results: A statistically significant difference was determined between the case and control groups in terms of levels of diagnosis of ADHD and SLD. Significant differences were determined between verbal/performance/total IQ scores when IDDM and GDM were compared with the control group. When the IDDM and GDM subgroups were compared among themselves, no significant difference was determined between verbal/performance/total IQ scores. Significant variation was observed between the IDDM and GDM groups in terms of ADHD and SLD diagnoses. IQ scores decreased as fasting blood sugar increased in all parameters.

Conclusion: Significantly, more diagnoses of ADHD and SLD were observed in children born to diabetic mothers compared to those of non-diabetic mothers. Further, wide-ranging studies on the subject of the effect of diabetic pregnancy and blood sugar control on infant neurodevelopmental disorders are now needed. (Anatolian Journal of Psychiatry 2019; 20(4):442-448)

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Ann Med Psychol (Paris). 2019 Oct;177:758-64.

NEAR (NEUROPSYCHOLOGICAL EDUCATIONAL APPROACH TO COGNITIVE REMEDIATION) COGNITIVE REMEDIATION PROGRAM IN ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND/OR AUTISM SPECTRUM DISORDER.

Renou S, Doyen C.

Cognitive Remediation is a therapeutic approach based on the notion of brain plasticity. It aims to improve certain cognitive function deficits through the repetition of specific exercises and to promote the metacognitive dimension (the awareness and reflection of an individual on his cognitions, his behaviors and the strategies he uses to solve a problem). Several programs have already been validated in adult patients with schizophrenia and have shown improvements in cognitive performance and functioning. Some of the programs were later applied to other pathologies such as anorexia nervosa or autism spectrum disorders (ASD). Remedial programs have also been developed for children and adolescents because the early symptomatic expression of certain disorders such as Attention Deficit Hyperactivity Disorder (ADHD) or ASD makes one suspect a neurodevelopmental origin and all have in common an alteration of the executive functions. There are programs of cognitive stimulation or cognitive training, particularly in the context of ADHD. Although the results do show benefits in terms of visual and verbal working memory, the effects of cognitive training seem to be difficult to generalize to other everyday learning and have only limited effects on the symptoms. The objective of this study is to assess the feasibility and acceptability of the Neuropsychological Educational Approach to Cognitive Remediation for Adolescents (NEAR)

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Appl Neuropsychol Child. 2019 Oct;8:347-54.

OXIDATIVE STRESS CONTRIBUTION TO ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH EPILEPSY.

Elhady M, Youness ER, Mostafa RSI, et al.

Children with epilepsy have a high incidence of attention deficit hyperactivity disorder (ADHD). Oxidation stress and disturbed neurotransmitters are suggested mechanisms; however, their role is not fully explored. This study evaluates the association between circulating malondialdehyde as an oxidation stress marker, apelin neuropeptide, and ADHD in children with epilepsy. Fifty children with epilepsy of unknown etiology, of which 25 have ADHD, as well as 35 healthy children were included. Serum levels of malondialdehyde and apelin were estimated. We investigated the association between seizure severity, response to medications, malondialdehyde, apelin levels, and ADHD in children with epilepsy. Serum malondialdehyde and apelin levels were higher in children with epilepsy, especially those with ADHD. Malondialdehyde and apelin levels have significant positive correlation with the Chalfont Seizure Severity Score. Regression analysis showed that elevated malondialdehyde is an independent risk factor for ADHD in children with epilepsy (OR: 1.401, 95%CI: 1.056–1.859, p = 0.02). No significant association was found between malondialdehyde and apelin levels and the type of epilepsy or ADHD. Longer duration of epilepsy, increased seizure severity, and uncontrolled seizures are associated with increased oxidation stress, which further increased susceptibility for ADHD. In spite of elevated apelin in children with ADHD, the elevation did not increase the risk of ADHD in children with epilepsy

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Appl Neuropsychol Child. 2019 Oct;8:307-18.

FLUID REASONING AND READING DIFFICULTIES AMONG CHILDREN WITH ADHD.

Mano QR, Jastrowski Mano KE, Guerin JM, et al.

Background: Children with attention-deficit/hyperactivity disorder (ADHD) commonly experience difficulties in reading and in fluid reasoning (Gf). According to Cattell's Investment Theory (1987), Gf is a causal factor in the development of crystallized knowledge (Gc) and academic skills; therefore, the co-occurrence of reading and Gf difficulties within ADHD may not be coincidental.

Methods: In the present study with children with both ADHD and reading difficulties (n = 187; 61% male; Mage = 9.2), we utilized mediation analyses to test direct and indirect (through Gc, phonemic awareness, and rapid automatized naming [RAN]) effects of Gf on four basic reading skills: untimed word recognition, untimed phonemic decoding, word reading efficiency, and phonemic decoding efficiency.

Results: The direct effect of Gf on all reading skills was nonsignificant; however, significant indirect effects were observed. Specifically, Gf exerted an effect indirectly onto all reading skills through a serial and joint mechanism comprised of Gc and phonemic awareness (i.e., Gf ? Gc ? phonemic awareness ? reading achievement). Gf also exerted an effect indirectly onto untimed word recognition and phonemic decoding through phonemic awareness (i.e., Gf ? phonemic awareness ? untimed word recognition/untimed phonemic decoding).

Conclusion: Results build upon Cattell's Investment Theory by linking Gf with reading difficulties among children with ADHD, suggesting that such difficulties may arise from weaknesses in Gf and insufficient investment of Gf into reading through Gc and phonemic awareness

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Autism Res. 2019.

LANGUAGE DEFICITS IN SPECIFIC LANGUAGE IMPAIRMENT, ATTENTION DEFICIT/HYPERACTIVITY DISORDER, AND AUTISM SPECTRUM DISORDER: AN ANALYSIS OF POLYGENIC RISK.

Nudel R, Christiani CAJ, Ohland J, et al.

Language is one of the cognitive domains often impaired across many neurodevelopmental disorders. While for some disorders the linguistic deficit is the primary impairment (e.g., specific language impairment, SLI), for others it may accompany broader behavioral problems (e.g., autism). The precise nature of this phenotypic overlap has been the subject of debate. Moreover, several studies have found genetic overlaps across neurodevelopmental disorders. This raises the question of whether these genetic overlaps may

correlate with phenotypic overlaps and, if so, in what manner. Here, we apply a genome-wide approach to the study of the linguistic deficit in SLI, autism spectrum disorder (ASD), and attention deficit/hyperactivity disorder (ADHD). Using a discovery genome-wide association study of SLI, we generate polygenic risk scores (PRS) in an independent sample which includes children with language impairment, SLI, ASD or ADHD and age-matched controls and perform regression analyses across groups. The SLI-trained PRS significantly predicted risk in the SLI caseΓÇôcontrol group (adjusted R2 = 6.24%; P = 0.024) but not in the ASD or ADHD case-control groups (adjusted R2 = 0.0004%, 0.01%; P = 0.984, 0.889, respectively) nor for height, used as a negative control (R2 = 0.2%; P = 0.452). Additionally, there was a significant difference in the normalized PRS between children with SLI and children with ASD (common language effect size = 0.66; P = 0.044). Our study suggests no additive common-variant genetic overlap between SLI and ASD and ADHD. This is discussed in the context of phenotypic studies of SLI and related disorders. Autism Res 2019. -® 2019 The Authors. Autism Research published by International Society for Autism Research published by Wiley Periodicals, Inc. Lay Summary: Language deficits are characteristic of specific language impairment (SLI), but may also be found in other neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD). Many studies examined the overlaps and differences across the language deficits in these disorders, but few studies have examined the genetic aspect thereof. In this study, we use a genome-wide approach to evaluate whether common genetic variants increasing risk of SLI may also be associated with ASD and ADHD in the same manner. Our results suggest that this is not the case, and we discuss this finding in the context of theories concerning the etiologies of these disorders

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Autism Res. 2019.

AUTISM SPECTRUM DISORDER POLYGENIC SCORES ARE ASSOCIATED WITH EVERY DAY EXECUTIVE FUNCTION IN CHILDREN ADMITTED FOR CLINICAL ASSESSMENT.

Torske T, et al.

Autism spectrum disorder (ASD) and other neurodevelopmental disorders (NDs) are behaviorally defined disorders with overlapping clinical features that are often associated with higher-order cognitive dysfunction, particularly executive dysfunction. Our aim was to determine if the polygenic score (PGS) for ASD is associated with parent-reported executive dysfunction in everyday life using the Behavior Rating Inventory of Executive Function (BRIEF). Furthermore, we investigated if PGS for general intelligence (INT) and attention deficit/hyperactivity disorder (ADHD) also correlate with BRIEF. We included 176 children, adolescents and young adults aged 5ΓÇô22 years with full-scale intelligence quotient (IQ) above 70. All were admitted for clinical assessment of ASD symptoms and 68% obtained an ASD diagnosis. We found a significant difference between low and high ASD PGS groups in the BRIEF behavior regulation index (BRI) (P = 0.015, Cohen's d = 0.69). A linear regression model accounting for age, sex, full-scale IQ, Social Responsiveness Scale (SRS) total score, ASD, ADHD and INT PGS groups as well as genetic principal components, significantly predicted the BRI score; F(11,130) = 8.142, P < 0.001, R2 = 0.41 (unadjusted). Only SRS total (P < 0.001), ASD PGS 0.1 group (P = 0.018), and sex (P = 0.022) made a significant contribution to the model. This suggests that the common ASD risk gene variants have a stronger association to behavioral regulation aspects of executive dysfunction than ADHD risk or INT variants in a clinical sample with ASD symptoms. Autism Res 2019. -® 2019 International Society for Autism Research, Wiley Periodicals, Inc. Lay Summary: People with autism spectrum disorder (ASD) often have difficulties with higher-order cognitive processes that regulate thoughts and actions during goal-directed behavior, also known as executive function (EF). We studied the association between genetics related to ASD and EF and found a relation between high polygenic score (PGS) for ASD and difficulties with behavior regulation aspects of EF in children and adolescents under assessment for ASD. Furthermore, high PGS for general intelligence was related to social problems

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Biol Psychiatry. 2019;85:S235.

CHILDREN WITH ADHD HAVE DEFICIT IN REPRODUCING THE REY-OSTERRIETH COMPLEX FIGURE IN DELAYED RECALL CONDITION.

Kiselev S.

Background: It was shown that children with ADHD have cognitive deficit, particularly deficit in working memory (Martinussen et al., 2012). In our previous research we have revealed that ADHD children have deficit in visual and verbal memory in delayed recall condition in comparison to immediate condition (Kiselev & Lvova, 2016; Kiselev, 2018). The goal of this research was to examine the hypothesis that children with ADHD have deficit in reproducing the Rey-Osterrieth Complex Figure in delayed recall condition.
Methods: The experimental group included 16 children with ADHD at the age of 7-8 years. The control group included 16 typically developing children. The children from groups were matched for IQ, gender and age. Children from both groups were assessed with Rey Osterrieth complex figure test (ROCF). This test is designed to assess reproducing the complex figure in immediate and delayed recall conditions. ANOVA with repeated measures was used to reveal group differences in reproducing the figure in two conditions.
Results: We have not revealed significant differences between children from experimental and control group in reproducing the figure in immediate condition. However, the interaction of condition type and group was significant [F(1,30)=10,58; p=0,003)]. Children with ADHD had deficit in the accurate reproduction and placement of specific design elements of Rey-Osterieth Complex Figure in Delayed Recall condition.
Conclusions: In view of our previously received results in children with ADHD, we can propose that deficit in memory in delayed recall condition can be one of the key symptoms in this disorder.
Supported By: Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.
Keywords: ADHD, The Rey-Osterrieth Complex Figure, Memory Deficit

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Biol Psychiatry. 2019;85:S153.

BODY-ORIENTED THERAPY HAS POSITIVE EFFECT ON EXECUTIVE ABILITIES IN PRESCHOOL CHILDREN WITH ADHD.

Kiselev S.

Background: It is known that children with ADHD are deficit in executive abilities. We have revealed that body-oriented therapy can impact executive abilities in 6-7 years age children with ADHD (Kiselev & Parshakova, 2018). The goal of this study was to reveal the effect of body-oriented therapy on executive abilities in 4-5 years of age children with ADHD. We compared the efficacy of two methods of treatment (body-oriented therapy for children vs. conventional motor exercises) in a randomized controlled pilot study.
Methods: 16 children with ADHD at the age of 4-5 years were included and randomly assigned to treatment conditions according to a 2+ù2 cross-over design. The body-oriented therapy included the exercises from yoga and breathing techniques. To assess the executive functions and attention in children we used 3 subtests from NEPSY (Auditory Attention and Response Set, Visual Attention, Statue). Effects of treatment were analyzed by means of an ANOVA for repeated measurements.
Results: The ANOVA has revealed (p<.05) that for all used subtests (Auditory Attention and Response Set, Visual Attention, Statue) the body-oriented therapy was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.48-0.89).
Conclusions: The findings from this pilot study suggest that body-oriented therapy has positive effect on executive abilities in preschool children with ADHD. It influences predominantly the selective and sustained attention, inhibition, monitoring, and self-regulation. However, it is necessary to do further research into the impact of body-oriented therapies on the prevention and treatment of ADHD in children.
Supported By: Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.
Keywords: ADHD, Body-Oriented Therapy, Executive Abilities

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Biol Psychiatry. 2019;85:S145-S146.

WHITE MATTER TRACT SIGNATURES OF EMOTIONAL LABILITY AND ADHD TRAITS IN YOUNG CHILDREN.

Rohr C, Dimond D, Ip A, et al.

Background: 40-50% of children with ADHD present with significant levels of emotional lability, which is associated with poorer outcomes. Characterizing how emotional lability interacts with the diagnostic dimensions of inattention and hyperactivity is therefore critical for effective treatment. As a starting point, we here interrogate the brain basis of this relationship in two white matter tracts crucial for attention and emotion processing: the superior longitudinal fasciculus (SLF) and the uncinate fasciculus (UF).
Methods: Diffusion-weighted images (b-value=0/2000, 45 directions) were acquired in 58 typically developing children aged 4-7 years and preprocessed using motion and signal-dropout correction (FSL/MRTrix). Emotional lability was assessed with the Emotion Regulation Checklist; inattention and hyperactivity were assessed with the SNAP-IV Parent Questionnaire. In a voxel-based analysis, we investigated linear associations between the interaction of emotional lability and ADHD traits, and fractional anisotropy (FA) and mean diffusivity (MD) in the SLF and UF (controlling for main effects, handedness and motion).
Results: Emotional lability, inattention and hyperactivity scores all correlated (r s>.63). The interaction between hyperactivity and emotional lability negatively correlated with FA in bilateral UF, and negatively with MD in left anterior SLF. MD in left anterior SLF also negatively correlated with the interaction between inattention and hyperactivity, and with the interaction between inattention and emotional lability at trend-level.
Conclusions: Our findings suggest that UF and SLF diffusion properties underlie crucial links between emotional lability and ADHD traits in early childhood and demonstrate the utility of behavioral scores to elucidate the brain basis of potential vulnerabilities in young children.
Supported By: Alberta Innovates; NSERC; NSERC CREATE I3T (Canada); CIHR (Canada)
Keywords: Emotion Regulation, ADHD, White Matter, Resilience And Vulnerability, Traits

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Biol Psychiatry. 2019;85:S39.

TIRED AND IMPULSIVE: PRELIMINARY EVIDENCE OF THE VULNERABILITY OF YOUTH WITH ADHD TO THE NEURAL CONSEQUENCES OF INSUFFICIENT SLEEP.

Saletin J, De Queiroz CG, Haddad J, et al.

Background: Attention-deficit-hyperactivity-disorder (ADHD) is a common disorder of childhood and associated with sleep dysregulation. How ADHD and sleep interact in moderating brain function is unknown. Here we present preliminary evidence highlighting the neural vulnerability of those with ADHD to sleep-loss.
Methods: We first conducted an ALE meta-analysis of 134 fMRI articles, investigating whether ADHD and sleep-loss share common neural effects. We then quantified sleep in ADHD using 12 weeks of actigraphy in 13 children (8F; 12.6-¦0.7y). We finally examined how ADHD symptoms moderate the effects of acute sleep-loss on brain function (go/no-go inhibition task; resting-state) in 12 children (6F; 11.5-¦1.1y). We assessed ADHD severity in all children using the Conners-3.
Results: Our meta-analysis revealed ADHD and sleep-loss share reductions in activation within inhibitory-control networks: dorsal anterior cingulate (dACC) and middle/inferior frontal (M/IFG) cortices (p<.005; k=20mm). In our experimental work, hyperactivity-symptoms were associated with irregular sleep patterns (b=-0.0025; p=.032). Moreover, following acute sleep restriction, relative to rested wakefulness, those with higher hyperactivity experienced greater reductions in inhibition-related dACC and M/IFG activations (p<.005; k=20mm), together with greater reductions in resting default-mode connectivity (r=-.50; p=.049 [one-tailed]).
Conclusions: These results support a new appreciation for sleep in ADHD. First, ADHD and sleep-loss share common reductions in inhibition-related brain activation. Second, ADHD-symptoms index greater dysregulation of sleep. Finally, more severe symptoms were associated with greater neural impairments as a consequence of sleep-loss. In sum, ADHD is associated with vulnerability to the neural consequences of short sleep. Mitigating insufficient sleep may improve clinical status among youth with ADHD.

Supported By: K01MH109854 (to JMS); Rhode Island Foundation Medical Research Grant (to JMS).
Keywords: ADHD, Sleep Deprivation, Child and Adolescent Psychiatry, Brain Imaging, fMRI, Impulsivity

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Biol Psychiatry. 2019;85:S234-S235.

TASK-EVOKED EFFECTIVE CONNECTIVITY IN SALIENCE AND CENTRAL EXECUTIVE NETWORKS PREDICTS COGNITIVE CONTROL ABILITY AND INATTENTION SYMPTOMS IN CHILDREN WITH ADHD.

Cai W, Griffiths K, Korgaonkar M, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is associated with pervasive impairments in attention and cognitive control. Although these impairments have been extensively investigating with resting-state fMRI little is known about task-evoked functional brain circuits and their relation to inattention symptoms and cognitive control deficits in children with ADHD.
Methods: We used a task fMRI dataset with 27 children with ADHD and 30 matched typically-developing (TD) children, and dimensional analyses, to investigate the relation between inattention symptoms, Go/NoGo task performance, and task-evoked functional brain circuits. We examined effective connectivity using psychophysiological interactions in two core cognitive control systems: (i) cingulo-opercular salience (SN) and (ii) fronto-parietal central executive (CEN) networks.
Results: We found that multivariate patterns of effective connectivity between brain regions in SN and CEN predicted children's performance on the Go/NoGo task. Specifically, the strength of task-evoked effective connectivity between right dorsal anterior cingulate cortex (rdACC) and right ventrolateral prefrontal cortex (rVLPFC) was significantly and positively correlated with NoGo accuracy. Furthermore, the strength of task-evoked connectivity in rdACC-rVLPFC was significantly and negatively correlated with the severity of inattention symptoms in children with ADHD. Brain-behavior relationships were robust against potential age, gender and head motion confounds.
Conclusions: Our findings highlight aberrations of task-evoked connectivity in SN and CEN in children with ADHD, its relation to inattention symptoms and cognitive control deficits, and suggest potential biomarkers for predicting clinical symptoms and treatment outcomes in childhood ADHD.
Supported By: National Institutes of Health grants EB022907, NS086085 and MH105625, and Children Health Research Institute grant.
Keywords: Human,fMRI, iSPOT-A, Response Inhibition, Psychophysiological Interaction Analysis

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Biol Psychiatry. 2019;85:S194-S195.

DISTINCT PATTERNS OF SCHIZOPHRENIA, ADHD, AND COGNITION POLYGENIC SCORES IN SCHIZOPHRENIA SUBGROUPS DEFINED BY COGNITIVE DEVELOPMENT TRAJECTORIES.

Dickinson D, Gregory M, Berman K.

Background: Different patterns of premorbid vs. current IQ in schizophrenia suggest distinct trajectories of cognitive development through childhood and adolescence, including early life cognitive impairment in some. Different cognitive patterns may reflect different patterns of underlying genetics associated with schizophrenia, cognition, ADHD, and related phenotypes. We tested whether IQ-defined cognitive trajectory subgroups also showed distinct polygenic score (PGS) profiles across schizophrenia, ADHD and cognition PGS.
Methods: Schizophrenia cases and controls provided blood and completed an assessment protocol. Cognitive trajectory subgroups were derived from premorbid (WRAT) and current (WAIS) IQ. In 470 SZ cases and 844 controls (all Caucasian) ΓÇô separately for schizophrenia, ADHD and cognition ΓÇô PGS were calculated at ten different p-value thresholds, then concentrated by deriving the first principal component (PC1) for each PGS set. We analyzed the resulting PC1 scores across groups using GLM, controlling for age, sex, and population stratification.
Results: Three premorbid vs. current IQ subgroups, Cognitively Stable, Pre-Adolescent Impairment, and Adolescent Decline, differed on demographic, cognitive, and clinical variables. The schizophrenia subgroups had elevated schizophrenia PGS relative to controls (pΓÇÖs<1x10E-10), with the Adolescent Decline

subgroup most elevated. The Pre-Adolescent Impairment and Adolescent Decline subgroups had lower cognitive PGS than the Cognitively Stable and control groups (pΓÇÖs<.002). The Pre-Adolescent Impairment subgroup, alone, showed an elevated ADHD PC1 relative to the other groups (p s<.003). The PC1s accounted for between 2% and 3% of variance in the SZ subgrouping scheme.
Conclusions: Analyses revealed an interesting convergence between subgrouping based on IQ measures and stratification based on schizophrenia, ADHD and cognitive genetics.
Supported By: NIMH Division of Intramural Research
Keywords: Schizophrenia, IQ, Polygenic Scores, ADHD, Cognition

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Biol Psychiatry. 2019;85:S33.
SUBCORTICAL BRAIN VOLUME, REGIONAL CORTICAL THICKNESS AND SURFACE AREA ALTERATIONS ACROSS ADHD, ASD, AND OCD.
Boedhoe P, Van RD, Hoogman M, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common childhood-onset neurodevelopmental disorders. No structural imaging study to date has compared these disorders. The ENIGMA consortium is ideally positioned to investigate structural brain abnormalities across these disorders on a large scale.
Methods: Structural T1-weighted MRI scans of controls (n=5.827) and individuals with ADHD (n=2.271), ASD (n=1.777), and OCD (n=2.323) from 151 samples worldwide were analyzed with FreeSurfer using standardized processing protocols. We examined subcortical volume, regional cortical thickness and surface area differences within a mega-analytical framework, pooling extracted measures from each site. Analyses were performed separately for pediatric, adolescent, and adult subgroups using linear mixed-effects models controlling for age, sex, and site (and ICV for subcortical and surface area measures). FDR was used for multiple testing correction.
Results: Pediatric OCD patients had larger hippocampal volumes compared to ADHD patients. Pediatric and adolescent ADHD patients also showed smaller ICV than controls, OCD and ASD patients. No subcortical differences were observed across disorders in adulthood. On the cortical level, adult ASD patients showed thicker cortices in frontal areas compared to controls, OCD and ADHD patients, while no differences were observed in surface area between the disorders across the lifespan. Overall, subcortical and cortical effects were subtle (Cohenɔs d -0.22-0.30).
Conclusions: These findings suggest that subcortical differences between ADHD ASD and OCD seem most distinct in childhood while differences seem to diminish in adolescence and adulthood. Cortical differences across the disorders seem to be most pronounced in adulthood.
Supported By: NIH: BD2k (Big Data), U54 EB020403-02 (PI: Thompson) Neuroscience Campus Amsterdam (NCA), IPB-grant (PI s: Schmaal / van den Heuvel)
Keywords: Structural Brain Imaging, OCD, ADHD, ASD, Neurodevelopmental Disorders

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Biol Psychiatry. 2019;85:S6.
PREDICTING COMORBID DISORDERS IN ADHD USING MACHINE LEARNING.
Faraone S, James YZ, Chen Q, et al.
Background: Substantial research shows that ADHD is frequently comorbid with other psychiatric disorders and with some medical outcomes such as obesity and asthma. We also know from genome-wide association studies that common genetic variants account for some of this comorbidity. Because ADHD is typically an early-onset disorder, ADHD youth are an ideal group for applying prediction models to predict comorbidity from clinical and biological data.
Methods: We will apply machine learning models to the prediction of comorbid disorders (substance abuse, depression, anxiety & obesity) in a sample of 34,009 ADHD patients from the Swedish medical registries. Predictors are social and environmental exposures (e.g., SES, pregnancy and delivery complications), the presence of other diagnoses and family history of diagnoses known to be comorbid with ADHD.

Results: Applying a random forests machine learning model to the Swedish data achieved an area under the curve (AUC) statistic of 0.74 (95%CI 0.72-0.76) for the prediction of SUD in an independent validation sample. The strongest predictors of SUD in the random forests model were education scores achieved by the child, social class of the parents, crimes committed by the parents, severity of ADHD and maternal pregnancy complications. We are currently in the process of analyzing the other comorbid disorders in Sweden.
Conclusions: Our results indicate that by combining clinical features, environmental exposures and family history variables, we are able to achieve a level of predictive accuracy that could be useful to identify a subset of patients for clinical monitoring or enrollment in high-risk research studies.
Supported By: This project has received funding from the European Union's Horizon 2020 research and innovation programme grant agreement No 667302
Keywords: ADHD, Machine Learning, Substance Use Disorders, Psychiatric Comorbidities, Prospective Prediction

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Biol Psychiatry. 2019;85:S6-S7.

BRAIN IMAGING OF ADHD ACROSS THE LIFESPAN RESULTS OF THE LARGEST STUDY WORLDWIDE FROM THE ENIGMA ADHD WORKING GROUP.

Hoogman M, Muetzel R, ENIGMA-ADHD c, et al.

Background: Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD. However, these studies are often underpowered and heterogeneous in their methods. Our aim is to map the characteristics of the brains of people with ADHD across the life span.
Methods: The ENIGMA-ADHD collaboration is the largest collaboration of neural substrates of ADHD, and consist of 37 cohorts, with more than 4000 subjects of all ages. Both cortical and subcortical brain measures are studied for children, adolescents and adults separately. Knowing that ADHD is the extreme of a continuum, the association between cortical measures and ADHD symptom scores of the CBCL in the general population of children aged 9 and 10 years old (Generation R study, n=2900), are also studied. Finally, also a family-based design is used to unravel more characteristics of the ADHD brain.
Results: Differences between cases and controls were only found in the group of children both for subcortical as well as cortical brain measures. Surprisingly, there was an overlap between the affected cortical measures in the case/control study, the results of the population-based study and those of the family-based study.
Conclusions: Subtle differences in the subcortex and cortex were found between children with ADHD and healthy controls, not in the other age groups. The overlap between the affected brain regions in the clinical, population and family-based studies, shows that, besides from a genetic and behavioral perspective, now also from a neuroimaging perspective there is evidence for the ADHD continuum.
Supported By: National Institutes of Health (NIH) Consortium grant U54 EB020403
Keywords: ADHD, Neuroimaging, Cortex, Mega Analysis

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Biol Psychiatry. 2019.

POLYGENIC RISK SCORES FOR DEVELOPMENTAL DISORDERS, NEUROMOTOR FUNCTIONING DURING INFANCY, AND AUTISTIC TRAITS IN CHILDHOOD.

Serdarevic F, Tiemeier H, Jansen PR, et al.

Background: Impaired neuromotor development is often one of the earliest observations in children with autism spectrum disorder (ASD). We investigated whether a genetic predisposition to developmental disorders was associated with nonoptimal neuromotor development during infancy and examined the genetic correlation between nonoptimal neuromotor development and autistic traits in the general population.
Methods: In a population-based cohort in The Netherlands (2002-2006), we calculated polygenic risk scores (PRSs) for ASD and attention-deficit/hyperactivity disorder (ADHD) using genome-wide association study summary statistics. In 1921 children with genetic data, parents rated autistic traits at 6 years of age. Among them, 1174 children (61.1%) underwent neuromotor examinations (tone, responses, senses, and other

observations) during infancy (9ΓÇô20 weeks of age). We used linear regressions to examine associations of PRSs with neuromotor scores and autistic traits. We performed a bivariate genome-based restricted maximum likelihood analysis to explore whether genetic susceptibility underlies the association between neuromotor development and autistic traits.
Results: Higher PRSs for ASD were associated with less optimal overall infant neuromotor development, in particular low muscle tone. Higher PRSs for ADHD were associated with less optimal senses. PRSs for ASD and those for ADHD both were associated with autistic traits. The single nucleotide polymorphismΓÇôbased heritability of overall motor development was 20% (SE = .21) and of autistic traits was 68% (SE = .26). The genetic correlation between overall motor development and autistic traits was .35 (SE = .21, p < .001).
Conclusions: We found that genetic liabilities for ASD and ADHD covary with neuromotor development during infancy. Shared genetic liability might partly explain the association between nonoptimal neuromotor development during infancy and autistic traits in childhood

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Biol Psychiatry. 2019;85:S20.
A POLYGENIC SCORE FOR COURSE OF ILLNESS IN ADHD.
Sprooten E, Soheili-Nezhad S, Mota NR, et al.
Background: Twin studies indicate that genetic factors contributing to ADHD onset are partly distinct from those underlying symptom persistence into adulthood. This genetic heterogeneity, where genetic effects on a diagnosis change over time, is poorly characterized so far. To address this, we derived a new polygenic score that captures genetic variation underlying course of illness in ADHD.
Methods: Two polygenic scores were calculated for each individual in a longitudinal cohort of patients with ADHD (NeuroIMAGE). First, a standard polygenic onset score was based on the children-only ADHD case-control GWAS of the psychiatric genomics consortium (excluding NeuroIMAGE). Second, a polygenic persistence score was derived by subtracting the children-only effect-sizes from those of a case-control GWAS of adults with persistent ADHD conducted by the IMpACT Consortium. Generalized mixed linear models were run with ADHD remission versus persistence as outcome, and both polygenic scores as predictors, adjusting for family relationships.
Results: The newly derived persistence score significantly (P=0.016) predicted NeuroImage patients who remitted at a later timepoint (N=75) from those who did not (N=297), independent of the polygenic onset score (P=0.048). The persistence score explained 1.7% of variance in remission-persistence likelihood among patients. Covarying for sex and age at last assessment did not change the results.
Conclusions: Polygenic effects on ADHD persistence over time can be isolated from genetic effects underlying ADHD onset by contrasting case-control GWAS of different age-groups. The derived polygenic persistence score can be used for stratification and combined with other clinical and biological measurements to give new insights in the processes behind course of illness in ADHD.
Supported By: Hypatia Fellowship
Keywords: Course of Illness, Polygenic Risk, ADHD, Remission, Adult ADHD

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Biol Psychiatry. 2019;85:S234.
AN IMAGE-BASED META-ANALYSIS OF SUCCESSFUL AND FAILED STOPPING IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER USING STATISTICAL PARAMETRIC MAPS.
Norman L, Taylor S, Morrison C, et al.
Background: Patients with Attention Deficit/Hyperactivity Disorder (ADHD) often demonstrate abnormal brain functioning during the stop signal task, although previous work has typically used small samples thereby limiting conclusions.
Methods: A preliminary image-based meta-analysis (n=834) comparing patients with ADHD (n=379; age range= 8-50 years, 269 males) and controls (n=455; age range=8-50 years, 273 males) on the stop signal task was performed using Seed-based d Mapping. The protocol was registered with Prospero (CRD42018095365).

Results: Groups did not differ according to mean stop-signal reaction time (d=0.24 p=.11). During successful stopping, patients with ADHD showed underactivation in left orbitofrontal cortex (OFC) and left amygdala as well as in bilateral thalamus and inferior frontal gyrus. Reduced deactivation was observed in precuneus/posterior cingulate cortex (PCC). During failed stopping, patients showed underactivation in dorsomedial prefrontal cortex and left IFG/OFC/anterior insula as well as reduced deactivation in precuneus/PCC and bilateral putamen (SDM-Z >2, p<.005).
Conclusions: A lack of performance differences may be due to pre-scan practice sessions and the removal from some studies of poorly performing subjects. During successful and failed stopping, patients with ADHD showed reduced activation in predominantly left-sided salience network in conjunction with reduced deactivation in bilateral basal ganglia and posterior default mode network. Underactivation in the left amygdala aligns with recent mega-analysis findings of relatively reduced amygdala gray matter volume in ADHD, and suggests that abnormalities in this region may underlie deficits in task-related salience. Overall, findings suggest a deficit in performing dynamic adjustments between DMN and task positive networks in ADHD.
Supported By: NIMH ROI1
Keywords: ADHD, Attention Deficit Hyperactivity Disorder, Adolescence, Meta-Analysis, Brain Imaging

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Biol Psychiatry. 2019;85:S355.
INVESTIGATING THE GENETIC ARCHITECTURE OF PSYCHIATRIC DISORDERS AND THEIR MEDICAL COMORBIDITY.
Merikangas A, Kember R, Ruparel K, et al.
Background: Previous work has demonstrated pervasive comorbidity between medical and psychiatric disorders in both adults and youth. In this study, we examine these patterns of comorbidity across development and evaluate the extent to which they may result from common underlying genetic etiologic factors.
Methods: The sample includes 5175 European-ancestry youth (ages 8 to 21 years; 51.7% female) from the University of Pennsylvania Neurodevelopmental Cohort Study sampled from pediatric clinics at the Children's Hospital of Philadelphia. Medical conditions were derived from interview data and medical record information. Psychiatric disorders were assessed with a structured diagnostic interview. Polygenic Risk Scores (PRS) were calculated with the PRSice2 software package using publicly available GWAS summary statistics. Sex and age-adjusted logistic regression models were used to evaluate the associations between medical and psychiatric disorders, and for PRS predicting medical and psychiatric disorders.
Results: Specific associations emerged between ear, nose, and throat disorders with psychosis symptoms; central nervous system disorders with ADHD, behavior disorders, and general psychopathology; whereas developmental disorders were associated with a broad range of psychiatric disorders. The overall medical disorder severity rating was associated with anxiety, ADHD, behavior disorders, mood disorders, and overall psychopathology. There was no evidence for associations between psychiatric PRS and comorbid medical disorders.
Conclusions: These findings a demonstrate strong overlap between medical and psychiatric conditions in youth, but common psychiatric genetic risk factors do not appear to underlie this comorbidity early in development. Other mechanisms (including environmental factors) that may influence these associations are examined.
Supported By: NIH NCATS UL1TR001878
Keywords: Polygenic Risk Score, Comorbidity, Developmental Psychopathology, Medical Co-Morbidities

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Biol Psychiatry. 2019;85:S233-S234.
NEUROMARKERS OF BEHAVIOUR REGULATION IN 7-17 YEAR OLD CHILDREN WITH ADHD, DCD AND ADHD-DCD.
Rohr C, Bray S, Dewey D.
Background: Children with ADHD show elevated scores in behaviour regulation, which translates to daily-life challenges. ADHD often co-occurs with Developmental Coordination Disorder (DCD); however,

behaviour regulation in DCD is not well understood. Here, we investigate differences in amygdala and dorsolateral prefrontal cortex (dlPFC) functional connectivity (FC) related to behaviour regulation, between children with ADHD, DCD, combined ADHD-DCD and typically developing (TD) children.
Methods: Resting-state fMRI data from 104 children (31 TD, 31 ADHD, 16 DCD, 26 ADHD-DCD; aged 7-17 years) were preprocessed and cleaned with ICA-AROMA. Emotional control, inhibition and shifting were assessed as aspects of behaviour regulation using the Behavior Rating Inventory of Executive Function. Amygdala and dlPFC FC maps were computed for each participant, and tested for group differences that related to aspects of behaviour regulation, at $p<0.01$ cluster correction.
Results: Children with DCD scored lowest in all domains, followed by TD children, and children with ADHD and ADHD-DCD, with a significant difference between DCD/TD and ADHD/ADHD-DCD. FC findings revealed several differences between groups. For example, stronger amygdala-ventromedial FC associated with emotional control was found in TD/DCD compared to ADHD; stronger amygdala-caudate FC associated with shifting was found in DCD vs. all other groups; and stronger dlPFC-vmPFC FC related to inhibition was found in ADHD vs. TD.
Conclusions: Our findings suggest that behaviour regulation problems in ADHD-DCD are likely attributable to ADHD, and that an intricate balance of FC strength in amygdala and prefrontal networks supports varying behaviour regulation in TD children, and children with DCD, ADHD and ADHD-DCD.
Supported By: Alberta Innovates; NSERC; NSERC CREATE I3T (Canada); CIHR (Canada)
Keywords: Emotion Regulation, ADHD, Inhibition, Set-Shifting, Self-Regulation

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Biopsychosoc Med. 2019 Oct;13.
THE EFFECTIVENESS OF INTERVENTION WITH BOARD GAMES: A SYSTEMATIC REVIEW.
Noda S, Shirotsuki K, Nakao M.
To examine the effectiveness of board games and programs that use board games, the present study conducted a systematic review using the PsycINFO and PubMed databases with the keywords 'board game' AND 'trial;' in total, 71 studies were identified. Of these 71 studies, 27 satisfied the inclusion criteria in terms of program content, intervention style, and pre–post comparisons and were subsequently reviewed. These 27 studies were divided into the following three categories regarding the effects of board games and programs that use board games: educational knowledge (11 articles), cognitive functions (11 articles), and other conditions (five articles). The effect sizes between pre- and post-tests or pre-tests and follow-up tests were 0.12–1.81 for educational knowledge, 0.04–2.60 and - 1.14 – - 0.02 for cognitive functions, 0.06–0.65 for physical activity, and - 0.87 – - 0.61 for symptoms of attention-deficit hyperactivity disorder (ADHD). The present findings showed that, as a tool, board games can be expected to improve the understanding of knowledge, enhance interpersonal interactions among participants, and increase the motivation of participants. However, because the number of published studies in this area remains limited, the possibility of using board games as treatment for clinical symptoms requires further discussion

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BMC Psychol. 2019 Jul;7:43.
GUIDELINE USE AMONG DIFFERENT HEALTHCARE PROFESSIONALS IN DIAGNOSING ATTENTION DEFICIT HYPERACTIVITY DISORDER IN DUTCH CHILDREN; WHO CARES?
Levelink B, Walraven L, Dompeling E, et al.
OBJECTIVE: Current data about Attention Deficit Hyperactivity Deficiency (ADHD) guideline use in the Netherlands are absent. This study analysed ADHD guideline use among different healthcare workers, and the use of key elements from these guidelines to diagnose ADHD.
METHOD: A survey assessing ADHD guideline use was distributed throughout the Netherlands to various health care professionals. Only professionals involved during the diagnostic process were included.
RESULTS: Response rate among GPs was low (111/1450), but high among other health care professionals (251/287). A total of 362 surveys were analysed, 186 responders (51%) were involved during the diagnostic process. Overall guideline use was 64.5%; the national multidisciplinary guideline or a guideline made by a

professional's own institution were most used. Psychiatrists, psychologists and paediatricians reported compliance with key elements of the guidelines such as gathering information from a third party (> 90%) and carrying out a developmental history (> 88%). Use of a standardized interview (< 52% often use) was low. Only paediatricians performed a physical examination regularly (88%).
CONCLUSION: Despite low general use of guidelines, psychiatrists, psychologists and paediatricians use similar key elements of ADHD guidelines. This study provides opportunities to improve care through increasing familiarity with ADHD guidelines and the use of standardized interviews

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Br J Nurs. 2019 Jun;28:678-80.
A NURSE'S INTRODUCTION TO ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Nicholson T.

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Brain Behav Immun. 2019;82:302-08.
PARENTAL ASTHMA OCCURRENCE, EXACERBATIONS AND RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Liu X, Dalsgaard S, Munk-Olsen T, et al.
Objective: To investigate whether intrauterine exposure to maternal asthma or asthma exacerbations increases the risk of attention-deficit/hyperactivity disorder (ADHD).
Methods: Using Danish register data, this cohort study comprised of 961,202 live singletons born in Denmark during 1997-2012. Children were followed to a maximum of 20.0 years from birth until the first of ADHD-diagnosis/prescription, emigration, death, or 31 December 2016. Cox regression models were used to evaluate the association between maternal or paternal asthma, asthma exacerbations and offspring ADHD.
Results: During 11.4 million person-years of follow-up, 27,780 (2.9%) children were identified as having ADHD. ADHD risk was increased among offspring born to asthmatic mothers (hazard ratio (HR) 1.41, 95% CI: 1.36-1.46) or asthmatic fathers (HR 1.13, 95% CI: 1.08-1.18). Antenatal antiasthma medication treatment did not increase offspring ADHD. However, higher risks were observed among offspring of mothers with asthma exacerbations compared with children of asthmatic mothers with no exacerbations: HR 1.12 (95% CI: 1.00-1.25) for pre-pregnancy exacerbations; 1.21 (95% CI: 1.00-1.47) for exacerbations during pregnancy; and 1.25 (95% CI: 1.08-1.44) for exacerbations after delivery.
Conclusions: These results support theories regarding shared genetic and environmental risk factors having a role in the development of ADHD

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Br J Psychiatry. 2019;215:615-20.
SUICIDAL BEHAVIOUR AMONG PERSONS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Fitzgerald C, Dalsgaard S, Nordentoft M, et al.
Background Persons diagnosed with attention-deficit hyperactivity disorder (ADHD) have been found to have an increased risk of suicidal behaviour, but the pathway remains to be thoroughly explored.
Aims To determine whether persons with ADHD are more likely to present with suicidal behaviour (i.e. suicide attempts and deaths by suicide) if they have a comorbid psychiatric disorder.
Method Using nationwide registers covering the entire population of Denmark, this cohort study of 2.9 million individuals followed from 1 January 1995 until 31 December 2014, covers more than 46 million person-years. All persons aged 10 years with Danish-born parents were identified and persons with a diagnosis of ADHD were compared with persons without. Incidence rate ratios (IRRs) were calculated by Poisson regression, with adjustments for sociodemographics and parental suicidal behaviour.
Results Persons with ADHD were followed for 164 113 person-years and 697 suicidal outcomes were observed. This group was found to have an IRR of suicidal behaviour of 4.7 (95% CI, 4.3-5.1) compared with those without ADHD. Persons with ADHD only had a 4.1-fold higher rate (95% CI, 3.5-4.7) when compared

with those without any psychiatric diagnoses. For persons with ADHD and comorbid disorders the IRR was higher yet (IRR: 10.4; 95% CI, 9.5-11.4).
Conclusions This study underlines the link between ADHD and an elevated rate of suicidal behaviour, which is significantly elevated by comorbid psychiatric disorders. In sum, these results suggest that persons with ADHD and comorbid psychiatric disorders are targets for suicide preventive interventions. Declaration of interest None

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Cells. 2019;8.
GENETIC VARIATION UNDERPINNING ADHD RISK IN A CARIBBEAN COMMUNITY.
Puentes-Rozo PJ, Acosta-L+¦pez JE, Cervantes-Henr+¡quez ML, et al.
Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable and prevalent neurodevelopmental disorder that frequently persists into adulthood. Strong evidence from genetic studies indicates that single nucleotide polymorphisms (SNPs) harboured in the *ADGRL3* (*LPHN3*), *SNAP25*, *FGF1*, *DRD4*, and *SLC6A2* genes are associated with ADHD. We genotyped 26 SNPs harboured in genes previously reported to be associated with ADHD and evaluated their potential association in 386 individuals belonging to 113 nuclear families from a Caribbean community in Barranquilla, Colombia, using family-based association tests. SNPs rs362990-*SNAP25* (T allele; $p = 2.46 \times 10^{-4}$), rs2282794-*FGF1* (A allele; $p = 1.33 \times 10^{-2}$), rs2122642-*ADGRL3* (C allele, $p = 3.5 \times 10^{-2}$), and *ADGRL3* haplotype CCC (markers rs1565902-rs10001410-rs2122642, OR = 1.74, $P_{permuted} = 0.021$) were significantly associated with ADHD. Our results confirm the susceptibility to ADHD conferred by *SNAP25*, *FGF1*, and *ADGRL3* variants in a community with a significant African American component, and provide evidence supporting the existence of specific patterns of genetic stratification underpinning the susceptibility to ADHD. Knowledge of population genetics is crucial to define risk and predict susceptibility to disease

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Child Abuse Negl. 2019.
COMPARING MENTAL HEALTH DISORDERS AMONG SEX TRAFFICKED CHILDREN AND THREE GROUPS OF YOUTH AT HIGH-RISK FOR TRAFFICKING: A DUAL RETROSPECTIVE COHORT AND SCOPING REVIEW.
Palines PA, Rabbitt AL, Pan AY, et al.
Background: Individuals at high-risk for trafficking are often subject to preexisting complex trauma that only intensifies during the trafficking experience. This greatly increases their risk of mental illness, although the actual prevalence of mental health disorders in children who are sex trafficked remains unclear.
Objective: To examine the prevalence of mental health diagnoses among a sample of youth identified as being sex trafficked, and to discuss these rates in relation to other high-risk groups reported in the literature.
Participants and setting: 143 female and male child trafficking victims in Wisconsin.
Methods: We retrospectively reviewed individual medical records, identifying mental health diagnoses and behaviors. The results were compared to summarized prevalence data for mental health disorders in sex trafficked, runaway children, juvenile offenders, and foster care children identified via a scoping review.
Results: We observed significantly higher rates of ADHD (52.4%, $p < 0.0001$), bipolar disorder (26.6%, $p < 0.0001$), and PTSD (19.6%, $p < 0.05$ to $p < 0.0001$) in our sample of trafficked youth compared to all high-risk groups, as well as for depression (45.5%), anxiety (19.6%), conduct disorder (19.6%), ODD (25.9%), and psychosis (14.0%) relative to multiple groups individually.
Conclusions: The complex trauma suffered by child survivors of sex trafficking can impart numerous effects with overlapping symptomatology of many mental health disorders. SurvivorsΓÇÖ adaptive responses to complex trauma may lead to improper diagnosis and treatment of mental health disorders at the expense of prompt access to trauma-focused therapies. Alternative diagnoses and treatments of this complex dysfunction are discussed

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Child Adolesc Ment Health. 2019;24:318-28.

IMPACT OF MENTORING ON SOCIO-EMOTIONAL AND MENTAL HEALTH OUTCOMES OF YOUTH WITH LEARNING DISABILITIES AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Haft SL, Chen T, LeBlanc C, et al.

Background: Learning disabilities (LD) and attention-deficit hyperactivity disorder (ADHD) are often accompanied by significant socio-emotional impairments and mental health challenges. However, there is a lack of controlled, quantitative research on potential interventions to address this issue. The current study evaluated the impact of a near-peer mentoring program for youth with LD/ADHD designed to promote socio-emotional well-being.

Methods: Youth with LD/ADHD who participated in the mentoring program (Mentored; n-á=-á99) were compared to both-ánonmentored youth with LD/ADHD (Control-NM; n-á=-á51) and typically developing youth without LD/ADHD (Control-TD; n-á=-á81) prementoring in the fall and postmentoring in the spring. Participants were assessed using self-report measures of anxiety, depression, interpersonal relations, and self-esteem.

Results: Youth with LD/ADHD showed significantly higher scores of depression and significantly lower scores of interpersonal relations compared to the Control-TD group at fall baseline. The depression and self-esteem scores of the Mentored group significantly decreased and increased, respectively, after mentoring. These changes were associated with mentee-perceived mentorship quality. The Control-NM group showed significant decreases in both self-esteem and interpersonal relations, as well as increases in depression over time, while the Control-TD group remained stable across all measures.

Conclusions: Results suggest that mentoring shows promise as a potential intervention for youth with LD/ADHD who experience co-occurring socio-emotional and mental health difficulties. The study is the first, to our knowledge, to quantify the effect of a near-peer mentoring program on youth with LD/ADHD in a design with two control groups. Implications for research and practice involving LD, ADHD, and mental health disorders are discussed. Key Practitioner Message LD and ADHD are associated with increased anxiety, depression, and impaired self-esteem and interpersonal relationships. There is a lack of research on interventions that could address the mental health problems and socio-emotional difficulties that co-occur with learning disabilities and ADHD. Near-peer mentoring is a promising intervention that can improve socio-emotional well-being and mental health in youth with learning disabilities and ADHD, and highlights the importance of strong interpersonal relationships as a protective factor

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Child Care Pract. 2019 Oct;25:419-38.

A RANDOMISED CONTROL TRIAL OF PARENT AND CHILD TRAINING PROGRAMMES (VERSUS WAIT LIST CONTROL) FOR CHILDREN WITH ADHD-TYPE BEHAVIOURS: A PILOT STUDY.

Leckey Y, McGilloway S, Hickey G, et al.

Objective: A randomised control trial was conducted to assess whether the combined Incredible Years parent training and child training programmes (PT + CT) led to improvements in ADHD-type behaviours in children, when compared to a PT-only group and a Wait List Control (WLC) group.

Method: Forty-five families with a child aged 3–7 years who displayed ADHD-type behaviours were referred for treatment and randomised to a combined treatment group (PT + CT; n = 12), a PT group (n = 19) or a WLC group (n = 14). Programmes were delivered by community-based organisations. Short-term follow-up (six months) assessments were undertaken with parents and children based on parent reports of child behaviour and parent well-being and behaviour. A qualitative sub-study was also conducted with parent participants (n = 8) and programme facilitators (n = 5) to explore experiences and views of the combined programme.

Results: Statistically significant differences were found between the PT group and the WLC group with regard to child hyperactivity ($p < 0.001$) and pro-social skills ($p < 0.05$). No significant differences were found between the combined group (PT + CT) and the PT group except for child hyperactivity ($p < 0.05$), which was significantly lower in the PT-only group. Significant effects were found for PT + CT versus WLC on the Strengths and Difficulties Questionnaire Impact subscale only.

Conclusion: These findings suggest that the combined treatment (PT + CT) produced little added benefit for child hyperactive/inattentive behaviour post-intervention despite the very positive views expressed by

parents in the qualitative interviews. The PT training alone was more effective in tackling some core ADHD behaviours when compared to the WLC group, but a need for further more large-scale research is indicated

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Child Neuropsychol. 2019.

VITAMIN D DEFICIENCY IN SCHOOL-AGE IRANIAN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS: A CRITICAL COMPARISON WITH HEALTHY CONTROLS.

Fasihpour B, Moayeri H, Shariat M, et al.

The associations between serum vitamin D levels and the severity of attention-deficit/hyperactivity disorder (ADHD) symptoms were assessed among Iranian hospitalized children (50 ADHD cases and 50 healthy (non-ADHD) controls) during 2014-2015. Levels of ADHD severity and serum 25-hydroxyvitamin D (25OHD) were determined by the Conners' Parent Rating Scale (CPRS) test and an ELISA kit, respectively. The serum 25OHD concentrations of <10, 10-29, and >30 ng/mL were respectively considered as deficient (severe deficiency), insufficient (mild deficiency), and sufficient levels of vitamin D. The association of nutrient bioavailability with ADHD was evaluated by statistical and regression analyses.There was no significant difference in the mean of socio-demographic variables (e.g., gender, age, weight, BMI, daily intake of dairy products, and daily sunlight exposure) between ADHD and non-ADHD subjects. The mean serum 25OHD concentration (16.57 ± 9.09 ng/mL) was found to be significantly lower in ADHD children with more parathyroid hormone (PTH) levels as compared to controls (22.01 ± 12.67ng/mL). The sufficient 25OHD concentration was more predominant in the controls than the cases (p = 0.002). A severe deficiency of vitamin D was more found in children with ADHD (3.36 times). There was a negative and significant association between the participants' age and their serum 25OHD levels. Although 25OHD levels in boys were significantly more than those in girls, the reduction of serum 25OHD concentration among boys with ADHD was more severe compared to the patient girls (p = 0.014). The results support the importance of vitamins D role in ADHD patients through the regular monitoring of serum 25OHD levels

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Clinical Epidemiology and Global Health. 2019.

DETERMINATION OF ASSOCIATION BETWEEN THE POLYMORPHISM IN EXON 3 OF DOPAMINE RECEPTOR GENE TYPE 4 WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Effatpanah H, Effatpanah M, Mohammadi MJ, et al.

Introduction: Evidences suggest that attention deficit-hyperactivity disorder (ADHD) is a hereditary disorder and at least 20 potential genes associated with ADHD have been identified. Dopamine receptor gene type 4 (DRD4) has been more considered due to a stronger relationship with ADHD. However, no study has yet been conducted on the Iranian population to assess the association.

Objective: In this study, the association between polymorphism of DRD4 gene with ADHD has been studied among capital of Iran population. Materials and methods: This study is a case-control study conducted on children aged 6-12 years with ADHD referred to child and adolescent psychiatric clinic Imam Hussein (AS) and normal subjects in 2011. Diagnosis was done based on the DSM-IV-TR criteria and interviewing by two child and adolescent psychiatrists. If parental were consent, then saliva samples of subjects were prepared and DRD4 gene and related allele were evaluated using PCR method. The K-SADS questionnaire was also used to assess comorbid disorders.

Results: In this study, 114 patients in ADHD group and 109 patients in the control group were studied. The most frequency was obtained for allele 4 allele that has been observed in about 90% of both case and control groups. However, frequency of allele 6 in the case group was 8.8% where the frequency was 5% in the control group (p = 0.02). The presence of repeat of allele 6 increased chance of suffering from ADHD to 1.809 (95% equal to 3.871-0.845).

Conclusion: For the first time this study showed that in Iranian population repeat of DRD4 gene allele 6 unlike the other geographic areas is relatively common and it will increase the chances of suffering from ADHD. However, additional studies are required

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Dev Psychopathol. 2019 Oct;31:1477-87.

FRIENDSHIP AND SOCIAL FUNCTIONING FOLLOWING EARLY INSTITUTIONAL REARING: THE ROLE OF ADHD SYMPTOMS.

Humphreys KL, Gabard-Durnam L, Goff B, et al.

Early institutional rearing is associated with increased risk for subsequent peer relationship difficulties, but the underlying mechanisms have not been identified. Friendship characteristics, social behaviors with peers, normed assessments of social problems, and social cue use were assessed in 142 children (mean age = 10.06, SD = 2.02; range 7–13 years), of whom 67 were previously institutionalized (PI), and 75 were raised by their biological families. Anxiety and attention-deficit/hyperactivity disorder (ADHD) symptoms, often elevated among PI children, were examined as potential mediators of PI status and baseline social functioning and longitudinal follow-ups (2 and 4 years later). Twenty-seven percent of PI children fell above the Child Behavior Checklist Social Problems cutoff. An examination of specific social behaviors with peers indicated that PI and comparison children did not differ in empathic concern or peer social approach, though parents were more likely to endorse aggression/overarousal as a reason that PI children might struggle with friendships. Comparison children outperformed PI children in computerized testing of social cue use learning. Finally, across these measures, social difficulties exhibited in the PI group were mediated by ADHD symptoms with predicted social problems assessed 4 years later. These findings show that, when PI children struggle with friendships, mechanisms involving attention and behavior regulation are likely contributors

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Dev Psychopathol. 2019 Oct;31:1255-69.

INFORMANTS' RATINGS OF ACTIVITY LEVEL IN INFANCY PREDICT ADHD SYMPTOMS AND DIAGNOSES IN CHILDHOOD.

Meeuwsen M, Perra O, van Goozen SHM, et al.

We tested the hypothesis that high activity levels in infancy would predict self-regulatory problems and later symptoms of attention deficit and hyperactivity disorder (ADHD) in a longitudinal study of British families (N = 321). Infants' activity levels were assessed at 6 months, using 3 informants' reports from the Infant Behavior Questionnaire (IBQ) and ActiGraphs during baseline, attention, and restraint tasks. At a mean of 33 months, the children were assessed on self-regulatory tasks; at a mean of 36 months, 3 informants reported symptoms of ADHD. At a mean of 7.0 years, the children were assessed on executive function tasks; 3 informants reported on the child's symptoms of ADHD; and diagnoses of disorder were obtained using the Preschool Age Psychiatric Assessment. Informants' reports of high activity levels at 6 months predicted ADHD symptoms in early childhood and diagnoses of ADHD with clinical impairment at age 7. The IBQ activity scale was also associated with the children's later performance on self-regulation tasks in early and middle childhood. Activity level in infancy reflects normal variation and is not a sign of psychopathology; however, these findings suggest that further study of the correlates of high activity level in infancy may help identify those children most at risk for disorder

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Dev Neuropsychol. 2019 Sep;44:468-80.

TEMPORAL REWARD DISCOUNTING IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD), AND CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD): A SYSTEMATIC REVIEW.

de Castro Paiva GC, de Souza Costa D, Malloy-Diniz LF, et al.

Children with ADHD and ASD may present differences in the affective-motivational processes. We systematically review the literature regarding temporal discounting in children up to 12 years with ADHD and ASD. Six articles were included, five studies with ADHD children (n = 231), one with ASD children (n = 21),

all including typically developing children as controls (n = 210). Five studies (four with ADHD and one with ASD) found greater temporal reward discounting for clinical groups. Occurrence of ADHD appears to rush even more the decision-making process at this stage of development, but there is still a lack in the literature, especially evaluating individuals with ASD

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Dusunen Adam. 2019;32:185-93.

INTERNET USE AND AGGRESSION IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Izmir SBI, Ipci M, Ercan ES.

Objective: The aim of this study was to investigate the relationship between internet addiction and aggression in adolescents with Attention Deficit Hyperactivity Disorder (ADHD). In addition, we aimed to explore the differences between ADHD subtypes (inattentive type; combination type; hyperactive-impulsive type).

Method: The sample consisted of a total of 120 adolescents. The study group included 60 individuals aged between 13 and 17 years (14.70-¦2.07) who had presented to a child and adolescent psychiatry clinic and received a diagnosis of ADHD according to the DSM-IV after being interviewed by a specialist, while 60 adolescents without a diagnosis of ADHD made up the control group. Kiddie-Schedule for Affective Disorders and Schizophrenia, present and life time version (K-SADS-PL), Buss-Perry Aggression Questionnaire (BPAQ), Internet Addiction Diagnostic Questionnaire (IADQ), and a semi structured sociodemographic form were used as measurement devices.

Results: According to the results of statistical analyses, the ratio of internet addiction and aggression were higher in adolescents with ADHD than in the control group. Especially the rate of internet addiction and aggression was higher in adolescents with ADHD combination type. In addition, there is a positive relationship between internet addiction and aggression in adolescents with ADHD.

Conclusion: According to our study results, there is a positive relationship between internet addiction and aggression in adolescents with ADHD. The results of our study will be helpful to develop future protective measures in internet addiction aimed at preventing aggressive behavior of adolescents with ADHD

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Encephale. 2019.

PRACTICAL CONSIDERATIONS FOR THE EVALUATION AND MANAGEMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS.

Weibel S, Menard O, Ionita A, et al.

Attention deficit with or without hyperactivity disorder (ADHD) is one of the most frequent neuropsychiatric disorders, and affects 2-4% of adults. In contrast with many European countries, the identification and management of adult ADHD remains underdeveloped in France, and a subject of controversy. This review provides a practical update on current knowledge about ADHD in adults for French-speaking professionals who have to detect or manage adult patients with ADHD. ADHD is classified as a neurodevelopmental disorder in the recent update of the international diagnostic classification. While symptoms and impairment due to ADHD are frequently severe during childhood, they often evolve as children grow older, with frequent persistent disabilities in adulthood. In adulthood, the clinical presentation, as in childhood, involves the symptom triad of inattention, hyperactivity and impulsivity. However, differences are noted: hyperactivity is more often internalized, symptoms of inattention may be masked by anxiety symptoms or obsessive-like compensation strategies. ADHD is often diagnosed during childhood, but it is not rare for the diagnosis to be made later. Failure to recognise symptoms resulting in misdiagnosis, or alternatively well-developed compensation factors could be two underlying reasons for the long delay until diagnosis. Other symptoms, such as emotional deregulation or executive function-related symptoms are also usually observed in adults. In addition, in adults, ADHD is often associated with other psychiatric disorders (in 80% of cases); this makes the diagnosis even more difficult. These disorders encompass a broad spectrum, from mood disorders (unipolar or bipolar), to anxiety disorders, and other neurodevelopmental disorders and personality disorders, especially borderline and antisocial personality disorder. Substance-use disorders are very common, either

as a consequence of impulsivity and emotional dysregulation or as an attempt at self-treatment. Sleep disorders, especially restless leg syndrome and hypersomnolence, could share common pathophysiological mechanisms with ADHD. ADHD and comorbidity-related symptoms are responsible for serious functional impairment, in various domains, leading to academic, social, vocational, and familial consequences. The impact on other psychiatric disorders as an aggravating factor should also be considered. The considerable disability and the poorer quality of life among adults with ADHD warrant optimal evaluation and management. The diagnostic procedure for ADHD among adults should be systematic. Once the positive diagnosis is made, the evaluation enables characterisation of the levels of severity and impairment at individual level. A full examination should also assess medical conditions associated with ADHD, to provide personalized care. In recent years, a growing number of assessment tools have been translated and validated in French providing a wide range of structured interviews and standardized self-report questionnaires for the evaluation of core and associated ADHD symptoms, comorbidities and functional impairment. The treatment of ADHD in adults is multimodal, and aims to relieve the symptoms, limit the burden of the disease, and manage comorbidities. The most relevant and validated psychological approaches are psycho-education, cognitive-behavioural therapy and third wave therapies with a specific focus on emotional regulation. Cognitive remediation and neurofeedback are promising strategies still under evaluation. Medications, especially psychostimulants, are effective for alleviating ADHD symptoms with a large effect size. Their safety and tolerance are satisfactory, although their long-term clinical benefit is still under discussion. In France, methylphenidate is the only stimulant available for the treatment of ADHD. Unfortunately, there is no authorization for its use among adults except in continuation after adolescence. Hence the prescription, which is subject to the regulations on narcotics, is off-label in France. This article aims to provide practical considerations for the management of ADHD and associated disorders in adults, in this particular French context

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Environ Res. 2019 Oct;177:108641.

ENVIRONMENTAL EXPOSURE TO LOW-LEVEL LEAD (PB) CO-OCCURRING WITH OTHER NEUROTOXICANTS IN EARLY LIFE AND NEURODEVELOPMENT OF CHILDREN.

Dorea JG.

Lead (Pb) is a worldwide environmental contaminant that even at low levels influences brain development and affects neurobehavior later in life; nevertheless it is only a small fraction of the neurotoxicant (NT) exposome. Exposure to environmental Pb concurrent with other NT substances is often the norm, but their joint effects are challenging to study during early life. The aim of this review is to integrate studies of Pb-containing NT mixtures during the early life and neurodevelopment outcomes of children. The Pb-containing NT mixtures that have been most studied involve other metals (Mn, Al, Hg, Cd), metalloids (As), halogen (F), and organo-halogen pollutants. Co-occurring Pb-associated exposures during pregnancy and lactation depend on the environmental sources and the metabolism and half-life of the specific NT contaminant; but offspring neurobehavioral outcomes are also influenced by social stressors. Nevertheless, Pb-associated effects from prenatal exposure portend a continued burden on measurable neurodevelopment; they thus favor increased neurological health issues, decrements in neurobehavioral tests and reductions in the quality of life. Neurobehavioral test outcomes measured in the first 1000 days showed Pb-associated negative outcomes were frequently noticed in infants (<6 months). In older (preschool and school) children studies showed more variations in NT mixtures, children's age, and sensitivity and/or specificity of neurobehavioral tests; these variations and choice of statistical model (individual NT stressor or collective effect of mixture) may explain inconsistencies. Multiple exposures to NT mixtures in children diagnosed with 'autism spectrum disorders' (ASD) and 'attention deficit and hyperactivity disorders' (ADHD), strongly suggest a Pb-associated effect. Mixture potency (number or associated NT components and respective concentrations) and time (duration and developmental stage) of exposure often showed a measurable impact on neurodevelopment; however, net effects, reversibility and/or predictability of delays are insufficiently studied and need urgent attention. Nevertheless, neurodevelopment delays can be prevented and/or attenuated if public health policies are implemented to protect the unborn and the young child

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Environ Sci Pollut Res Int. 2019 Aug;26:23739-53.

SERUM CONCENTRATIONS AND DETECTION RATES OF SELECTED ORGANOCHLORINE PESTICIDES IN A SAMPLE OF GREEK SCHOOL-AGED CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Makris G, Chrousos GP, Anesiadou S, et al.

Prospective studies indicate that the exposure to organochlorine pesticides (OCPs) during fetal life, infancy, and early childhood may be associated with features of neurodevelopmental disorders in children. However, few studies have investigated the concentrations of serum OCPs in children with categorically diagnosed neurodevelopmental disorders. The aim of this study was to assess the concentrations and detection rates of dichlorodiphenyltrichloroethane (DDT) metabolites, hexachlorocyclohexane (HCH) isomers, cyclodienes, and methoxychlor in serum samples of children with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and specific learning disorder (SLD), all of normal intelligence, compared to typically developing controls (TD). In total, 114 schoolchildren, aged 6-13 years old, were assessed and distributed into four groups: ASD (n = 39), ADHD (n = 21), SLD (n = 32), and TD (n = 18). Each clinical group was compared to the TD group. Concentrations of serum OCPs were determined by gas chromatography and are presented as ng/g lipid. Concentrations of β-HCH, the sum of HCH isomers, and o,p'-DDD were significantly higher in ASD children: ASD vs. TD (mean ± SD): 10.5 ± 7.7 vs. 6.1 ± 4.0, (p = 0.049); 12.0 ± 10.3 vs. 6.6 ± 4.0, (p = 0.025); 7.4 ± 6.5 vs. 2.8 ± 2.3, (p = 0.0019), respectively. The detection rates of p,p'-DDT, at least one substance from DDTs detected, and the cyclodiene heptachlor epoxide, were significantly lower in the ASD group: ASD vs. TD: 12.8% vs. 38.9%, (p = 0.037); 69.2% vs. 94.4%, (p = 0.044); 10.3% vs. 38.9%, (p = 0.026), respectively. No significant differences between the ADHD or SLD groups and the TD group were observed. We demonstrated higher serum concentrations and lower detection rates of selected OCPs in ASD than TD children. Our results add to potential neurodevelopmental concerns surrounding OCPs and provide evidence of specificity in the relations between HCHs and ASD

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Environ Int. 2019;133.

PRENATAL EXPOSURE TO AIR POLLUTION AS A POTENTIAL RISK FACTOR FOR AUTISM AND ADHD.

Oudin A, Frondelius K, Haglund N, et al.

Genetic and environmental factors both contribute to the development of Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD). One suggested environmental risk factor for ASD and ADHD is air pollution, but knowledge of its effects, especially in low-exposure areas, are limited. Here, we investigate risks for ASD and ADHD associated with prenatal exposure to air pollution in an area with air pollution levels generally well below World Health Organization (WHO) air quality guidelines. We used an epidemiological database (MAPSS) consisting of virtually all (99%) children born between 1999 and 2009 (48,571 births) in the study area, in southern Sweden. MAPSS consists of data on modelled nitrogen oxide (NOx) levels derived from a Gaussian dispersion model; maternal residency during pregnancy; perinatal factors collected from a regional birth registry; and socio-economic factors extracted from Statistics Sweden. All ASD and ADHD diagnoses in our data were undertaken at the Malm+Â and Lund Departments of Child and Adolescent Psychiatry, using standardized diagnostic instruments. We used logistic regression analyses to obtain estimates of the risk of developing ASD and ADHD associated with different air pollution levels, with adjustments for potential perinatal and socio-economic confounders. In this longitudinal cohort study, we found associations between air pollution exposure during the prenatal period and and the risk of developing ASD. For example, an adjusted Odds Ratio (OR) of 1.40 and its 95% Confidence Interval (CI) (95% CI: 1.02ΓÇô1.93) were found when comparing the fourth with the first quartile of NOx exposure. We did not find similar associations on the risk of developing ADHD. This study contributes to the growing evidence of a link between prenatal exposure to air pollution and autism spectrum disorders, suggesting that prenatal exposure even below current WHO air quality guidelines may increase the risk of autism spectrum disorders

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Epilepsy Behav. 2019.

THE NATURAL HISTORY OF SEIZURES AND NEUROPSYCHIATRIC SYMPTOMS IN CHILDHOOD EPILEPSY WITH CENTROTEMPORAL SPIKES (CECTS).

Ross EE, Stoyell SM, Kramer MA, et al.

Objective: Childhood epilepsy with centrotemporal spikes (CECTS) (formally benign epilepsy with centrotemporal spikes, BECTS) is a common childhood epilepsy syndrome characterized by psychiatric, behavioral, and cognitive abnormalities and self-limited seizures. Although CECTS is one of the most well-characterized electroclinical epilepsy syndromes, the natural history of neuropsychiatric outcomes is poorly understood. We report the psychiatric, behavioral, and cognitive profiles over the course of disease from a large, prospectively-enrolled, longitudinal cohort of children with CECTS. We further characterize the detailed seizure course and test the relationship between several proposed risk factors and neuropsychiatric and seizure outcomes in these children.

Methods: Patients diagnosed with CECTS were enrolled as part of a community-based study and followed from diagnosis through disease resolution (16.0 -¦ 3.1 years, N = 60). Twenty sibling controls were also recruited. We report the natural history of premorbid neuropsychiatric concerns, postmorbid neuropsychiatric diagnoses, long-term neuropsychological performance, seizure course, antiseizure medication (ASM) treatment response, and the relationship between duration seizure-free and remission. Age at onset and premorbid neuropsychiatric concerns were tested as predictors of seizure count, epilepsy duration, postmorbid neuropsychiatric diagnoses, and long-term neuropsychological performance. Antiseizure medication treatment duration, seizure count, and epilepsy duration were tested as predictors of postmorbid neuropsychiatric diagnoses and long-term neuropsychological performance.

Results: Children with CECTS had a high incidence of ADD/ADHD symptoms (18.3%) or learning difficulties (21.7%) before diagnosis. New or persistent ADHD (20%), mood disorders (23.6%), learning difficulties (14.5%), and behavioral disorders (7.3%) were common after CECTS diagnosis. At 9-year follow-up, performance on formal neuropsychological testing was comparable to population statistics and sibling controls. More than two-thirds of treated children experienced at least one seizure during treatment. Most children (61.7%) had entered terminal resolution after 12 months seizure-free. Among all children, for each month seizure-free, there was a 6-7% increase in the probability of achieving terminal remission ($p < 1e-10$). The presence of a premorbid neurodevelopmental concern predicted a longer epilepsy duration ($p = 0.02$), higher seizure count ($p = 0.02$), and a postmorbid psychiatric or neurodevelopmental diagnosis ($p = 0.002$). None of the tested features predicted long-term neuropsychological performance.

Significance: Children are at high risk of neuropsychiatric symptoms along the course of the disease in CECTS, however, long-term cognitive performance is favorable. The majority of children had a seizure while being treated with ASMs, suggesting that CECTS is not as pharmacoresponsive as assumed or that treatment approaches are not optimized. Among treated and untreated children, future seizure-risk can be estimated from duration seizure-free. The presence of a premorbid neuropsychiatric concern predicted a more severe disease course in CECTS

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Epilepsy Behav. 2019.

NEUROPSYCHOLOGICAL GROUP REHABILITATION ON NEUROBEHAVIORAL COMORBIDITIES IN CHILDREN WITH EPILEPSY.

Rantanen K, Vierikko E, Eriksson K, et al.

Neurobehavioral comorbidities, particularly attention-deficits, are common in children with epilepsy (CWE). Neurobehavioral problems are manifested in school performance, peer relations, and social competence. Although the high prevalence of these comorbid behavioral problems is fully recognized, there remains to be a lack of studies on the interventions targeted for CWE. A manualized neuropsychological group intervention, Rehabilitation of EXecutive Function and ATtention (EXAT) has been developed for school-aged children (aged 6ΓÇô12 years) with executive function (EF) and attention-deficits. This study aimed to explore the effects of EXAT on parent- and teacher-rated attention and behavior problems in CWE compared with children with the diagnosis of attention-deficit hyperactivity disorder (ADHD) and children with no formal diagnosis but prominent deficits in EF and attention. Forty-two children attending in neuropsychological group rehabilitation EXAT between the years 2006 and 2017 participated in this retrospective registry study. The

CWE group consisted of 11 children, the ADHD group with 16 children, and EF/attention group consisted of 15 children with EF attention and/or problems without diagnosis of ADHD. The CWE group did not differ from the other two study groups (ADHD and no formal diagnosis) before the EXAT intervention. This indicates that attention problems in CWE are similar to those with diagnosed ADHD. The results were promising for applying structured multilevel intervention for CWE and neurobehavioral comorbidities. Lack of group differences between the groups participating EXAT suggests similar intervention effects between CWE, ADHD, and those with less severe EF and attention problems. In parent ratings, intervention effects were higher in hyperactivity and oppositional behavior for children with attention problems and without epilepsy. Parents in the CWE group reported no effects except for one subscale related to hyperactivity. However, teachers reported consistently positive intervention effects for both inattention and hyperactivityΓÇôimpulsivity along with anxiety and emotional lability. The results suggest that neurobehavioral comorbidities in CWE could be targeted in neuropsychological group intervention. In conclusion, CWE seem to benefit from interventions and behavior modification techniques first developed for children with ADHD

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Eur J Paediatr Dent. 2019 Jun;20:127-32.

THE EFFECT OF ADDED SUGARS ON CHILDREN'S HEALTH OUTCOMES: OBESITY, OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS), ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND CHRONIC DISEASES.

Paglia L, Friuli S, Colombo S, et al.

Increasing attention has been paid to how dietary sugars affect not only tooth decay, but also obesity, Type 2 diabetes mellitus, and cardiometabolic and kidney diseases. Therefore, possible connections of these diseases with oral health and diet are analysed. Healthy approaches to beverage and dietary consumption should be recommended and hopefully established in infancy, with the aim of preventing negative effects on general health in later childhood and adulthood

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Eur Child Adolesc Psychiatry. 2019.

TIME SPENT GAMING AND PSYCHIATRIC SYMPTOMS IN CHILDHOOD: CROSS-SECTIONAL ASSOCIATIONS AND LONGITUDINAL EFFECTS.

Stenseng F, Hygen BW, et al.

There is sparse knowledge on how the amount of gaming overlaps with nd is longitudinally related to-psychiatric symptoms of ADHD and emotional problems throughout early and middle childhood. In this prospective study of 791 Norwegian children, we investigated the amount of electronic gaming at ages 6, 8, and 10 while also measuring DSM symptoms of such disorders. Cross-lagged longitudinal analyses showed that more ADHD symptoms at age 8 predicted more gaming at age 10, whereas gaming did not predict more psychiatric symptoms, controlled for gender and socio-economic status. Cross-sectional overlaps between gaming and symptoms were marginal but nonetheless increased with each age level. Hence, time spent gaming did not forecast more psychiatric problems at these ages, but children with more ADHD symptoms were more likely to increase their amount of gaming throughout middle childhood. Results indicate that the sheer amount of gaming is not harmful to childrenΓÇÖs mental health, but that poorly regulated children become more attracted to games throughout childhood. Findings are discussed in light of the coexistence of problematic gaming and psychiatric problems reported among adolescents and adults, as well as the potential beneficial psychological outcomes from gaming

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Eur J Hum Genet. 2019;26:938.

"ADHD MOVES", A NOVEL NETWORK FOCUSSING ON MENDELIAN SUBTYPES AND ENDOPHENOTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Schote AB, May P, et al.

Traits underlying "complex" inheritance (i.e., multiple genes and environmental factors contributing to the phe-notype), such as a variety of psychological and psychiatric disorders, depend largely on generalized therapies, since biological markers are rare or absent. Accordingly, research aiming at the identification of genetic markers relevant for diagnosis or therapy of attention deficit hyperactivity disorder (ADHD) was not successful so far. ADHD is the most common mental disorder in children and adolescents, and can persist into adulthood. It has a high heritability of 75%-91%, which indicates a strong genetic influence. Intense research by large international consortia focuses on ADHD as a complex disorder. Thousands of samples of affected and non-affected subjects were genotyped in hypothesis-free genome-wide association studies (GWAS). One of the biggest of those studies conducted by Elia and coworkers in 2011 identified deletions and duplications of genes coding for glutamate receptors in some ADHD patients and their siblings. Thus, subtypes of ADHD following a Mendelian pattern of inheritance could be assumed. Only a small number of publications on linkage analyses of large multiplex families with ADHD (Lin et al., 2013, Vegt et al., 2010; Amin et al., 2009, Romanos et al., 2008, Arcos-Burgos et Al., 2004) exist to date. In our newly founded "ADHD MoveS" network, geneticists, psychologists, physicians and bioinformaticians will continue this promising line of research investigating pedigrees with an ADHD phenotype, and additionally apply genetic, psychometrically measurable and stable cognitive and biological parameters, so called endophenotypes

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Eur J Hum Genet. 2019;26:733-34.

LONG-TERM PRENATAL EXPOSURE TO PARACETAMOL IS ASSOCIATED WITH DNA METHYLATION CHANGES AND ADHD: IDENTIFICATION OF DYSREGULATED PATHWAYS INVOLVED IN OXI-DATIVE STRESS AND THE OLFACTORY SYSTEM.

Lyle R, Nordeng H, Ystrom E, et al.

Epidemiological studies have shown that long-term exposure to paracetamol during pregnancy is associated with attention-deficit/hyperactivity disorder (ADHD). The mechanism by which paracetamol modulates the increased risk of developing ADHD is currently unknown. We have conducted an epigenome-wide association study to investigate whether prenatal exposure to paracetamol is associated with DNA methylation changes and ADHD. Participants (n = 384) were selected from a large prospective birth cohort (Norwegian Mother and Child Cohort Study), which contains information about medication use during pregnancy. The ADHD diagnoses were obtained from the Norwegian Patient Registry. Case-control analysis of paracetamol or ADHD alone did not reveal any differential DNA methylation. However, comparison of samples with ADHD exposed to paracetamol for more than 20 days to healthy controls identified differentially methylated CpGs (n = 6 211). In addition, these samples were differentially methylated compared to samples with ADHD exposed to paracetamol for less than 20 days (n = 2 089 CpGs) and not exposed to paracetamol (n = 193 CpGs). Interestingly, several of the top genes ranked according to significance and effect size have been linked to ADHD, neural development and neurotransmission. Gene ontology analysis revealed enrichment of pathways involved in oxidative stress, neurological processes and the olfactory sensory system, which have previously been implicated in the etiology of ADHD. These results lend novel insights into the epigenetic aspect of ADHD and provide a possible pharmaco-epigenetic link between the prenatal exposure to paracetamol and ADHD development. Norwegian Research Council (32251), Southern and Eastern Norway Regional Health Authority (39671), ERC Starting Grant (678033)

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Eur Neuropsychopharmacol. 2019;29:S221-S222.

T3 GENETIC FACTOR AND GRAY MATTER CO-VARIATION UNDERLYING PERSISTENT WORKING MEMORY UNDERPERFORMANCE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Duan K, Chen J, Calhoun V, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders with 3-5% prevalence. In about 15% of cases, ADHD persists into adulthood, affecting 2.5-4.4% of general adult population. Our previous work has identified that brain abnormalities in superior/inferior frontal and cerebellum are consistently associated with working memory deficit or inattention in both ADHD children and adults, while underlying genetic factor is little studied. In this work, we conducted a multivariate analysis on ADHD risk single-nucleotide polymorphisms (SNP) and structural MRI (sMRI) data to investigate the underlying genetic factor of persistent ADHD.

Methods: ADHD risk SNPS were selected from ADHD GWAS results with p < 0.001 and pruned with R square > 0.9. SMRI data were focused only on superior/inferior frontal and cerebellum components consistently related to working memory deficit or inattention across adolescents and adults. We performed parallel independent component analysis (pICA) on 341 independent adult participants including ADHD patients and healthy controls. Then we projected the identified sMRI-SNP components to additional 81 participants who were relatives of independent participants. On all adult participants, we assessed associations between sMRI and SNP components, and their relations with working memory performance/inattention. Additionally, the identified sMRI-SNP pairs were projected onto 462 children/adolescent data (including ADHD cases and controls) to valid genetic effect on brain structure. Moreover, the identified sMRI components were projected onto 875 independent subjects from ADHD 200 project to evaluate case vs. control difference for different age ranges.

Results: A superior frontal component was significantly and positively associated with one genetic component: R square = 4.08%, p = 3.39 +ù 10E-05, beta = 0.20, confidence interval (CI) of beta [0.11, 0.30], dominantly contributed by 26 SNPs in chromosomes 5, 6 and 12 (|z| threshold = 3) in the adult cohort. The association was replicated in the ADHD children cohort (R square = 0.87%, p = 0.04, beta = 0.04, CI of beta [4.43E-04, 0.08]). we also observed that the older the subject, the stronger the sMRI-SNP association. Importantly, superior frontal component was significantly and positively related to working memory performance in both adults and children. Specific to this brain region, individuals with ADHD showed gray matter (GM) reduction only in younger children and the reduction diminished along the age. The highlighted SNPs were in non-coding RNAs and expressed highly in testis and the caudate nucleus.

Discussion: We identified one genetic factor in long non-coding RNAs underlying GM of superior frontal region, which was related to working memory deficit in adult and children ADHD. The higher the genetic factor carried by individuals, the more the GM volume. These associations were stronger in adults compared to children. Together with ADHD patients showing GM reduction in the superior frontal region only in younger kids, our results suggest that this genetic factor likely plays a protective role towards the working memory deficit and a potential role in persistent ADHD, and this specific genetic regulation varies with age, i.e., it is stronger in late adolescence or early adulthood than at younger ages. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S44-S45.

THE BRAIAN IN ADHD AND THE ROLE OF GENETICS.

Franke B.

Attention-deficit/hyperactivity disorder (ADHD) is a frequent psychiatric disorder that affects approximately 5% of children and 2-3% of adults worldwide. ADHD is highly heritable in both children and adults, and recent genome-wide association studies (GWAS) have identified the first (reproducible) genetic risk variants for the disorder. Brain alterations have been frequently reported in ADHD, but most of the studies have been performed in small sample sizes and have been limited to children. The ENIGMA-ADHD Working Group has the aim to increase the knowledge on the brain in ADHD by integrating data from multiple samples and investigating the entire lifespan. Two studies of the working group, performed with contributions from over 30 samples collected worldwide, showed that people with ADHD have subtly smaller brain volumes in many brain regions (Hoogman M et al., 2017) as well as subtly smaller brain surface areas (Hoogman M et al., 2019). The findings were most pronounced in early childhood, and no brain differences were observed in

adolescents and adults with the disorder. Importantly, the largest effect sizes were seen for global brain measures, i.e. intracranial volume (ICV) and total surface area. This fact suggests that among the biological processes underlying ADHD-related brain alterations are those acting on the entire brain. In line with this finding, we recently showed that overlap exists between genetic contributions to ADHD risk and ICV (Klein M et al., 2019) as well as total surface area (Grasby K L et al., 2018). For the ADHD-ICV finding we were subsequently able to show that a gene-set involved in neurite outgrowth was involved in the observed genetic overlap (Klein M et al., 2019). Even in light of such promising findings, the overlap between the genetic findings for ADHD risk and for brain measures is surprisingly low, suggesting that the resolution of the brain imaging data and/or the selection of brain measures investigated might not yet reflect optimally the unit of the ADHD brain that is influenced by genetic risk for the disorder. We will discuss directions for future research. Disclosure: Medice, Shire - Honoraria, Self

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Eur Neuropsychopharmacol. 2019;29:S103-S104.

78 POLYGENIC RISK FOR THE PERSISTENCE OF ADHD.

Sprooten E, Soheili-Nezhad S, Mota NR, et al.

Background: Twin studies indicate that genetic factors contributing to ADHD onset are partly distinct from that underlying persistence into adulthood. While the genetic variants contributing to ADHD diagnosis are now well characterized in case-control genome-wide association studies (GWAS), the genetic variants associated with persistence of ADHD over time remain largely unknown. We derived a new polygenic score that captures genetic variation underlying course of illness in ADHD, and we investigated its effect on the persistence of symptoms and impairment in a prospective cohort. We further characterized the relationship of this new genetic factor with other major psychiatric disorders.

Methods: Two polygenic risk scores (PRS) were calculated for each individual in a longitudinal cohort of patients with ADHD in the Netherlands (NeuroIMAGE). First, a standard polygenic onset score was based on the children-only ADHD case-control GWAS of the Psychiatric Genomics Consortium, excluding NeuroIMAGE (9,917 cases, 16,137 controls). Second, a new polygenic persistence score was derived by subtracting the children-only effect-sizes from those of a case-control GWAS of adults with persistent ADHD conducted by the IMpACT Consortium, excluding the participants from The Netherlands (6,408 cases, 15,762 controls). Generalized mixed models were run with ADHD remission (N=75) versus persistence (N=297) as outcome, and both onset and persistence PRSs as predictors, adjusting for family relationships. Next, the effect of the persistence PRS on diagnosis-change was further investigated in terms of its effect on symptom change and reductions in clinical impairment over time. Finally, using LD-score regression, we calculated genetic correlations of the polygenic persistence factor with 5 major psychiatric disorders given the latest GWAS of autism spectrum disorder, schizophrenia, bipolar disorder, major depression and anxiety disorders.

Results: A lower persistence PRS was associated with partial (P=0.02) and full remission(P=0.04) of ADHD, independently of any effects of the onset PRS (partial remission: P=0.46, full remission: P=0.01). Covarying for sex, age at first and last assessment, and 4 principal population stratification components did not change the results. The persistence PRS was associated with a reduction in clinical impairment (P=0.02), but not with reductions in number of symptoms. LD-score regression revealed a genetic correlation of the genomic persistence factor with major depression (rho=0.45; P=0.0005), and with schizophrenia (rho=0.30, P=0.007).

Discussion: Polygenic effects on ADHD persistence with age can be isolated from genetic effects underlying ADHD onset by contrasting case-control GWAS of different age groups. The derived persistence PRS can be used for stratification and combined with other clinical and biological measures to give new insights in the processes behind course of illness in ADHD. The genomic signature for ADHD persistence is closely related to genetic liability for major depression. Further study of ADHD comorbidity with depression in prospective cohorts will be valuable to advance the clinical impact of this research. Importantly, the genetic liability for persistence of ADHD appears to be associated with impairment rather than with continuous symptom ratings. Thus, genetic factors that influence important clinical variables such as impairment and remission may not always be optimally captured by studying symptom dimensions alone.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:1102-16.

METHYLPHENIDATE AND ATOMOXETINE NORMALISE FRONTO-PARIETAL UNDERACTIVATION DURING SUSTAINED ATTENTION IN ADHD ADOLESCENTS.

Kowalczyk OS, Cubillo AI, Smith A, et al.

Problems with sustained attention are a key clinical feature of Attention Deficit/Hyperactivity Disorder (ADHD) which also manifests in poor performance and abnormal fronto-striato-parietal activation during sustained attention. Methylphenidate and atomoxetine improve attention functions and upregulate abnormal fronto-cortical activation during executive function tasks in ADHD patients. Despite this, no functional Magnetic Resonance Imaging (fMRI) study has compared the effects of methylphenidate and atomoxetine on the neurofunctional substrates of sustained attention in ADHD. This randomised, double-blind, placebo-controlled, cross-over study investigated the comparative normalisation effects of methylphenidate and atomoxetine on fMRI correlates and performance in 14 ADHD adolescents relative to 27 age-matched healthy controls during a parametric sustained attention/vigilance task with progressively increasing load of sustained attention. ADHD patients were scanned three times under a single clinical dose of either methylphenidate, atomoxetine, or placebo in pseudo-randomised order. Healthy controls were scanned once and compared to patients under each drug condition to test for potential drug-normalisation effects. Relative to controls, ADHD boys under placebo were impaired in performance and had underactivation in predominantly right-hemispheric fronto-parietal, and striato-thalamic regions. Both drugs normalised all underactivations, while only methylphenidate improved performance deficits. Within patients, methylphenidate had a drug-specific effect of upregulating left ventrolateral prefrontal/superior temporal activation relative to placebo and atomoxetine, while both drugs increased activation of right middle/superior temporal cortex, posterior cingulate, and precuneus relative to placebo. The study shows shared normalisation effects of methylphenidate and atomoxetine on fronto-striato-thalamo-parietal dysfunction in ADHD during sustained attention but a drug-specific upregulation effects of methylphenidate on ventral fronto-temporal regions

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Eur Neuropsychopharmacol. 2019;29:S102.

75 POLYGENIC RISK FOR ADHD AND EXPOSURES DURING PREGNANCY IN THE NORWEGIAN MOTHER AND CHILD COHOR STUDY (MOBA).

Havdahl A, Hannigan L, Askeland RB, et al.

Background: Over the past decade, there has been an increase in studies showing associations between a broad range of lifestyle factors (e.g., smoking and alcohol intake) and health-related exposures (e.g., gestational diabetes) in pregnant women and ADHD in their children. It is, however, unclear whether the observed associations are causal or not. They may reflect confounding by unmeasured shared familial factors that influence both the maternal exposure and offspring ADHD. In the present study we assess the potential contribution of maternal polygenic risk for ADHD to pregnancy exposures linked to this disorder.

Methods: We use data from the Norwegian Mother and Child pregnancy cohort study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 40.6 % of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Genotyping is ongoing. A wide range of pregnancy exposures have been measured through the Medical Birth Registry and questionnaires. Summary statistics from the largest available genome-wide association study of ADHD (Demontis et al., 2019) were used to calculate polygenic risk scores (PRS).

Results: Preliminary results from up to 9,073 mothers with available genotype and pregnancy exposure data suggest that maternal PRS for ADHD is associated with a range of pregnancy exposures, including smoking, coffee intake, non-use of nutritional supplements and use of pain medications. At WCPG, results will be presented from analyses of more than 20,000 mothers. For comparison purposes, associations between ADHD PRS and lifestyle and health-related factors in fathers (n>20,000) will be shown. Finally, we will present analyses of the extent to which accounting for genetic confounding attenuates associations between maternal pregnancy exposures and offspring ADHD in the MoBa cohort.

Discussion: The results indicate that observed associations between pregnancy exposures and offspring ADHD could at least partly be explained by shared genetic influences/gene-environment correlations.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S114.

S1 PARENT-OF-ORIGIN AND MATERNAL EFFECTS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Corfield E, Smajlagic D, Connoly S, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common and most heritable childhood-onset neuropsychiatric disorders, characterized by multifaceted genetics. To date, genetic studies of ADHD focused on additive effects only, explaining just a fraction of its heritability. In this study, we aimed at examining parent of origin and maternal effects together with the additive direct effects, providing novel insight into the complex genetic architecture of ADHD. Methods: We compiled parent-offspring data collected through the Psychiatric Genomics Consortium and the Norwegian Mother, Father and Child Cohort (MoBa), consisting of 2,060 trios and 328 duos. Additional parent-offspring data is being added from MoBa (approximately 514 trios and 725 duos). ADHD was diagnosed based on DSM-IV and child behavior checklist (CBCL). Parent of origin, maternal and additive genetic effects are being evaluated using multinomial modelling implemented in EMIM software. We explored our signals in the light of known imprinted genes (parent of origin effect) and the largest ADHD genome-wide association study (N = 55,374). Gene-based analyses are being performed using MAGMA software. Heritability estimates of the examined genetic effects are being calculated suing LD score regression.
Results: Our preliminary results indicate the presence of examined non-additive genetic effects in the development of ADHD. Several genes implicated by our top preliminary signals (e.g. rs6860868 in LOC105377733 gene, p = 1.07 +ù 10-7) are affiliated with the non-coding RNA (ncRNA), adding to the recent observations in neuropsychiatric genetics of gene regulation playing a pivotal role in the development of disorders of mental health.
Discussion: In conclusion, this is the largest parent-of-origin study in ADHD, exploring its non-additive genetic effects by detecting and distinguishing between direct and indirect genetic effects. As we increase the number of analysed samples, we will provide estimates of such effects as well as those of their heritability.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S167-S168.

M3 EPIGENOME.WIDE ASSOCIATION STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS.

Rovira P, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that persists into adulthood in 40-65% of cases. There is growing evidence that DNA methylation participates in ADHD and may be a candidate mediator linking environmental exposures with long-lasting behavioural alterations found in psychiatric disorders. Given that most of the previous epigenome-wide association studies (EWAS) on ADHD have been conducted in pediatric and population-based samples, we have undertaken the first EWAS in a clinical sample of adults with ADHD.
Methods: Genomic DNA was extracted from peripheral blood mononuclear cells of 103 ADHD patients and 102 controls and DNA methylation was assessed with the Illumina Infinium MethylationEPIC array. Each CpG site was tested individually in a linear regression model with normalized and batch-corrected beta values as the dependent variable and the ADHD status as independent predictor, adjusted by sex, age, cell type composition, smoking score and plate. Comb-p with Sidak correction was implemented to identify differentially methylated regions. We tested whether there was an enrichment for transcription factor binding sites (TFBS) and DNase I hypersensitive sites (DHS) from the ENCODE project in our top probes and also whether our EWAS results overlapped with results from previous GWAS on ADHD. The Trait Enrichment Analysis (TEA) online tool was used to calculate the co-occurrence probability between our top probes and

trait-related DNA methylation probes. Gene set enrichment analyses were conducted with the gsameth function of the missMethyl R package.
Results: We found two differentially methylated regions between patients and controls located in the DENND2D and UBASH3A genes and one differentially methylated CpG site, cg07143296, at the PCNXL3 gene. The top CpGs were located in genes involved in brain development and function, circadian rhythm and ADHD-related traits such as C1orf159, CREM, ADK and PBXIP1. When considering nominally associated CpGs (P<0.01), we found an enrichment of DHS (OR=1.68, p<2.20E-16) and a depletion of TFBS (OR=0.75, p=1.65E-09). Moreover, we found a nominally significant overlap between epigenetic and genetic signatures in ADHD (p=0.01) and a significant overlap between epigenetic marks in ADHD and several traits that have been previously related with the disorder, such as maternal smoking, child abuse, prenatal paracetamol exposure, smoking, obesity and alcohol consumption (p<2.66E-04). The gene set enrichment analysis revealed pathways significantly associated with ADHD (false discovery rate<0.05) mainly related to immune function.
Discussion: Taking into account that this is the first EWAS on ADHD performed to date identifying a CpG associated to ADHD, further analyses in larger sample sizes are still needed to elucidate the epigenetic mechanisms associated with ADHD.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S167.

M2 THE ROLE OF LOW FREQUENCY VARIANTS ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDERS.

Leppälä K, Als T, Grove J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neuropsychiatric condition that often persists into adulthood. The adult form of ADHD is associated with high rate of unemployment, incarceration, accidental death and suicide. The biology underlying ADHD as well as its genetic architecture is not fully understood. Several twin studies have estimated ADHD heritability to be 70% 80%, while the heritability estimated from the common SNPs varies between 10% 28%. The discrepancy in these estimates is often attributed, among other factors, to rare variants (MAF < 1%) as well as the polygenic nature or phenotypic heterogeneity of the condition. Autism spectrum disorders (ASD) is a developmental disorder characterized by problems in social interaction and restricted or narrow patterns of behavior and interests. It as well is associated with negative circumstances such as epilepsy, often intellectual disability and getting bullied, and commonly exists with other neuropsychiatric diagnoses. Twin study estimations for heritability of ASD vary between 64% 91%, while the common SNP heritability is mere 12%. This is thought to be because ASD so often coexists with rare monogenic or chromosomal conditions, and because ASD is known to exhibit phenotypic heterogeneity. According to the Centers for Disease Control and Prevention, about 14% of children diagnosed with ADHD also have ASD, and conversely ADHD is also common among children with ASD. Both conditions are several times more common among boys than girls. Furthermore, deleterious rare variants in PLI genes seem to be shared between the two conditions. Indeed, the contemporary view is to see them as interweaved. The genetic correlation between ADHD and ASD has been recently estimated at 29% 36%.
Methods: This study is based on the iPSYCH2012 sample consisting of all the Danes born between 1981 and 2005 and diagnosed with either ADHD, ASD, major depressive disorder, schizophrenia or bipolar disorder (about 57 000 individuals), as well as 30 000 randomly selected individuals. The participants were genotyped using a custom Illumina PsychChip that contains about 90 000 low frequency variants with 0.01% < MAF < 1%. We performed a strict quality control of the genotyped data and excluded variants with low genotyping rate or out of Hardy Weinberg equilibrium as well as individuals revealing low genotyping quality, high levels of relatedness or heterozygocity or non-European ancestry. Using genotyping waves, 10 principal components and sex as covariates, we performed genome-wide association analyses to assess the contribution of uncommon variants to ADHD and ASD and to the union of ADHD and ASD. The association was also tested using SKAT on the gene level by grouping the rare variants by (1) known genes, (2) their missense status within known genes (with and without MPC scores), (3) their loss of function status within

known genes (with and without PLI scores) and (4) known brain expressed genes. We shall compare the genetic factors associated with ADHD to those associated with ASD.
Results: We found a variant 2010-08-Y-1189 in the Y chromosome significantly associated with ADHD. We also found that the gene C10orf68 in the chromosome 10 has significantly more missense variation among ADHD cases than controls. The results about ASD and about the union of ADHD and ASD will be finished shortly.
Discussion: This study will contribute to the understanding of the disentangled genetics of ADHD and ASD, in the less studied range of low frequency variants.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S116-S117.
S5 INVESTIGATION OF SHARED GENETIC RISK BETWEEN CARDIOMETABOLIC MORBIDITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN A NORWEGION FAMILY COHORT USING POLYGENIC TRANSMISSION DISEQUILIBRIUM TEST.
Tesli M, Corfield E, Zayats T, et al.
Background: Large studies have found an increased mortality rate in individuals suffering from attention deficit hyperactivity disorder (ADHD) and a positive correlation between ADHD and cardiometabolic risk factors like body mass index (BMI). Recent molecular genetic studies have indicated shared genetic factors between cardiometabolic risk and ADHD. However, the underlying mechanisms of such genetic overlap are unknown and its previous investigations might be confounded by e.g. ancestral stratification and socioeconomic status. We aim to determine whether genetic risk for a range of cardiometabolic traits is over-transmitted to children suffering from ADHD. By using the recently developed polygenic transmission disequilibrium test (pTDT), our findings are less likely to be influenced by the aforementioned confounding factors.
Methods: Our target sample is a subset of the Norwegian Mother and Child cohort study (MoBa) consisting of 5,400 individuals in total, including 1,500 ADHD cases, their parents, and 1,500 controls matched with the cases on age, sex and region. As discovery samples for creating the polygenic risk scores (PGRS) we used summary statistics from the largest available independent genome-wide association studies (GWAS) of each cardiometabolic phenotype (e.g. BMI, smoking, cholesterol, triglycerides, coronary artery disease, stroke). In each trio, we compared the mid-parent (average for mother and father) PGRS with the PGRS in the ADHD child. These PGRS were also compared with those in the matched control children. To assess sex specificity, analyses were performed in the total sample as well as for males and females separately.
Results: Genotyping and pre-imputation quality control of the data has been performed. Imputation is ongoing. All steps are in accordance with the Picopili pipeline. The pTDT analyses will be performed this summer and ready for presentation in October.
Discussion: The investigation of shared genetics between cardiometabolic phenotypes and ADHD with the recently developed pTDT will enable us to avoid bias resulting from population structure. Thus, our results might be closer to the true genetic correlation between each cardiometabolic trait and ADHD and provide a better understanding of the causal mechanisms.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S222.
T5 THE USE OF PRS ANALYSIS TO VALIDATE THE PARTIAL ADHD SYNDROME.
Rovaris DL, Vitola ES, Bau CHD, et al.
Background: According to DSM-5, the diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) in adults requires the presence of a persistent and pervasive pattern of inattention and hyperactivity/impulsivity causing impairment in life, as well as the presence of several ADHD symptoms before the age of twelve (ADHD-FC, full criteria). However, it is also frequently observed another clinical presentation where patients

present a full syndrome in adulthood but lack a clear history of childhood symptoms (OS-ADHD-wao, without age-of-onset criterion).
Methods: The aim of this study is to test the convergent diagnostic validity for adults with OS-ADHD-wao. We calculated Polygenic Risk Scores (PRSs) in the Pelotas Birth Cohort (N = 3,574) with the intent to assess potential biological similarities between these two groups. The publicly available GWAS summary statistics file from the PGC-iPSYCH study (N = 55,374) was used to derive PRSs.
Results: There were no significant differences between ADHD-FC and OS-ADHD-wao for all P-values thresholds used for SNP selection (5e-08, 5e-06, 0.05, 0.5, and 1). This finding was corroborated by the lack of significant differences between the groups regarding environmental, neuropsychological profile, symptomatology, comorbidity, severity, as well as the factorial structure of symptoms.
Discussion: This is the first population-based study supporting convergent validity of the Other Specified ADHD in adults not endorsing symptoms before the age of twelve. Thus, epidemiological studies should consider the OS-ADHD-wao group as genuine cases of ADHD and count them in prevalence calculations differentiating them with the appropriate label. Besides, our results on the validation of the OS-ADHD-wao represent an essential step to operationalize the upcoming clinical trials testing the predictive validity for this diagnostic category.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S115.
S3 ADHD DIAGNOSTIC & GENETIC HETEROGENEITY IN THE IPSYCH CASE-COHORT STUDY.
LaBianca S, Brikell I, Helenius D, et al.
Background: Clinically, ADHD is a heterogeneous disorder. Patients present with a spectrum of symptoms and experience different courses of illness, varying in number and type of hospitalizations, medication use, co-morbidities and thus may be identified in national health registers under a variety of diagnostic codes and/or through treatment related variables. However, little is known about how this clinical heterogeneity is related to the underlying genetic architecture of ADHD.
Methods: The iPSYCH2012 case-cohort is a Danish population study that ascertained 60,000 psychiatric patients and 30,000 random population controls born between 1981 and 2005, using diagnoses recorded in the Danish national health registers and genotypes from neonatal bloodspots. Under the initial ascertainment, 18726 patients were labeled as ADHD based on the combined inattentive/hyperactive subtype diagnosis (ICD10: F90.0). In this study, we aggregated more than 30 additional variables summarizing the presentation of ADHD within all case and control subjects in the iPSYCH2012 study from the Danish Central Psychiatry Register (DCPR), the National Patient Registry (LPR), the Danish National Prescription Registry (DNPR). These variables include all ADHD subtype diagnoses; combined (ICD10: F90.0), hyperactive (ICD10: F90.1 F90.8 F90.9) and inattentive (ICD10:F98.8, incl. F98.8c), as well as medication use patterns, basic demographics, and information on comorbid diagnoses. Based on this aggregated definition, we identified a total of 19017 ADHD cases, that were taken in further analyses. To test for genetic heterogeneity within the ADHD case subgroups, we used GCTA-GREML to estimate the observed scale SNP-heritability in a selection of dichotomous summaries of these variables including first hospitalization with an ADHD diagnosis as an adult, ever and never medicated, multiple comorbid statuses and sex. We further asked if course of illness related variables, such as number of hospital contacts, number of prescriptions, number of comorbidities were heritable phenotypes within the case group.
Results: Our initial aggregation of variables derived from the Danish national health registers describes substantial phenotypic heterogeneity in ADHD. Our GCTA-GREML analyses revealed significant observed scale heritability in a selection of dichotomous features within ADHD cases including: first diagnoses as an adult, comorbid autism, comorbid affective disorder and comorbid addiction. Medication use was not significantly heritable in our analyses. For continuous traits, we estimated a significant observed scale SNP-heritability for two intensity variables; number of hospital contacts and number of co-morbidities, among the ADHD cases.
Discussion: In these analyses, we used a case-only SNP-heritability approach to suggest that phenotypic heterogeneity relating to the age of first ADHD hospitalization, comorbidity status, and number of hospital

contacts with ADHD reveal evidence of genetic heterogeneity within a large population-based ADHD patient cohort.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S220-S221.

T1 METHYLPHENIDATE'S KINETICS OF ELIMINATION IN CHILDREN WITH ADHD IN TWO DIFFERENT SCENARIOS OF NON-OCCUPATIONAL EXPOSURE TO ORGANOPHORUS PESTICIDES.

Alva R, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) has in Mexico an estimated prevalence of 8 to 12% in the pediatric population. First line pharmacology treatment is methylphenidate (MPH). In addition to this, children in rural areas have the problem of contamination by pesticides. Organophosphates pesticides are a type of pesticides used in agriculture that when in contact with the organism inhibit the action of esterases, including carboxylesterase 1. This enzyme is responsible for metabolizing MPH to its inactive metabolite which is excreted by urine. Exposure to this pesticide could mean a significant inhibition carboxylestarase 1 enzyme activity for the exposed population, which could modify the pharmacokinetic profile of MPH by decreasing its metabolism and consequently its elimination. At this moment, there are no studies that relate the effects of environmental contaminants such as pesticides on the pharmacokinetic profiles of drugs.
Methods: Two study populations were included, a group consisting of 6 children living in the agricultural city of Rioverde and another group of children from the capital of the state of San Luis Potos+¡. Participants were chosen for inclusion if they were in age between 6 and 15 years old, taking methylphenidate, and with TDAH diagnosis. Drug concentrations were quantified in urine samples. Five urine samples were collected at 2, 4, 6, 10 and 24 hours after the dose. The exposure to organophosphate pesticides is determinate by the presence of its non-specific metabolites known as dialkyl phosphates (DAPs). These compounds were measured in a composite sample made up of the first urine of the morning of 6 consecutive days. Drug and DAPs were measured using gas chromatography ΓÇô mass spectrometry (GC-MS).
Results: For MPH and RA in the non-exposed group t1/2ke mean was 4,5 h (+/-2,8) and 7,6 h (+/-3,2), respectively. Regarding the expose group, for MPH the t1/2Ke mean was 4,67 h (+/- 4,4) and for RA 4,7 (+/-2). For MPH Ku, t1/2ku and AURC_last were statistically significant, being Ku higher in non-exposed than in the ones exposed (p = 0,2) and therefore the t1/2ku lower in non-exposed and higher in exposed (p = 0,1). AURC_last was found significantly lower in non-exposed than in the group of children exposed. For the metabolic ratio, a tendency was found to be bigger in the group of children non-exposed than the ones exposed. RA showed no statistically significant difference between the groups
Discussion: No previous research comparing the effect of pesticides in pharmacokinetics profiles have been reported at the moment this work was done. Metabolic ratios are an indirect way to determinate carboxylesterase activity. This has been previously done to determinate the effect of polymorphisms in the gen that codifies for carboxylesterase 1 in the hydrolysis of methylphenidate (Stage et al 2019). They found that subjects with certain SNPs had lower median metabolic ratio, which indicate decreased activity of carboxylesterase 1. Similar to these findings we have found a tendency to have a bigger metabolic ratio in the children not exposed than in the ones living in places where they are exposed to pesticides, suggesting a decreased activity of the enzyme. Alterations in the carboxylestarase's activity have been related to side effects previously [Johnson et al 2013]. Our work isn't finish yet, more children are being invited to participate and further samples are going to be analyzed. Another statistics tests are going to be realized once the population is complete.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S13.

INVESTIGATION THE GENETIC ARCHITECTURE OF CHILD AND ADOLESCENT MENTAL DISORDERS AND THEIR MEDICAL COMORBIDITY.

Merikangas A, Kember R, Calkins M, et al.

Background: Mental disorders are a leading cause of disability worldwide. One of the major sources of disability is comorbidity among and between mental and medical conditions. Previous work on the Children's Hospital of Philadelphia (CHOP)/University of Pennsylvania Philadelphia Neurodevelopmental Cohort (PNC) has demonstrated pervasive comorbidity between medical and mental disorders in youth. Shared genetic etiology between some seemingly disparate disorders has been identified; establishing the genetic architecture underlying this comorbidity across development may provide insight into etiology and identify key pathways for treatment of both disorders.

Method: 5175 European-ancestry youth from the PNC, sampled from pediatric clinics in the greater Philadelphia area through CHOP were included in this study. The participants were ages 8 to 21 years and the sample was 51.7% female. Medical conditions were classified from interview data on 42 medical conditions of 14 organ systems/specialties. Mental disorders were assessed with an abbreviated Kiddie-Schedule for Affective Disorders and Schizophrenia. Genotyping was completed on Illumina SNP arrays. Polygenic Risk Scores (PRS) were calculated using PRSice2 software package and summary data from publicly available GWAS. Patterns of comorbidity across development were established with logistic regression, adjusted for the participant's age and sex. Models with PRS predicting the comorbid medical or mental disorder were also performed, adjusted for the participant's age and sex.

Results: Models adjusted for sociodemographic correlates revealed broad patterns of associations between medical and mental disorders: ear nose and throat disorders predicted psychosis symptoms. Central Nervous System disorders were associated with ADHD, behavior, and an overall rating of psychopathology. Developmental disorders were associated with ADHD, behavior disorders, psychosis symptoms, and overall psychopathology. The overall medical rating was associated with anxiety, ADHD, behavior disorders, mood disorders, and overall psychopathology. However, we did not find strong associations between PRS and disorders; the ADHD PRS predicted ADHD and behavior disorders, and the MDD PRS were associated with mood disorders, but no other mental PRS were associated psychopathology or medical disorders.

Discussion: To our knowledge, our study is the first to examine the genetic architecture underlying comorbid medical/mental conditions in a large diverse sample of children. Our findings show a strong overlap between medical and mental conditions and the specific patterns of comorbidity have important implications for etiology. However, this overlap is not well explained by psychopathology PRS predicting medical comorbidity. Prospective tracking of cross-disorder morbidity will be important to establish more effective mechanisms for prevention and intervention since the order of onset cannot be determined from these data.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S168-S169.

M6 USING PRS SCORES TO CLARIFY NOSOLOGICAL STRUCTURE OF ADHD AND OVERLAPPING EMOTION-RELATED TRAIT MEASURES.

Nigg J, Karalunas S, Gustafsson H, et al.

Background: A central controversy in ADHD nosology concerns the etiological relation of measures of emotion dysregulation with ADHD. One view (reflected in the DSM-5) holds that these are secondary features related to comorbid psychopathology particularly for mood disorder. An alternative view holds that these are central elements of the ADHD syndrome. Both irritability (anger dysregulation) and emotional dysregulation (encompassing both negative and positive valence responses) have been proposed. This question intersects with questions of heterogeneity in ADHD. Assessing the relationship between polygenic risk burden and measures of emotional dysregulation may clarify matters.

Methods: Participants were 514 community-recruited children of Northern European descent age 7-11 defined as ADHD or non-ADHD by detailed research evaluation. Parents rated ADHD on standardized ratings and child temperament on the Temperament in Middle Childhood Questionnaire (TMCQ) and reported on ADHD and comorbid disorders by semi-structured clinical interview. Categorical and dimensional variables were created for ADHD, emotional dysregulation (implicating disruption of regulation of both anger-

irritability and of positive valence surgency-sensation seeking), and irritability alone (anger dysregulation). Genome-wide polygenic risk scores (PRS) were computed for ADHD, depression, and bipolar disorder genetic liability, using the PGC data as the discovery set. Structural equation models examined ADHD and emotion traits simultaneously to isolate effects. Computationally derived emotion profiles were used to differentiate potential clinical subgroups for group analysis.
Results: The ADHD PRS was associated in variable centered analyses with irritability (+¦ =.179, 95% CI=.087-.280; Γêå$R2=.034, p <.0002), but also with surgency/sensation seeking (B=.146, 95%CI=.052-.240, Γêå$R2=.022, p=.002). In person-centered analysis, the ADHD PRS was elevated in the emotion dysregulation ADHD group versus other ADHD children (OR=1.44, 95% CI=1.03-2.20, Nagelkerke Γêå$R2=.013, p=.033) but did not differentiate irritable from Surgent ADHD profiles. All effects were independent of variation in ADHD severity across traits or groups. The depression PRS was related to oppositional defiant disorder but not to ADHD emotion dysregulation. The bipolar PRS was unrelated to these constructs.
Discussion: Irritability-Anger and Surgency-sensation-seeking, as forms of negative and positively valenced dysregulated affect in ADHD populations, both relate principally to ADHD genetic risk and not mood-related genetic risk. ADHD may be better conceptualized from a genetic perspective as a disorder of self-regulation that encompasses not just inattention but also emotional dysregulation in key domains. Results encourage integration of diagnostic categories with dimensional polygenic trait measures in clinical nosology.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S240.

T45 TRANSDIAGNOSTIC FAMILY HISTORY OF MENTAL ILLNESS, POLYGENIC RISK AND DEVELOPMENTAL PSYCHOPATHOLOGY LEADING TO SEVERE MENTAL ILLNESS.

Zwicker A, Fullerton J, De La Serna E, et al.

Background: Family history is the best-known predictor of mental illness. One out of every three offspring of a parent with a major depressive disorder, bipolar disorder, or schizophrenia will develop a major mood or psychotic disorder themselves by adulthood. The familial risk is partly diagnosis-specific and partly transdiagnostic. However, family history information is not always known in full and diminishing family sizes limit the predictive ability of complete family history information. The increasing predictive power of polygenic scores derived from genome-wide association studies may enable molecular genetic information to complement family history in predicting risk of mood and psychotic disorders among youth.
Methods: To examine the complementary predictive value of polygenic scores with family history information, we have formed the Developmental Psychopathology and Offspring of Affected Parents Consortium. We have combined prospective studies of youth including offspring of parents living with major mood and psychotic disorders. We have collected genotypes and prospective clinical assessment data from 1384 children and youth, including 517 offspring of parents with major depressive disorder, 486 offspring of parents with bipolar disorder, and 45 offspring of parents with schizophrenia. The majority of these participants have been followed up through ages 12 to 24 years. We have constructed polygenic scores indexing genetic predisposition to schizophrenia, bipolar disorder, major depressive disorder, attention-deficit/hyperactivity disorder, neuroticism, insomnia, and intelligence.
Results: Preliminary results show that psychopathology is more prevalent among offspring of affected parents than control offspring, including attention-deficit/hyperactivity disorder (18% vs. 6%), major depressive disorder (17% vs. 7%), or bipolar disorder (4% vs. 0.5%). We will present tests of whether polygenic scores, alone or in combination with environmental factors, improve the prediction of psychopathology over family history alone. Data analysis is underway and final results will be presented at the conference.

Discussion: Our combined analyses will allow for us to test the combined predictive value of polygenic scores, environmental factors, and family history of mood and psychotic disorders with adequate power. We will present the results in the framework of early identification of risk and indications for preventive interventions.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S102-S103.

76 GENETIC ARCHITECTURE OF PERSISTENT ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Rajagopal V, Grove J, Zayats T, et al .

Background: Approximately two third of the children with attention deficit/hyperactivity disorder (ADHD) continue to experience ADHD symptoms during adulthood and are diagnosed as having persistent ADHD. A recent meta-analysis has found no difference in the genetic architecture between childhood and adult ADHD. However, heterogeneity might exist in the adult ADHD group arising from individuals diagnosed only during adulthood (late diagnosed ADHD) and individuals diagnosed both during childhood and adulthood (persistent ADHD). Here we report a comprehensive analysis of the genetic architecture of childhood ADHD (diagnosed only in childhood), persistent ADHD (diagnosed both in childhood and adulthood) and late diagnosed ADHD (diagnosed only in adulthood) using both common variants and rare variants in the Danish iPSYCH cohort.
Methods: Danish Psychiatric Central Research Register contains the ICD-10 diagnoses of all inpatient and outpatient visits in the psychiatric hospitals in Denmark. We extracted the date of registration of ICD-10 code, F90, during the inpatient and outpatient visits of 20,026 individuals with ADHD in the Danish iPSYCH cohort. We defined three categories: individuals only before 18 years of age (childhood ADHD; N=9,241), individuals diagnosed only after 18 years of age (late diagnosed ADHD; N=3,594) and individuals diagnosed both before as well as after 18 years of age (persistent ADHD; N=1,217). All three groups were compared between each other as well as with controls (N=Γê+20,000) for differences in polygenic scores for ADHD, ADHD main dimensions (inattention and hyperactivity/impulsivity), educational attainment, intelligence, autism, schizophrenia, major depression and bipolar disorder. SNP heritability was calculated for all three groups separately with common controls using GCTA GREML analysis. Using exome sequencing data that are available for a subset of these individuals (total N=21,400), burden of deleterious ultra-rare variants (dURVs) in genes intolerant to loss of function mutations (pLI>0.90) will be quantified and compared between the three groups as well as with controls.
Results: Individuals with persistent ADHD were more often males compared to individuals with childhood (P=7.4e-23) or late diagnosed (P=0.0003) ADHD; also, comorbidity with at least two other psychiatric disorders was higher for persistent ADHD compared to childhood (P=1.6e-14) or late diagnosed ADHD (P=0.001). Differences in the polygenic scores between persistent, childhood and late diagnosed ADHD were only moderate with regard to all phenotypes analyzed. However, when benchmarked against controls, the variance explained and the odds ratios from quintile analyses were consistently stronger for persistent ADHD than for childhood or late diagnosed ADHD. GREML analysis showed substantial heritability estimates for all three groups (persistent: h2=0.22; SE=0.04; late diagnosed: h2=0.24; SE=0.01, childhood: h2=0.17; SE=0.01). We will present the results from dURVs burden analysis.
Discussion: Phenotype presentation suggests that persistent ADHD is more severe than other groups, which is also in line with past epidemiological and clinical studies. Preliminary analysis suggests that persistent ADHD may have a higher load of common risk variants than childhood and late diagnosed ADHD. The results together suggest that the genetic architectures of childhood ADHD, persistent ADHD and late diagnosed ADHD may differ with respect to common variants.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S108-S109.

88 RESULTS: FROM THE FIRST GWAS OF NOCTURNAL ENURESIS AND ASSESSMENT OF THE GENETIC OVERLAP WITH PSYCHIATRIC DISORDERS.

Jorgensen CS, Horsdal HT, Rajagopal V, et al.

Background: Nocturnal enuresis (NE) also known as bedwetting is a common disorder affecting more than 10-15% of all 6-year-old children and 1-2% of young adults. NE is a difficult-to treat condition that heavily influences the functioning and well-being of the child/young and severe comorbidities are common. As many as 20-30% of NE cases suffer from psychiatric disorders - especially ADHD and ASD. NE is highly heritable with twin-based heritability estimates close to 70%. Common genetic variants may play a substantial role in NE risk, but this has never been evaluated in large hypotheses free case-control studies. Here, we present the results from the first GWAS of NE and the assessment of the evidence for shared genetic risk with ADHD and ASD using polygenic risk score analyses. The study is based in iPSYCH2012 which is a large population-based case-cohort sample established to investigate major psychiatric disorders in the Danish population.
Methods: Genotyped individuals in iPSYCH2012 included approximately 50,000 individuals with schizophrenia, ADHD, ASD, anorexia nervosa and affective disorder and approximately 25,000 randomly selected individuals. Individuals within iPSYCH2012 with NE (5-25 years of age) were identified either by information from the The Danish National Patient Register and The Danish Psychiatric Central Register on ICD10 diagnosis codes, or by information from the The Danish Register for Medicament Statistics on desmopressin prescriptions. In total, 496,370 SNPs were analyzed in 3,882 NE cases and 31,073 controls. Analyses were conducted in R, PLINK, Stata, and GCTA.
Results: We identified 6 variants surpassing the threshold for genome-wide significance (P<5 +ù 10-8) in two loci on chromosomes 6q16.2 and 13q22.3. Positional, cis-eQTL and chromatin interaction gene mapping based in the NE associated variants and their LD friends (r2-0.6) identified 12 protein coding candidate NE risk genes (PRDM13, PNISR, FAXC, COQ3, CCNC, SIM1, SLAIN1, EDNRB, POU4F1, RNF219, and RBM26). Their role will be discussed at the meeting. Assuming a population prevalence of NE between 7-15%, GREML analyses gave liability-scale SNP heritability estimates ranging from 0.239 (SE=0.031) to 0.304 (SE=0.039) (P=2.22 10-16). When omitting individuals with psychiatric diagnoses from the association analysis, we found the same direction of the NE odds ratios (ORs) for all 6 risk variants and for all risk variants in the chromosome 6 locus, NE ORs were consistently higher. We further found the same direction of the NE ORs for all risk variants when evaluated in an independent European sample counting 1,643 NE cases and the deCODE population-based controls. Standardized polygenic risk scores (PRSs) for ADHD, calculated based on summary statistics from a combined iPSYCH-PGC sample with five different sets of target and training samples, demonstrated significant positive association with risk of NE without comorbid ADHD (z-score=2.55, P=0.0108) whereas equivalent PRSs for ASD did not associate with risk of NE without comorbid ASD (z-score=1.50, P=0.1343).
Discussion: Although sample sizes are modest in the present study, we have identified the first ever genome-wide significant loci in NE, estimated the SNP heritability and provided evidence for shared genetic risk with ADHD. This was only possible because we were able to identify NE cases in iPSYCH2012 not only based in information about diagnoses from hospital records but also by using register-based information on redeemed desmopressin prescriptions.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S69.

19 THE EFFECTS OF POLYGENIC RISK FOR NEUROPSYCHIATRIC DISORDERS ARE PARTIALLY MEDIATED BY STRUCTURAL AND FUNCTIONAL NEUROIMAGING PHENOTIPES.

Thompson W, Fan C.

Background: Twin and genome wide association studies in adults have revealed that neuropsychiatric phenotypes are highly heritable, and that brain imaging phenotypes are moderately heritable. We aimed to determine if the relationship between common genetic variation and neuropsychiatric outcomes is mediated by multi-modal brain imaging in the context of the developing brain. Specifically, we questioned if neuropsychiatric polygenic scores derived from a large GWAS significantly predicted variation in prodromal

symptoms, and if these were mediated by differences in cortical brain morphology and functional activation measured using MRI scans.
Methods: We utilized emerging data from the landmark Adolescent Brain Cognitive Development (ABCD) study. The ABCD study (http://abcdstudy.org) consists of N=11,878 individuals aged 9/10 years old at baseline. This longitudinal study was designed to follow the development of children at 21 sites across the US for ten years. The cohort exhibits a large degree of socio-economic and demographic diversity. Here, we utilized baseline data from ABCD release 2.0 (DOI: 10.15154/1503209). A wide range of measurements were collected for each individual. In addition to demographic and socio-economic variables, for the current study we utilized three data sources: 1) whole-genome genotyping data from the Smokescreen array, 2) structural and functional magnetic resonance imaging, and 3) parent and child psychopathology-related data from validated instruments (e.g., the Child Behavior Checklist, KSADS). After imputation, polygenic scores for neuropsychiatric outcomes, personality traits, and intelligence/educational attainment were obtained on a sample of >10,000 children. The psychopathology variables were input into a group factor analyses (GFA), from which scores were obtained as dependent variables. Mediation analyses were performed used mixed models (for nesting within family), with multi-modal imaging measures (cortical and subcortical morphometry, resting state networks, and event-related MRI) as mediating variables.
Results: GFA produced replicable factors from psychopathology-related variables, the first two roughly corresponding to "p-factors" (one child assessed, the other parental). A third factor corresponds to externalizing vs. internalizing symptoms. Polygenic scores for schizophrenia, ADHD, educational attainment, and personality traits were highly-significantly related to factor scores in differing patterns, with strongest associations seen in the child-reported p-factor. Both structural and functional brain imaging measures partially mediated the relationship between polygenic scores and GFA factors, accounting for between 5-10% of the relationship in most associations, after accounting for demographic covariates and genetic ancestry.
Discussion: While many large-scale studies of neuropsychiatric outcomes have shown significant associations with polygenic scores, the brain mechanisms through which these effects are mediated are substantially unknown. These results demonstrate that common polygenic variation associated with neuropsychiatric outcomes is partially mediated by brain imaging in a population sample of 10,000 9/10-year-old children. These results set the stage for developmental analyses of longitudinal imaging as these children progress through adolescence and early adulthood.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S70-S71.

22 CANONICAL CORRELATION ANALYSIS OF ADHD POLYGENIC RISK AND FUNCTIONAL BRAIN CONNECTIVITY.

Mooney M, Hermosillo R, Bhatt P, et al.

Background: Recent large-scale GWAS meta-analyses and follow-up studies have demonstrated the association of polygenic risk burden with ADHD and other intermediate phenotypes (e.g. executive function). However, determining functional mechanisms from polygenic risk scores (PRS) remains a significant challenge. Functional connectivity MRI, along with partitioning the PRS into components (e.g. gene sets) with known functions, may assist with such a problem. The current study uses a multivariate method (sparse CCA) to associate functionally related ADHD PRSs with the functional connectome across a large well-characterized ADHD dataset.
Methods: Genotypes and resting-state functional MRI data were measured for 315 children (196 ADHD cases, and 119 controls) of northern European ancestry, ages 7 to 15. A genome-wide PRS for ADHD was calculated for each subject, based on results from the recent PGC ADHD GWAS meta-analysis. This PRS was then partitioned into 99 separate sub-scores, which represent biological pathways or processes hypothesized to play a role in ADHD (e.g. ion transport, neuron development, immunity-related genes), as well as gene sets based on gene expression patterns in the brain. Instead of using all ADHD-associated variants across the genome, only those mapped to each gene set were used to calculate 99 separate sub-PRSs. Redundant gene sets those scores highly correlated (r>0.8) with another were removed, resulting in a total of 94 gene sets in the final analysis. A parcellated brain connectivity matrix from 353 ROIs, was reduced to 13 brain networks using established methods. Brain connectivity was summarized as the first

principal component of: (1) connectivity measures between all ROIs within each of the 13 networks (within-network connectivity measures; N=13), or (2) connectivity measures between all pairs of networks (between-network connectivity measures; N=78). Sparse canonical correlation analysis, implemented with the nscancor package in R, was used to investigate the relationship between the 91 summarized brain connectivity measures and the 94 sub-PRSs. Multiple testing corrected, statistically significant association between genetic and imaging measures was determined by comparison to a null distribution of correlation measures created by repeatedly permuting subjects.
Results: Canonical variates representing polygenic risk for ADHD and within-module functional connectivity were correlated (r=0.66, permutation p=0.049). The networks contributing most to the connectivity variate were the retrosplenial cortex and salience network, while gene sets related to autophagy, response to oxidative stress, and neuron projection development contributed most to the genetic variate. The genetic variate explained 16.3% of the variance of retrosplenial connectivity (p=5.4e-14), and the connectivity variate explained 4.6% of the variance in the autophagy-related ADHD sub-PRS (p=7.3e-5).
Discussion: Our study demonstrates the potential for integrating high-dimensional genomic and brain imaging data to generate hypotheses about the mechanisms of ADHD polygenic risk. Results suggest that genetic risk factors affecting cellular homeostasis, early neuron synaptogenesis, and importantly, dendritic pruning may influence network-specific functional connectivity patterns.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S15.

POLYGENIC ANALYSES OF CHILDHOOD PSYCHOPATHOLOGY IN LARGE POPULATION BASED SAMPLES PROVIDE INSIGHT INTO PERSISTENCE OF SYMPTOMS AND THE EFFECTS OF THE (EARLY) ENVIRONMENT.

Middeldorp CCM, Sallis C-C, Thapar DA.

Overall Abstract: The CAPICE project "Childhood and Adolescence Psychopathology: unravelling the complex etiology by a large Interdisciplinary Collaboration in Europe" focuses on the role of genetic factors, and their interplay with the environment, in the development of childhood psychopathology. The consortium brings together some of the largest birth, childhood and adolescent cohorts with repeated measures of childhood psychiatric symptoms as well as environmental circumstances, i.e., the Avon Longitudinal Study of Parents and children (ALSPAC), Child and Adolescent Twin Study in Sweden (CATSS), Generation R, Norwegian Mother and Child Cohort (MoBA), Netherlands Twin Register (NTR), Northern Finnish Birth Cohort (NFBC) and the Twins Early Development Study (TEDS). In this symposium we will present the results of different types of polygenic analyses to investigate the persistence of psychiatric symptoms from childhood psychopathology into adulthood as well as the mechanisms underlying the association with the parental or prenatal environment. The first presentation will show whether polygenic risk scores (PRS) based on genome-wide association analyses of adult psychiatric disorders and related traits (e.g., wellbeing or educational attainment) are associated with measures of internalizing, ADHD and social problems in childhood and adolescence. Data are used from the whole consortium resulting in a maximum sample size of over 30,000 subjects. In addition, the results will show whether the associations depend on age or type of childhood psychopathology. The next presentation will also use PRS based on GWA of adult psychiatric disorders and related traits but will include the interplay with environmental factors such as life events, home environment, and socio-economic status. A machine learning approach is used to analyze the prediction of behavioural, psychopathological and anthropometric measures, at ages 16 and 21. The third speaker will present the results of polygenic analyses using both parental as well as offspring genotypes, such as m-GCTA, indicating whether, in addition to the role of genetic factors, there is also a direct environmental effect underlying the association between childhood psychopathology and the parental environment, including parental depressive problems. The fourth presentation focuses on explaining whether the association between prenatal risk factors such as maternal smoking and alcohol use with childhood outcomes is due to a direct causal effect or whether the association is explained by genetic factors influencing both the substance use as well as the childhood psychopathology. This will be tested with phenome-wide association

analyses. This symposium will show how polygenic analyses in population-based cohorts can further our knowledge into mechanisms explaining associations between childhood psychopathology, adult traits and the environment.
Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S242.
T48 LARGE-SCALE EWAS AND METHYLATION QTL ANALYSIS IN ADHD.
Mooney M, Ryabinin P, Bhatt P, et al.
Background: Increasing evidence supports a role for regulatory genomic variation in the etiology of neuropsychiatric traits. Variation in DNA methylation, a key epigenetic process regulating gene expression, represents both a potential clue to functional mechanisms and a possible source of biomarker discovery. Because DNA methylation can be influenced by both genetic and environmental exposures, it represents a promising mechanistic hypothesis for susceptibility to complex disorders, like ADHD. Several environmental risk factors associated with ADHD have been associated with DNA methylation. At the same time, there is evidence that disease-associated methylation levels are genetically influenced. Here we report the first large-scale EWAS of a clinically-defined childhood ADHD case-control sample, and extend our previous research to incorporate analyses of genetic effects (mQTL and polygenic risk burden).
Methods: SNP genotypes and DNA methylation were measured genome-wide in saliva samples from 604 children recruited for a case-control study of ADHD (391 ADHD, 213 controls). An epigenome-wide association study (EWAS) was conducted to identify differentially methylated positions (DMPs) associated with ADHD and ADHD polygenic risk (PRS). DMPs were identified by regressing cell-type corrected methylation levels on ADHD status (or ADHD PRS), accounting for age, sex, smoking exposure, medication history, and the first three genomic principal components. Interactions with sex of child were also considered. Genetically-controlled methylation sites were investigated to determine whether mQTLs discovered in our cohort colocalize with ADHD-associated variants. All pairs of methylation probes and SNPs within each of 12 ADHD-associated regions, determined from results of the recent PGC ADHD GWAS meta-analysis, were evaluated. Statistical analyses were performed using summary data-based Mendelian randomization (SMR), as well as the Bayesian colocalization method in the coloc package in R.
Results: We observed a significant association between the ADHD PRS and DNA methylation at a site annotated to the promoter of the GART and SON genes ($p = 6.71E-8$). Seven probes were suggestively ($p<1e-5$) associated with ADHD, with the top-ranked probe annotated to MARK2. Sex-specific effects were confirmed for DMPs annotated to VIPR2 (sex-by-diagnosis interaction $p = 7.51e-6$), with male ADHD cases showing lower methylation levels than male controls. An additional 14 methylation probes show suggestive sex-by-diagnosis or sex-by-PRS interaction effects. Eleven of the 12 ADHD-associated regions contained cis-mQTLs with a p-value<1e-13. Evidence for colocalization/pleiotropy was found for variants in 5 of the 12 ADHD-associated regions, and for two of the regions, 12q21.33 and 15q21.1, both the SMR and coloc methods identify the same causal SNPs (rs2279574, SMR $p = 2.3e-8$, coloc posterior prob. = 0.98; and rs1656622, SMR $p = 3.6e-5$, coloc posterior prob. = 0.82).
Discussion: While disease-associated DNA methylation differences were small, genetic effects were stronger and our results point to regulation of DNA methylation as a mechanism for ADHD genetic risk factors. We found a significant DMP associated with ADHD polygenic risk burden. In addition, not only do we observe significant methylation QTLs in the same regions as ADHD-associated variants, but several variants appear to be pleiotropic or causal for ADHD susceptibility and therefore merit further study. Disclosure: Nothing to disclose

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Expert Review of Clinical Pharmacology. 2019;12:965-71.

AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Chow H.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder known to respond to amphetamine (AMPH). Multiple AMPH formulations have been developed during the past two decades and have focused mainly on extending the duration of effect. AMPH extended-release oral suspension, Dyanavel XR, (AMPH EROS) was developed to address the unmet needs of patients who have difficulty swallowing intact extended-release (ER) tablets and capsules.

Areas covered: The pharmacokinetic profile of the AMPH EROS in children and adults is discussed along with the technology responsible for its release profile. Efficacy data from two clinical trials are presented and AMPH EROS is compared with other marketed AMPH ER formulations in the United States. Expert opinion: Multiple AMPH ER formulations that do not require ingestion of an intact tablet or capsule have been developed. Initial products allowed for sprinkling or dissolving of capsule contents. Recently, oral disintegrating tablets, chewable tablets, and oral suspensions have been marketed. Each formulation has positive attributes. Tablets may be more portable. However, as a suspension, AMPH EROS dosing can differ depending on daily requirements. Dose can also be titrated with a single prescription. Despite its convenience, AMPH EROS is a branded product, so price may be prohibitive for some patients

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Frontiers in Genetics. 2019;10.

THE IMPLICATED ROLES OF CELL ADHESION MOLECULE 1 (CADM1) GENE AND ALTERED PREFRONTAL NEURONAL ACTIVITY IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: A GENE BRAIN-BEHAVIOR RELATIONSHIP?

Jin J, Liu L, Chen W, et al.

Background: Genes related to cell adhesion pathway have been implicated in the genetic architecture of attention-deficit/hyperactivity disorder (ADHD). Cell adhesion molecule 1, encoded by CADM1 gene, is a protein which facilitates cell adhesion, highly expressed in the human prefrontal lobe. This study aimed to evaluate the association of CADM1 genotype with ADHD, executive function, and regional brain functions.

Methods: The genotype data of 10-tag single nucleotide polymorphisms of CADM1 for 1,040 children and adolescents with ADHD and 963 controls were used for case-control association analyses. Stroop color word interference test, Rey Osterrieth complex figure test, and trail making test were conducted to assess inhibition, working memory, and set-shifting, respectively. A subsample (35 ADHD versus 56 controls) participated in the nested imaging genetic study. Resting-state functional magnetic resonance images were acquired, and the mean amplitude of low-frequency fluctuations (mALFF) were captured.

Results: Nominal significant genotypic effect of rs10891819 in ADHD-alone subgroup was detected (P = 0.008) with TT genotype as protective. The results did not survive multiple testing correction. No direct genetic effect was found for performance on executive function tasks. In the imaging genetic study for the ADHD-whole sample, rs10891819 genotype was significantly associated with altered mALFF in the right superior frontal gyrus (rSFG, peak t = 3.85, corrected P < 0.05). Specifically, the mALFFs in T-allele carriers were consistently higher than GG carriers in ADHD and control groups. Endophenotypic correlation analyses indicated a significant negative correlation between word interference time in Stroop (shorter word interference time indexing better inhibitory function) and mALFF in the rSFG (r =-0.29, P = 0.006). Finally, mediation analysis confirmed significant indirect effects from ΓÇ£rs10891819 genotype (T-allele carriers) via mALFF (rSFG) to inhibition (word interference time) (Sobelz =-2.47; B =-2.61, 95% confidence interval-0.48 to-4.72; P = 0.009).

Conclusions: Our study offered preliminary evidence to implicate the roles of CADM1 in relation to prefrontal brain activities, inhibition function, and ADHD, indicating a potential gene brain behavior relationship of the CADM1 gene. Future studies with larger samples may specifically test these hypotheses generated by our exploratory findings

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Front Integr Neurosci. 2019 Sep;13.

SENSORY OVER-RESPONSIVITY AS AN ADDED DIMENSION IN ADHD.

Lane SJ, Reynolds S.

Years of research have added to our understanding of Attention Deficit Hyperactivity Disorder (ADHD). None-the-less there is still much that is poorly understood. There is a need for, and ongoing interest in, developing a deeper understanding of this disorder to optimally identify risk and better inform treatment. Here, we present a compilation of findings examining ADHD both behaviorally and using neurophysiologic markers. Drawing on early work of McIntosh and co-investigators, we examined response to sensory challenge in children with ADHD, measuring HPA activity and electrodermal response (EDR) secondary to sensory stressors. In addition, we have examined the relationship between these physiologic measures, and reports of behavioral sensory over-responsivity and anxiety. Findings suggest that sensory responsivity differentiates among children with ADHD and warrants consideration. We link these findings with research conducted both prior to and after our own work and emphasize that there a growing knowledge supporting a relationship between ADHD and sensory over-responsivity, but more research is needed. Given the call from the National Institute of Health to move toward a more dimensional diagnostic process for mental health concerns, and away from the more routine categorical diagnostic process, we suggest sensory over-responsivity as a dimension in the diagnostic process for children with ADHD. (PsycINFO Database Record (c) 2019 APA, all rights reserved)

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Front Psychiatry. 2019;10.

NEURODEVELOPMENTAL DISORDERS AND ADAPTIVE FUNCTIONS: A STUDY OF CHILDREN WITH AUTISM SPECTRUM DISORDERS (ASD) AND/OR ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD).

Scandurra V, Emberti GL, Barbanera F, et al.

Introduction: Autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD) are the two most common neurodevelopmental disorders observed in childhood. The DSM-5 accepts a combined diagnosis of ADHD and ASD, while the DSM-IV did not. The aim of this study was to identify and evaluate the adaptive profile of children and adolescents with a diagnosis of comorbid ADHD and ASD, in comparison with adaptive functioning in subjects with a diagnosis of only ASD or ADHD. Materials and Methods: Ninety-one children (77 boys, 14 girls), aging from 3.1 to 13.4 years (mean age: 8.3 ± 7.2), who met the criteria for a diagnosis of ASD and/or ADHD were enrolled. A neuropsychological evaluation involving cognitive and adaptive assessment was conducted using the Autism Diagnostic Observation Schedule - Second Edition (ADOS-2), the Conners' Parent Rating Scale - Revised: Long Version (CPRS-R), the Wechsler Intelligence Scale - Fourth Edition or the Griffiths Mental Developmental Scales - Extended Revised, the Vineland Adaptive Behaviour Scale - Second Edition (VABS-II).

Conclusion: As to the adaptive skills in the three groups evaluated, a worse general profile was ascertained in the ASD and in ASD plus ADHD groups in comparison with respect to the ADHD-only group. With VABS-II evaluation, we found significant differences among the three groups across all domains and combined scores: Communication ($F = 18.960$; $p < 0.001$), Socialization ($F = 25.410$; $p < 0.001$), Daily Living Skills ($F = 19.760$; $p < 0.001$), Motor ($F = 9.615$; $p < 0.001$), and Adaptive behavior composite [ABC] ($F = 29.370$; $p < 0.001$). Implications of neurodevelopmental double diagnosis such as ASD plus ADHD are discussed

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Front Psychiatry. 2019;10.

THE ASSOCIATION OF NON-OBSCENE SOCIALLY INAPPROPRIATE BEHAVIOR WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS, CONDUCT PROBLEMS, AND RISKY DECISION MAKING IN A LARGE SAMPLE OF ADOLESCENTS.

Brandt V, Kerner auch KJ, Palmer-Cooper E.

Non-obscene socially inappropriate behavior (NOSI) is recognized as part of the tic disorder spectrum but has received little attention from researchers to date. A study in 87 patients with Tourette syndrome showed that comorbid attention-deficit/hyperactivity disorder (ADHD) and conduct disorder were also associated with an increase in socially inappropriate behavior. This study used data from the Millennium Cohort Study to

investigate the relationship between NOSI and emotional symptoms, conduct problems, and hyperactivity/inattention as assessed by the Strengths and Difficulties Questionnaire (SDQ) in 1,280 youths, aged 14 years. Furthermore, the relationship between NOSI and decision-making processes as assessed by the Cambridge Gambling Task (CGT) was investigated. Hyperactivity/inattention and conduct problems were significantly associated with NOSI; emotional problems were not. Risk taking was significantly associated with misbehaving in lessons but not with being rude or noisy in public. The results replicate and confirm the association of NOSI with ADHD and conduct problems in a large sample, although it should be stressed that the size of the association was small. The results also suggest that some inappropriate behaviors are related to risk-taking behavior, while others are not

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Front Psychiatry. 2019;10.

INCONSISTENCY IN ABNORMAL FUNCTIONAL CONNECTIVITY ACROSS DATASETS OF ADHD-200 IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zhou Z-W, Fang Y-T, Lan X-Q, et al.

Many studies have shown abnormal functional connectivity in children with attention deficit hyperactivity disorder (ADHD) by using resting-state functional magnetic resonance imaging (rs-fMRI). However, few studies illustrated that to what extent these findings were consistent across different datasets. The present study aimed to assess the consistency of abnormal functional connectivity in children with ADHD across the four datasets from a public-assess rs-fMRI ADHD cohort, namely, ADHD-200. We employed the identical analysis process of previous studies and examined a few factors, including connectivity with the seed regions of the bilateral dorsal anterior cingulate cortex, bilateral inferior frontal gyrus, and bilateral middle frontal gyrus; connectivity between default mode network and executive control network; stringent and lenient statistical thresholds; and the ADHD subtypes. Our results revealed a high inconsistency of abnormal seed-based connectivity in children with ADHD across all datasets, even across three datasets from the same research site. This inconsistency could also be observed with a lenient statistical threshold. Besides, each dataset did not show abnormal connectivity between default mode network and executive control network for ADHD, albeit this abnormal connectivity between networks was intensively reported in previous studies. Importantly, the ADHD combined subtype showed greater consistency than did the inattention subtype. These findings provided methodological insights into the studies on spontaneous brain activity of ADHD, and the ADHD subtypes deserve more attention in future studies

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Front Psychiatry. 2019;10.

SEX DIFFERENCES IN SOCIAL ADAPTIVE FUNCTION IN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Mahendiran T, Dupuis A, Crosbie J, et al.

Background: Social-communication difficulties, a hallmark of ASD, autism spectrum disorder (ASD) are often observed in attention deficit/ hyperactivity disorder (ADHD), although are not part of its diagnostic criteria. Despite sex differences in the prevalence of ASD and ADHD, research examining how sex differences manifest in social and communication functions in these disorders remains limited, and findings are mixed. This study investigated potential sex differences with age in social adaptive function across these disorders, relative to controls.

Method: One hundred fifteen youth with ASD, 172 youth with ADHD, and 63 typically developing controls (age range 7ΓÇô13 years, 75% males) were recruited from the Province of Ontario Neurodevelopmental Disorder (POND) Network. Social adaptive function was assessed using the Adaptive Behavior Assessment System-Second Edition (ABAS-II). The proportions of adaptive behaviors present in each skill area were analyzed as a binomial outcome using logistic regression, controlling for age, and testing for an age-by-sex interaction. In an exploratory analysis, we examined the impact of controlling for core symptom severity on the sex effect.

Results: Significant sex-by-age interactions were seen within ASD in the communication ($p = 0.005$), leisure ($p = 0.003$), and social skill areas ($p < 0.0001$). In all three areas, lower scores (indicating poorer function) were found in females compared to males at older ages despite females performing better at younger ages. There were significant differences in the sex-by-age interactions in the social and leisure domains between those with ASD and typically developing controls, with typically developing females showing better scores at older, compared to younger, ages. There were also significant differences in the sex-by-age interactions between ASD and ADHD on the social and leisure domains, as females with ADHD consistently scored higher on social skills than males across all ages, unlike those with ASD. Sex differences across age in the social domains for ADHD were similar to those in the typically developing group.
Conclusion: Sex differences in social and communication skill areas were observed between ASD and ADHD, and typically developing controls, with females with ASD performing worse than males at older ages, despite an earlier advantage. These findings reinforce the need to take a developmental approach to understanding sex differences which may have diagnostic, prognostic, and treatment implications

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Indian Journal of Public Health Research and Development. 2019;10:1497-502.
THE INFLUENCE OF LEAD (PB), ZINC (ZN), RATIO LEAD (PB) TO ZINC (ZN) IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).
Setiawati Y, Mukono HJ, Wahyuhadi J, et al .
Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood psychiatric disorder often encountered in clinical practice with major symptoms of inattention, hyperactivity, and impulsivity. Pollution of lead (Pb) is thought to be cause of ADHD that affects the cognitive deficit of the brain. Zinc supplementation (Zn) can improve the symptoms of ADHD by increasing dopamine transporters binding. The aims of this study is to compare the level of Pb and Pb to Zn ratio on the subject of ADHD and normal children.
Method: This is an observational analytic study with case control design on 44 respondents. Statistical analysis using non-parametric test Man Witney.
Result: There is no significant difference of Pb level in children with ADHD and normal children with $p = 0,431$ and there is a significant difference of Zn level in ADHD and normal children with $p = 0,011$ and significant difference in Pb to Zn ratio with $p = 0,015$

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Indian Journal of Public Health Research and Development. 2019;10:716-21.
MINDFULNESS TRAINING FOR ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Mahesh MM, Vinod KS.
Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood psychological disorders which are characterized by hyperactive/impulsive and inattentive symptoms1.Mindfulness training is one of the emerging intervention programs for the treatment of ADHD. Current study aimed at examining the influence of mindfulness training on ADHD. 10 adolescents were recruited based on inclusion and exclusion criteria using purposive sampling method. The study included experimental single group Pre-Post design and intervention was based on mindfulness training consisting of 10 sessions. The participants were assessed with ADHD Rating Scale-V, at before and after the intervention. Descriptive statistics and Wilcoxon signed ranks test were used. Significant reduction in ADHD symptoms was observed after the intervention

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Int J Pediatr Otorhinolaryngol. 2019 Aug;123:10-14.

VARIABLES ASSOCIATED WITH PEDIATRIC EMERGENCY DEPARTMENT VISITS FOR UNCONTROLLED PAIN IN POSTOPERATIVE ADENOTONSILLECTOMY PATIENTS.

Lavin J, Lehmann D, Silva AL, et al.

OBJECTIVE: Returns to the emergency department (ED) for pain or dehydration after adenotonsillectomy (T&A) are frequent. Attempts to associate the specific pain regimens with these visits have been unrevealing, suggesting a need to assess for other potential factors associated with readmission.

METHODS: A review of a 2:1 cohort matched by age, gender and payer status compared post-T&A patients who did not return ED for pain or dehydration within 21 days to those who returned. Factors investigated included patient demographics, comorbidities, medication regimen and the presence of postoperative telephone encounters. Patients returning to the ED were further assessed for rates of medication adherence.

RESULTS: 7493 patients underwent T&A during the period. Of these, 144 (1.9%) returned for pain/dehydration. Comparison to 285 matched patients revealed an association between ED returns and Hispanic ethnicity ($p<0.001$), Spanish language ($p=0.0002$), and comorbid Down syndrome and ADHD ($p=0.011$ in both). The incidence of parent telephone calls to the office was associated with ED returns (58.7 in the ED cohort, 28.4% in non-ED cohort, $p<0.0001$). On multivariable analysis, Hispanic ethnicity and phone calls were associated with ED returns ($p<0.0001$ and $p<0.0001$, respectively). Only 64.0% of patients returning to the ED were adherent with postoperative pain regimens.

CONCLUSIONS: While demographic factors may be associated with rate of ED returns for pain and dehydration, post-operative phone calls were most highly associated with returns. The majority of patients returning to the ED were non-adherent with recommended pain regimens, suggesting an opportunity to investigate medication adherence in all post-tonsillectomy patients

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Int J Dev Neurosci. 2019;79:32-36.

DEGREE CENTRALITY OF KEY BRAIN REGIONS OF ATTENTION NETWORKS IN CHILDREN WITH PRIMARY NOCTURNAL ENURESIS: A RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY.

Jiang K, Yi Y, Ding L, et al.

Primary nocturnal enuresis (PNE) is always associated with attention impairment, some of which even could develop to attention deficit hyperactivity disorder. The mechanism of attention impairment is not clear, especially lacking of objective indicators of neuroimaging. The aim of this study is to explore the possible functional imaging mechanism of impaired attention in PNE children. A total of 26 PNE children and 26 age-matched normal controls were recruited. Resting-state functional magnetic resonance imaging (rs-fMRI) was performed on these children. Degree centrality (DC) of key brain regions of DAN (lFEF, rFEF, lIFG, rIFG, lIPS, rIPS), VAN (TPJ, VFC) and DMN (PCC, aMPFC, lAG, rAG) were calculated and compared between PNE and normal children. And the correlations between DC values and attention behavioral results were measured. Compared with normal controls, PNE children exhibited lower DC value in the right frontal eye field (rFEF), left inferior parietal sulcus (lIPS), right inferior parietal sulcus (rIPS), temporal parietal junction (TPJ) and left angular gyrus (lAG). The correct number of continuous performance test (CPT) in the PNE group was significantly lower than the normal controls and there was no significant difference in the reaction time between the two groups. The correlation between DC values and attention behavioral results in PNE showed that the DC values of PCC and lAG were negatively correlated with the correct number. This work indicates that the damage of the key brain regions of DAN, VAN and DMN might be the possible functional imaging mechanism of impaired attention in children with PNE

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Iran J Psychiatry. 2019;14:242-47.

ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SUICIDE ATTEMPTS IN PATIENTS WITH BIPOLAR DISORDER.

Fili J, Nojomi M, Razjouyan K, et al.

Objective: The present study aimed to examine the association between ADHD and suicide attempts among adolescents with bipolar disorder.

Method: Participants were 168 adolescents who fulfilled DSM-IV-TR criteria for bipolar disorder. They were divided into 2 groups: The first group of patients with bipolar disorder with a history of suicide attempts (n = 84) and the second group without a history of suicide attempts (n = 84). ADHD and other variables were analyzed using a chi-squared test and logistic regression model.

Results: No significant difference was observed between the 2 groups in comorbidity of ADHD and other psychiatric disorders (P > 0/05). In the logistic regression model, and after controlling for other factors, gender (OR = 3.9, CI 95%: 1.5-9.6) and history of sexual abuse (OR = 3.4; CI 95%: 1.06-11.3) were the only 2 factors associated with a history of suicide attempts.

Conclusion: No significant association was found between ADHD and suicide attempts in adolescents with bipolar disorder

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J Dent Hyg. 2019 Apr;93:23-26.

NONMEDICAL USE OF PRESCRIPTION STIMULANTS IN DENTAL HYGIENE PROGRAMS: GUIDELINES FOR PREVENTION STRATEGIES.

A'see KM, Cantey KB.

Nonmedical use of prescription stimulants (NPS), drugs frequently prescribed to treat Attention-Deficit/Hyperactivity Disorder (ADHD), is defined as the use of medications without a prescription or in a way that is inconsistent with a medical diagnosis. These pharmaceuticals are frequently prescribed to increase attentiveness, decrease distractibility, and improve daily functioning in individuals diagnosed with ADHD. While medically prescribed stimulants, including amphetamine, methylphenidate, and dextroamphetamine, have been shown to be safe and effective for improving the symptoms of ADHD, they have also been classified by the United States Food and Drug Administration (FDA) as schedule II, due to their high potential for abuse. With the increased matriculation of college students diagnosed with ADHD, the number of stimulants available on college campuses has risen substantially; and misuse of NPS is becoming a serious issue amongst college-aged students, including those in health care professions. The most commonly reported reasons for NPS use among college students is to improve alertness and concentration while studying and to enhance overall academic achievement. Borrowing, sharing and selling prescription stimulants between peers and friends are the common routes for NPS diversion. Academic performance expectations in dental hygiene education programs can create a highly stressful environment increasing the susceptibility of dental hygiene students to NPS misuse. Dental hygiene education programs should promote an awareness of the ethical, legal and overall health harms of nonmedical use of prescription stimulants

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J Neurosurg Pediatr. 2019 Jan;23:455-64.

HEALTH-RELATED QUALITY OF LIFE FOLLOWING ADOLESCENT SPORTS-RELATED CONCUSSION OR FRACTURE: A PROSPECTIVE COHORT STUDY.

Russell K, Selci E, Black B, et al.

OBJECTIVE: The longitudinal effects of sports-related concussion (SRC) in adolescents on health-related quality of life (HRQOL) remain poorly understood. Hence, the authors established two objectives of this study: 1) compare HRQOL outcomes among adolescents with an acute SRC or a sports-related extremity fracture (SREF) who were followed up until physician-documented clinical recovery; and 2) identify the clinical variables associated with worse HRQOL among adolescent SRC patients.

METHODS: The authors conducted a prospective cohort study of adolescents with acute SRC and those with acute SREF who underwent clinical assessment and follow-up at tertiary subspecialty clinics.

Longitudinal patient-reported HRQOL was measured at the time of initial assessment and at each follow-up appointment by using the adolescent version (age 13-18 years) of the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale and Cognitive Functioning Scale.
RESULTS: A total of 135 patients with SRC (60.0% male; mean age 14.7 years; time from injury to initial assessment 6 days) and 96 patients with SREF (59.4% male; mean age 14.1 years; time from injury to initial assessment 8 days) participated in the study. At the initial assessment, the SRC patients demonstrated significantly worse cognitive HRQOL and clinically meaningful impairments in school and overall HRQOL compared to the SREF patients. Clinical variables associated with a worse HRQOL among SRC patients differed by domain but were significantly affected by the patients' initial symptom burden and the development of delayed physician-documented clinical recovery (> 28 days postinjury). No persistent impairments in HRQOL were observed among SRC patients who were followed up until physician-documented clinical recovery.
CONCLUSIONS: Adolescent SRC is associated with temporary impairments in HRQOL that have been shown to resolve in patients who are followed up until physician-documented clinical recovery. Future studies are needed to identify the clinicopathological features that are associated with impaired HRQOL and to assess whether the initiation of multidisciplinary, targeted rehabilitation strategies would lead to an improvement in HRQOL

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JAMA Netw Open. 2018 Aug;1:e181504.
PAYING ATTENTION TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Dickstein DP.

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JAMA Network Open. 2019;2.
ASSOCIATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH TEENAGE BIRTH AMONG WOMEN AND GIRLS IN SWEDEN.
Skoglund C, Kopp KH, Skalkidou A, et al.
Importance: Attention-deficit/hyperactivity disorder (ADHD) is associated with a plethora of adverse health outcomes throughout life. While Swedish specialized youth clinics have carefully and successfully targeted risk of unplanned pregnancies in adolescents, important risk groups, such as women and girls with ADHD, might not be identified or appropriately assisted by these interventions.
Objectives: To determine whether women and girls with ADHD are associated with increased risk of teenage birth compared with their unaffected peers and to examine the association of ADHD with risk factors for adverse obstetric and perinatal outcomes, such as smoking, underweight or overweight, and substance use disorder.
Design, Setting, and Participants: This nationwide cohort study included data from 6 national longitudinal population-based registries in Sweden. All nulliparous women and girls who gave birth in Sweden between January 1, 2007, and December 31, 2014, were included. Data analyses were conducted from October 7, 2018, to February 8, 2019. Exposures: Women and girls treated with stimulant or nonstimulant medication for ADHD (Anatomic Therapeutic Chemical classification code N06BA) in the Swedish Prescribed Drug Register between July 1, 2005, and December 31, 2014.
Main Outcomes and Measures: Maternal age at birth. Secondary outcome measures were body mass index, smoking habits, and psychiatric comorbidities. Results: Among 384103 nulliparous women and girls aged 12 to 50 years who gave birth between 2007 and 2014 included in the study, 6410 (1.7%) (mean [SD] age, 25.0 [5.5] years) were identified as having ADHD. The remaining 377693 women and girls without ADHD (mean [SD] age, 28.5 [5.1] years) served as the control group. Teenage deliveries were more common among women and girls with ADHD than among women and girls without ADHD (15.3% vs 2.8%; odds ratio [OR], 6.23 [95% CI, 5.80-6.68]). Compared with women and girls without ADHD, those with ADHD were more likely to present with risk factors for adverse obstetric and perinatal outcomes, including smoking during the third trimester (OR, 6.88 [95% CI, 6.45-7.34]), body mass index less than 18.50 (OR, 1.29 [95% CI, 1.12-

1.49]), body mass index more than 40.00 (OR, 2.01 [95% CI, 1.60-2.52]), and alcohol and substance use disorder (OR, 20.25 [95% CI, 18.74-21.88]).
Conclusions and Relevance: This study found that women and girls with ADHD were associated with an increased risk of giving birth as teenagers compared with their unaffected peers. The results suggest that standard of care for women and girls with ADHD should include active efforts to prevent teenage pregnancies

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J Abnorm Child Psychol. 2019 Oct;47:1599-610.
NETWORK ANALYSIS OF ADHD AND ODD SYMPTOMS: NOVEL INSIGHTS OR REDUNDANT FINDINGS WITH THE LATENT VARIABLE MODEL?
Preszler J, Burns GL.
A latent variable model (LVM) and network analysis (NA) were applied to mother and father ratings of attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms to determine if NA offers unique insights relative to the LVM. ADHD-inattention (IN), ADHD-hyperactivity/impulsivity (HI), and ODD symptoms along with academic competence behaviors (reading, arithmetic, and writing skills) were rated by mothers and fathers of Brazilian (n = 894), Thai (n = 2075), and United States (n = 817) children (Mage = 9.04, SD = 2.12, 49.5% females). LVM indicated that (1) the ADHD-IN, ADHD-HI, and ODD three-factor model yielded a close global-fit with no localized ill-fit; (2) nearly all loadings were substantial; (3) like-symptom loadings, like-symptom thresholds, and like-factor means showed invariance across mothers and fathers; (4) the three factors showed convergent and discriminant validity across mothers and fathers; and (5) only the ADHD-IN showed a unique negative relationship with academic competence. NA indicated that (1) a walktrap community analysis resulted in ADHD-IN, ADHD-HI, and ODD symptom communities; (2) the three symptom communities were consistent across mothers and fathers; (3) only three ADHD-IN symptoms showed unique relationships with the three academic competence items. NA has proven useful for numerous mental disorders. In the current study, NA results were mostly congruent with the LVM model, with a few notable exceptions. The results are discussed in the context of model assumptions and application considerations in the context of ADHD/ODD symptoms relative to other symptom dimensions

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J Abnorm Child Psychol. 2019 Oct;47:1583-97.
NEGATIVE PARENTING MODERATES THE PROSPECTIVE ASSOCIATION OF ADHD SYMPTOMS AND YOUTH SOCIAL PROBLEMS.
Fenesy MC, Teh SE, Lee SS.
Although ADHD and negative parenting are established predictors of youth outcomes, their independent and interactive effects on youth social functioning remain unclear. We tested childhood ADHD symptoms and negative parenting as independent and interactive predictors of prospective change in social problems across a four-year follow-up. At baseline, families of 221 (33% female) children with (n = 94) and without ADHD were rigorously assessed including observed positive and negative parenting behavior, youth ADHD symptoms, as well as multi-informant ratings of youth social problems at multiple occasions. Based on multiple regression with robust standard errors and full-information maximum likelihood procedures to address missing data, ADHD symptoms positively predicted social problems, even with control of observed parenting behavior, child age and sex, oppositional defiant disorder symptoms, and baseline social problems. Additionally, a child ADHD symptoms x negative parenting interaction uniquely predicted separate parent- and teacher-rated social problems where ADHD symptoms positively predicted social problems exclusively in the context of high (+1SD) and very high (+2 SD) negative parenting, respectively. When ADHD was separated into distinct dimensions (i.e., inattention, hyperactivity), an interaction between inattention

symptoms and negative parenting approached significance such that inattention symptoms positively predicted parent-rated social problems in the context of high negative parenting. We discuss the interaction between parenting and ADHD symptoms in predictions of youth social problems and implications for interventio

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J Autism Dev Disord. 2019;49:3999-4008.

AUDITORY ATTENTIONAL DISENGAGEMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Keehn B, Kadlaskar G, McNally KR, et al.

Despite early differences in orienting to sounds, no study to date has investigated whether children with ASD demonstrate impairments in attentional disengagement in the auditory modality. Twenty-one 9ΓÇô15-year-old children with ASD and 20 age- and IQ-matched TD children were presented with an auditory gap-overlap paradigm. Evidence of impaired disengagement in ASD was mixed. Differences in saccadic reaction time for overlap and gap conditions did not differ between groups. However, children with ASD did show increased no-shift trials in the overlap condition, as well as reduced disengagement efficiency compared to their TD peers. These results provide further support for disengagement impairments in ASD, and suggest that these deficits include disengaging from and shifting to unimodal auditory information

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J Autism Dev Disord. 2019.

ASSOCIATION BETWEEN PREMATURITY AND DIAGNOSIS OF NEURODEVELOPMENT DISORDER: A CASE-CONTROL STUDY.

Soncini TCB, Belotto GA, Diaz AP.

The aim of this study is to investigate the association between prematurity and diagnosis of neurodevelopmental disorders (ND) (attention deficit/hyperactivity disorder [ADHD] or autism spectrum disorder [ASD]) in Brazilian children and adolescents. CaseΓÇôcontrol study based on medical records data from a specialized outpatient clinic. Prematurity was defined as gestational age less than 37 weeks. Prematurity was independently associated with diagnosis of a ND (adjusted odds ratio [AOR] 3.46, 95% CI 1.15 - 7.92), as well as with ADHD and ASD diagnosis after a multiple logistic regression analysis. These findings from Brazilian patients are related to what is found in the literature worldwide. Efforts to modify risk factors, such as prematurity, may impact incidence reduction of both ADHD and ASD

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J Child Adolesc Psychopharmacol. 2019;29:592-98.

A NOVEL ASSESSMENT TOOL FOR IMPULSIVE AGGRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ceresoli-Borroni G, Liranso T, Brittain ST, et al.

Objective: To establish the validity and reliability of a provisional 30-item impulsive aggression (IA) diary in children (ages 6-12 years, inclusive) with attention-deficit/hyperactivity disorder (ADHD).

Methods: The provisional 30-item IA diary was administered for 14 days to parents of children with ADHD and IA symptoms (n = 103). Key inclusion criteria: confirmed ADHD diagnosis; signs of IA as measured by a Retrospective-Modified Overt Aggression Scale (R-MOAS) score ΓëÑ20 and an Aggression Questionnaire score of -2 to -5. Analyses included inter-item correlations, exploratory factor analysis (EFA), item response theory (IRT) modeling, internal consistency, test-retest reliability (TRT), concurrent validity (estimated by correlation between the IA diary and the R-MOAS/Nisonger Child Behavior Rating Form), and known-groups methods.

Results: The prevalence rates of 15 (50.0%) items were found to be too low (<1%) for analysis; three items with prevalence rates ΓëÑ1% were retained, as content validity was deemed high by clinical experts. The remaining 12 behavior items had prevalence rates of 2.7%-73.6%. EFA and IRT models confirmed two subdomains in the IA diary included within a general domain of IA behavior frequency, yielding a single total

behavioral frequency score (TBFS). Internal consistency was high for this TBFS (marginal reliability = 0.86 and +¦ = 0.73). TRT for the TBFS, based on the intraclass correlation coefficient, was 0.8. Concurrent validity of TBFS with R-MOAS ranged from r = 0.49 to r = 0.62.
Conclusion: The final 15-item IA diary is a reliable, psychometrically validated IA measurement tool that will allow clinicians and researchers to assess the frequency of IA behavior

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J Child Adolesc Psychopharmacol. 2019;29:649-50.
RAYNAUD'S PHENOMENON RELATED WITH ATOMOXETINE TREATMENT IN A CHILD WITH AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Gülle ZN, Karayagmurlu A, Coskun M.

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J Child Adolesc Psychopharmacol. 2019;29:599-607.
APPLICATION OF THE IMPULSIVE AGGRESSION DIARY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Ceresoli-Borroni G, Liranso T, Brittain ST, et al.
Objective: Impulsive aggression (IA) is a maladaptive form of aggressive behavior that is an associated feature of neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD). As one of the most common forms of aggressive behavior, IA is a serious clinical concern. Recognition, monitoring, and management of IA symptoms are complicated by the lack of IA-specific psychometric instruments and evidence-based treatments. A recently developed electronic observer-reported outcome instrument has been validated in children for monitoring the frequency of 15 IA-related behaviors in the context of ADHD. This study seeks to first determine if the behaviors included in the pediatric IA diary are applicable to adolescents with ADHD, and second, compare the reliability of adolescent versus parent reporters.
Methods: We evaluated the utility of the pediatric IA diary through concept elicitation and cognitive interviews with 17 pairs of parents and adolescents (aged 13-17 years) with IA and ADHD, supplemented with 15 new behaviors potentially applicable to adolescents.
Results: The behaviors most frequently reported by adolescents included arguing (93.8%), raising their voice/shouting/yelling (93.8%), hitting others (87.5%), slamming (87.5%), pushing/shoving (81.3%), breaking (75.0%), fighting (75.0%), throwing (75.0%), and cursing (68.8%). The behaviors most commonly reported by parents included raising their voice/shouting/yelling (94.1%), arguing (88.2%), being disrespectful/mean/rude (88.2%), slamming (88.2%), throwing (88.2%), cursing (82.4%), hitting others (82.4%), pushing/shoving (82.4%), breaking (76.5%), name-calling (76.5%), and threatening (70.6%). Of all commonly reported behaviors, only being "disrespectful/mean/rude" and "breaking" are not part of the pediatric IA diary, likely due to the imprecision of these terms. No significant usability issues were found for the IA diary device.
Conclusions: These findings suggest that the 15-item pediatric IA diary should be applicable to adolescent populations to appropriately characterize IA behaviors in individuals with ADHD. Furthermore, this study indicated that parents may be more reliable reporters of IA behavior than adolescents

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J Child Fam Stud. 2019 Sep;28:2429-42.
EMOTION REGULATION ACCOUNTS FOR THE RELATION BETWEEN ADHD AND PEER VICTIMIZATION.
Fogleman ND, Slaughter KE, Rosen PJ, et al.
Children with attention-deficit/hyperactivity disorder (ADHD) often experience higher rates of emotion regulation deficits and peer victimization relative to unaffected children; however, few studies have examined the extent to which emotion regulation is associated with peer victimization among children with ADHD. The current study proposed a model whereby ADHD was directly and indirectly related to peer victimization through emotion regulation, and that emotion regulation directly predicted peer victimization above and

beyond the effect of ADHD. Two hundred ten children (133 ADHD, 77 non-ADHD) enrolled in the present study. Parents completed measures to assess ADHD diagnostic status, and parents and children completed measures of emotion regulation and peer victimization. Model testing strongly supported the direct association of emotion regulation on peer victimization for children with and without ADHD, and also provided support for an indirect effect of ADHD on peer victimization through emotion regulation. Using a multi-informant approach, the current study demonstrated that emotion regulation directly effects peer victimization among children with and without ADHD and indirectly effects the relation between ADHD and peer victimization. For all children, the inability to regulate and cope with emotions appears to play a powerful role in the frequency with which they experience peer victimization, and for children with ADHD, increased rates of peer victimization are likely attributable to co-occurring deficits in emotion regulation

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Journal of Clinical Medicine. 2019;8.

PERIPHERAL BRAIN-DERIVED NEUROTROPHIC FACTOR AND CONTACTIN-1 LEVELS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang L-J, Wu C-C, Lee M-J, et al.

Brain-derived neurotrophic factor (BDNF) facilitates neuronal growth and plasticity, and is crucial for learning and memory. Contactin-1 (CNTN1) is a member of the subfamily of neural immunoglobulin and is involved in the formation of axon connections in the developing nervous system. This cross-sectional study investigates whether BDNF and CNTN1 affect susceptibility to attention deficit/hyperactivity disorder (ADHD). A total of 136 drug-na+»ve patients with ADHD (108 boys and 28 girls) and 71 healthy controls (45 boys and 26 girls) were recruited. Blood samples were obtained to measure the plasma levels of BDNF and CNTN1 in each child. We found that BDNF levels in the ADHD boys exceeded those in the control boys, but BDNF levels in the ADHD girls were lower than those in the control girls. Boys who had higher BDNF levels performed worse on the Wechsler Intelligence Scale for ChildrenΓÇöFourth Edition, but girls who had higher BDNF levels made fewer omission errors in the ConnersΓÇÖ Continuous Performance Test. However, CNTN1 level did not differ significantly between patients and controls, and were not correlated to ADHD characteristics, regardless of gender. The findings suggest BDNF may influence sex-specific susceptibility to ADHD, but CNTN1 was not associated with ADHD pathophysiology

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Journal of Clinical Medicine. 2019;8.

DEFICITS IN CONDITIONAL DISCRIMINATION LEARNING IN CHILDREN WITH ADHD ARE INDEPENDENT OF DELAY AVERSION AND WORKING MEMORY.

De MH, Beckers T, Tripp G, et al.

Adaptive behavior requires the adjustment of oneΓÇÖs behavioral repertoire to situational demands. The learning of situationally appropriate choice behavior can be operationalized as a task of Conditional Discrimination Learning (CDL). CDL requires the acquisition of hierarchical reinforcement relations, which may pose a particular challenge for children with Attention Deficit Hyperactivity Disorder (ADHD), particularly in light of documented deficits in short-term/working memory and delay aversion in ADHD. Using an arbitrary Delayed Matching-To-Sample task, we investigated whether children with ADHD (N = 46), relative to Typically Developing children (TD, N = 55), show a deficit in CDL under different choice delays (0, 8, and 16 seconds) and whether these differences are mediated by short-term/working memory capacity and/or delay aversion. Children with ADHD demonstrated poorer CDL than TD children under 8 and 16-second delays. Nondelayed CDL performance did not differ between groups. CDL differences were not mediated by short-term/working memory performance or delay aversion. Moreover, CDL performance under an 8-second delay was a better predictor of clinical status than short-term/working memory performance or delay aversion. CDL,

under conditions of delay, is impaired in children with ADHD. This may lead to difficulties discriminating between different situational demands and adapting behavior according to the prevailing reward contingencies or expectations

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Journal of Clinical Medicine. 2019;8.

ADVANCES IN UNDERSTANDING THE RELATIONSHIP BETWEEN SLEEP AND ATTENTION DEFICIT-HYPERACTIVITY DISORDER (ADHD).

Scarpelli S, Gorgoni M, DΙÇÖatri A, et al.

Starting from the consolidated relationship between sleep and cognition, we reviewed the available literature on the association between Attention Deficit-Hyperactivity Disorder (ADHD) and sleep. This review analyzes the macrostructural and microstructural sleep features, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA). We included the polysomnographic studies published in the last 15 years. The results of macrostructural parameters are mixed. Almost half of the 18 selected investigations did not find differences between sleep architecture of children with ADHD and controls. Five studies observed that children with ADHD show a longer Rapid Eye Movement (REM) sleep duration than controls. Eight studies included microstructural measures. Remarkable alterations in sleep microstructure of ADHD are related to slow wave activity (SWA) and theta oscillations, respectively, during Non-REM (NREM) and REM sleep. Specifically, some studies found higher SWA in the ADHD group than controls. Similarly, higher theta activity appears to be detrimental for memory performance and inhibitory control in ADHD. These patterns could be interpreted as a maturational delay in ADHD. Also, the increased amount of these activities would be consistent with the hypothesis that the poor sleep could imply a chronic sleep deprivation in children with ADHD, which in turn could affect their cognitive functioning

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Journal of Cognitive Psychology. 2019;31:725-49.

A META-ANALYSIS OF EXECUTIVE FUNCTIONING IN DYSLEXIA WITH CONSIDERATION OF THE IMPACT OF COMORBID ADHD.

Lonergan A, Doyle C, Cassidy C, et al.

This meta-analysis examined inhibition, switching attention and auditory working memory in children with dyslexia. As a secondary outcome the impact of comorbid ADHD on executive functions in dyslexia was examined. Twenty-six controlled studies examining executive functions in children with dyslexia alone and/or comorbid dyslexia/ADHD were reviewed. Outcomes were reaction times, errors and accuracy on measures of inhibition, switching attention and auditory working memory. Children with dyslexia demonstrated difficulty with inhibition, switching attention, and auditory working memory, with a medium to large effect relative to controls. Children with comorbid dyslexia/ADHD exhibited relatively the same degree of inhibition, switching attention and auditory working memory impairment compared to children with dyslexia alone. Findings support the presence of executive function deficits in children with dyslexia. Executive functioning may be a shared deficit, underpinning variants of neurodevelopmental disorders. Future studies may benefit from examining executive functions in children with dyslexia while controlling for attention difficulties

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Journal of Managed Care and Specialty Pharmacy. 2019;25:S53.

FACTORS ASSOCIATED WITH THE HEALTHCARE EFFECTIVENESS DATA AND INFORMATION SET FOLLOW-UP MEASURES IN MEDICAID-INSURED CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Earla J, Chen H.

BACKGROUND: Initiation rate and continuation and maintenance (C&M) rate are the two important Healthcare Effectiveness Data and Information Set (HEDIS) follow-up care performance measures for Attention-deficit hyperactivity disorder (ADHD) patients.

OBJECTIVE: To assess the factors associated with the C&M Phase follow-up in children with ADHD.

METHODS: A retrospective longitudinal observational study was conducted using 2013-2016 data from a large pediatric Managed Care Plan in Texas that covered more than 400,000 Medicaid enrolled children and adolescents. ADHD Children (aged 6-12 years) who received the ADHD diagnosis (ICD-9-CM code-314.XX or ICD-10 code-F90.9) and an index-prescription for ADHD were considered for the analysis. Initiation and C&M phase follow-up rates were measured as per the HEDIS specifications. A multivariable logistic regression model was performed, using SAS 9.4, to determine the factors associated with children who had C&M phase follow-up.
RESULTS: Among the 8,868 eligible children identified with ADHD diagnosis and prescription, 48.73% (n = 4,321) had initiation followup. From those who had initiation follow-up, 3,083 children were continuously eligible through the C&M phase i.e. 10 months after the index ADHD prescription. Among which, 14.95% (n = 461) of the patients had C&M phase follow-up. Children who had follow-up were significantly different in terms of race/ethnicity, provider specialty, and treatment category. The results of multivariable logistic analysis found that, compared to Caucasian children, Hispanic children were 66% (Odds ratio [OR]: 0.34, 95% confidence interval [CI]: 0.26-0.44) and African American children 67% (OR: 0.33, 95% CI: 0.25-0.45) less likely to fulfill C&M phase follow-up criteria, respectively. Further, patients who consulted psychiatrists were 1.78 times more likely to fulfill C&M phase follow-up criteria than those who consulted primary care physicians only (OR: 1.78, 95% CI: 1.41-2.24). Further, children who received combination therapy were 8 times more likely to fulfill C&M phase follow-up criteria than those who received monotherapy (OR: 8.20, 95% CI: 6.17-10.90).
CONCLUSIONS: Receiving combination therapy and consulting psychiatrist are positively associated with C&M phase follow-up. Whereas, Hispanic and African American race/ethnicity was negatively associated with C&M phase follow-up

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Journal of Medical Imaging and Health Informatics. 2019;9:1655-62.

BRAIN FUNCTION NETWORK ANALYSIS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BASED ON ADAPTIVE SPARSE REPRESENTATION METHOD.

Pan X, Jiang Z, Bi H, et al.

Attention-Deficit Hyperactivity Disorder (ADHD), as a neuro-developmental disorder, has a great impact on children's life. Brain function network analysis is one of the crucial means for ADHD diagnosis. To better understand the ADHD, the method combined with Adaptive Sparse Representation (ASR) method and graph theory was proposed to achieve the global functional network. First, ASR was applied to calculate the correlation to construct the brain function network. Second, the obtained optimal threshold based on an absolute selection strategy aimed to reduce the weak correlative connections. In order to understand the differences between the ADHD and the normal, graph theory was utilized for brain network evaluation. The connection sensitivity of ASR of the simulated data is 88.89% shows the validity of the proposed method. The experiments were conducted on clinical resting-state fMRI data of 30 ADHD patients and 30 normal persons. Compared to the normal, the average shortest path of the ADHD was 24% higher, the average degree distribution of the ADHD was 21% lower, the local efficiency of the ADHD was 14% higher and the global efficiency of the ADHD was 19% lower. Meanwhile, there were significant differences of the node efficiency between the ADHD and the normal in the temporal lobe and occipital cortex. The experimental results showed that the proposed method could show more clearly the differences between the normal and the ADHD

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Journal of Medical Imaging and Health Informatics. 2019;9:1717-24.

APPLICATION OF DEEP CONVOLUTIONAL NEURAL NETWORKS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CLASSIFICATION: DATA AUGMENTATION AND CONVOLUTIONAL NEURAL NETWORK TRANSFER LEARNING.

Zhu L, Chang W.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and controversial diseases in paediatric psychiatry. Recently, computer-aided diagnosis methods become increasingly popular in clinical

diagnosis of ADHD. In this paper, we introduced the latest powerful method-deep convolutional neural networks (CNNs). Some data augmentation methods and CNN transfer learning technique were used to address the application problem of deep CNNs in the ADHD classification task, given the limited annotated data. In addition, we previously encoded all gray-scale images into 3-channel images via two image enhancement methods to leverage the pre-trained CNN models designed for 3-channel images. All CNN models were evaluated on the published testing dataset from the ADHD-200 sample. Evaluation results show that our proposed deep CNN method achieves a state-of-the-art accuracy of 66.67% by using data augmentation methods and CNN transfer learning technique, and outperforms existing methods in the literature. The result can be improved by building a special CNN structure. Furthermore, the trained deep CNN model can be used to clinically diagnose ADHD in real-time. We suggest that the use of CNN transfer learning and data augmentation will be an effective solution in the application problem of deep CNNs in medical image analysis

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J Neural Transm. 2019;126:1135-44.

HAIR CORTISOL CONCENTRATION IN MOTHERS AND THEIR CHILDREN: ROLES OF MATERNAL SENSITIVITY AND CHILD SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schloß S, Müller V, Becker K, et al.

Associations between mothersΓÇÖ and childrenΓÇÖs cortisol secretion parameters are well established. According to the bio-behavioral synchrony model, these associations reflect influences of the mother child relationship, the child's social adjustment, and might also reflect shared genetic dispositions. From the bio-behavioral synchrony model, we predicted a stronger mother child hair cortisol concentration (HCC) link in mothers showing highly adequate (compared to those showing less adequate) parenting behaviors and in children showing low (compared to those showing high) ADHD symptoms. From a genetic perspective, no such moderator effects, or a stronger mother child HCC link in children with high ADHD symptoms, can be expected. The study sample consisted of 111 4ΓÇô5-year-old children (64 of whom screened positive for increased ADHD symptoms) and their mothers. ADHD symptoms were assessed by a clinical interview and parent and teacher questionnaires. Maternal sensitive/responsive parenting behavior was assessed by an at-home behavior observation procedure. In mothers and children, HCC in the most proximal 3-cm scalp hair segment was analyzed using luminescence immunoassay. Overall HCCs of mothers and their children correlated significantly. Maternal sensitivity/responsiveness and child ADHD symptoms proved to be significant moderator variables of this association: High maternal sensitivity/responsiveness and low ADHD symptoms of the child were associated with a stronger mother child link in HCC. The findings are in line with the bio-behavioral synchrony model in the mother child relationship, and are less compatible with a genetic perspective. The results might hint at environmental events influencing the development of stress axis functioning in subgroups of preschoolers with high ADHD symptoms

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J Neuropsychol. 2019 Sep;13:529-49.

IMPLICIT SEQUENCE LEARNING IN YOUNG PEOPLE WITH TOURETTE SYNDROME WITH AND WITHOUT CO-OCCURRING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shephard E, Groom MJ, Jackson GM.

Impaired habit-learning has been proposed to underlie the tic symptoms of Tourette syndrome (TS). However, accounts differ in terms of how habit-learning is altered in TS, with some authors proposing habit formation is impaired due to a deficient 'chunking' mechanism, and others proposing habit-learning is overactive and tics reflect hyperlearned behaviours. Attention-deficit/hyperactivity disorder (ADHD) frequently co-occurs with TS and is known to affect cognitive function in young people with co-occurring TS and ADHD (TS + ADHD). It is unclear, however, how co-occurring ADHD symptoms affect habit-learning in TS. In this study, we investigated whether young people with TS would show deficient or hyperactive habit-learning, and assessed the effects of co-occurring ADHD symptoms on habit-learning in TS. Participants aged 9–17 years with TS (n = 18), TS + ADHD (n = 17), ADHD (n = 13), and typical development (n = 20)

completed a motor sequence learning task to assess habit-learning. We used a 2 (TS-yes, TS-no) × 2 (ADHD-yes, ADHD-no) factorial analysis to test the effects of TS, ADHD, and their interaction on accuracy and reaction time indices of sequence learning. TS was associated with intact sequence learning, but a tendency for difficulty transitioning from sequenced to non-sequenced performance was suggestive of hyper-learning. ADHD was associated with significantly poorer accuracy during acquisition of the sequence, indicative of impaired habit-learning. There were no interactions between the TS and ADHD factors, indicating young people with TS + ADHD showed both TS- and ADHD-related atypicalities in habit-learning

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J Am Acad Child Adolesc Psychiatry. 2019;58:S161.

1.46 PSYCHOPHARMACOLOGICAL TREATMENTS OF ADHD-LIKE SYMPTOMS IN CHILDREN PRENATALLY EXPOSED TO ALCHOL/DRUGS: TOWARDS A MODEL OF CARE.

Ritfeld G, Holton J, Kable JA.

Objectives: Children prenatally exposed to alcohol/drugs present with ADHD-like symptoms in up to 74 percent of cases, but reduced efficacy of stimulant medications and high prevalence of comorbid look-alike symptoms in this population limits optimal mental illness treatment. The goal of the current presentation is to propose a model for mental health care for this population based on data from our clinical cohort.

Methods: Demographic, diagnostic, and treatment responsiveness data were collected from the medical records of 38 children with prenatal alcohol/drug exposures treated in our specialized clinic. In addition to traditional verbal reports and parent/teacher questionnaires, a brief objective continuous performance test (the Test of Variables of Attention [T.O.V.A.®]) was used to aid with diagnosing ADHD-like symptoms and monitoring responsiveness to medications.

Results: Children in our cohort presented with multiple mental illness symptoms, ADHD-like symptoms most prevalently (87%), and were often on complicated medication regimens (mean of 2.0 classes of medications, SD = 1.3). Stimulant responsiveness ranged from negative or no response to partial or complete response per traditional subjective reports. We found that T.O.V.A.® scores improved on average from 6.5 to 2.9 with psychotropic agents, in general ($p = 0.03$), and from −5.7 to −2.6 with stimulant medications specifically (not statistically significant). Thirty-eight percent of children no longer had symptoms in the clinical range as measured by T.O.V.A®, 25 percent of children were nonresponsive to medications per T.O.V.A®, and 38 percent improved but remained in the clinical range of the T.O.V.A® despite treatment. T.O.V.A.® measurements of attention were helpful in differentiating ADHD-like symptoms from comorbid look-alike symptoms and to guide decision-making on starting and changing medications.

Conclusions: Medication responsiveness to ADHD-like symptoms in children with prenatal alcohol/drug exposure is less robust than in the general population, and a comprehensive treatment approach is needed to provide optimal care for this vulnerable population. We highlight the value of objective computerized testing to supplement subjective reports. ND, PTA, STIM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S44.

30.2 REVIEW OF PHARMACOLOGICAL TREATMENTS FOR PSYCHIATRIC SYMPTOMS IN CHILDREN WITH NEUROBEHAVIORAL DISORDER ASSOCIATED WITH PRENATAL ALCOHOL EXPOSURE (ND-PAE) AND FETAL ALCOHOL SPECTRUM DISORDERS (FADS)

Ritfeld G.

Objectives: Mental health symptoms in children with neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE) and fetal alcohol spectrum disorders (FASD) present with high prevalence and morbidity, often across symptom domains (eg, ADHD-like symptoms and sleep problems). Polypharmacy is often used, but no guidelines exist regarding optimal treatment for these children. Moreover, stimulant use in these children is controversial, because their responsiveness may be different because of altered neural circuitry by prenatal alcohol exposure. In this presentation, we aim to give an overview of existing data on pharmacological treatments of mental health symptoms in children with ND-PAE/FASD.

Methods: We searched Cochrane Library and MEDLINE for clinical studies reporting on the effects of pharmacological treatments of psychiatric symptoms in children with ND-PAE/FASD, and we give a systematic overview of the yielded studies. In addition, we review medications that show promise in preclinical studies, are currently in a clinical trial per, or are routinely used in clinical practice.
Results: Our search yielded 7 clinical studies, ranging in size from n = 4 to 77. Among these, 6 articles studied the effects of stimulants, and 2 of these also reported on the effects of neuroleptics or mood stabilizers. The results ranged from negative or no effects to partial or positive effects of stimulants. Other observations included increased responsiveness to amphetamines compared with methylphenidate and superior response of mood stabilizers and neuroleptics compared with stimulants. Choline supplementation showed no effect on mental health symptoms in school-aged children. Two additional trials on choline supplementation are currently underway, and 2 atomoxetine trials have recently been completed. No clinical studies were found on the effectiveness of sleep medications, despite frequent use of sleep medications in this population. Similarly, data on the effectiveness of SSRIs to address depression and anxiety in this population are lacking.
Conclusions: A literature review yields limited and conflicting clinical data on the effectiveness of pharmacological treatments for mental health symptoms in children with ND-PAE/FASD, with some symptom domains lacking data altogether. We emphasize the need for clinical trials to guide pharmacological treatment in this complex population. PTA, TREAT, EBP

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J Am Acad Child Adolesc Psychiatry. 2019;58:S178.

2.24 THE EFFECT OF PRENATAL STRESS ON THE INCIDENCE OF ADHD IN OFFSPRING.

Sahgal P, Benge E.

Objectives: Data on the relationship between prenatal stress and subsequent ADHD diagnoses in offspring are limited. Previous studies examining this relationship either focused on animal models or were restricted by small sample group sizes. This study reports on the prevalence of maternal stressors during the gestation of children with ADHD diagnoses via data collected from a large, community sample group of women.
Methods: In 2016, members of online support groups for mothers of children with ADHD (n = 580) were invited to participate in a survey. The survey was distributed online by a random sampling group of the initial volunteers. Surveys contained 20 questions regarding the nature of maternal stressors that were/were not present during the pregnancy of the child diagnosed with ADHD. Parents who did not give birth to their child, parents without a child with clinically diagnosed ADHD, and individuals located outside of the United States were excluded from the study. The mean age of survey participants during their pregnancy was 27.4 years. Survey data were analyzed by calculating standard deviations, counts, means, and percentages. Questions with write-in responses were assessed and thematically summarized.
Results: The prevalence of psychosocial stressors experienced during pregnancy among survey participants was 69.0 percent. Among the survey participants, 50.4 percent reported no family history of ADHD, 33.1 percent were obese/overweight during their pregnancy, and 18.1 percent of survey respondents reported pregnancy complications, the most common of which were hypertensive disorders and gestational diabetes.
Conclusions: The descriptive research presented here shows compelling data for future investigation into the causative role that prenatal stress, including psychosocial stressors and medical conditions, plays in ADHD diagnoses in children. Recall bias is a limitation in the present study; collecting survey data on stress while study participants are pregnant is another potential area for further research. ADHD, STRESS, DEV

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J Am Acad Child Adolesc Psychiatry. 2019;58:S21.

14.4 ADHD IN JUVENILE JUSTICE.

Rostain AL.

Objectives: It has long been observed that ADHD in youth is a risk factor for delinquency, law breaking, and criminal behavior. For example, youths with ADHD have 2-fold higher rates of driver-related problems such as traffic violations for speeding and recklessness, and motor vehicle accidents. Impulsive decision-making

and risk-taking behaviors also predispose this population to involvement with the criminal justice system. Antisocial acts, arrests, and incarceration are highly prevalent in this population. There is a 5-fold increase in the prevalence of ADHD in youthful offenders and a 10-fold increase in adult prison populations. Substance misuse and abuse in youth with ADHD ranges from 1.5 to 2.8 times the rate in non-ADHD peers. Diversion of prescription medications is another antisocial behavior seen in this population.
Methods: Literature on the links between ADHD and involvement with the criminal justice system will be presented. The role of the child and adolescent psychiatrist working with youthful offenders with ADHD will be discussed, especially with respect to psychoeducation, health promotion, risk/harm reduction, family system involvement, and patient advocacy. Clinical examples will provide opportunities to discuss practical approaches to caring for this at-risk patient population.
Results: Children and adolescents with ADHD have trouble regulating their emotions and impulses and, as such, are at greater risk than peers for developing negative behaviors such as breaking rules, acting irresponsibly, fighting with others, driving recklessly, engaging in substance abuse, and getting into trouble with the law. Once they are involved in the criminal justice system, youth with ADHD have executive functioning deficits that lead them to having difficulty following instructions, maintaining rule-governed behaviors, managing conflicts with others, and meeting the demands of the court system. Moreover, access to health care services, including medications and psychosocial interventions, remains a major challenge for youth with ADHD in the criminal justice system.
Conclusions: It is crucial for clinicians working with patients suffering with ADHD to understand the risks for involvement in juvenile justice and how best to meet their needs in correctional placement. ADHD, JJS, RF

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J Am Acad Child Adolesc Psychiatry. 2019;58:S290-S291.

6.61 ADHD AND SUBSTANCE USE DISORDERS: AN ANALYSIS OF 0.8 MILLION ADOLESCENT INPATIENTS.

Patel R, Satodiya R.

Objectives: The goals of this session are to evaluate the demographic predictors of ADHD and its association with the spectrum of substance use disorders (SUD) and to discern the demographic differences between ADHD and comorbid SUD in hospitalized patients.
Methods: We analyzed 800,614 psychiatry inpatients (ages 18 years), of whom 11,233 were inpatients (1.4%) primarily for ADHD in the nationwide inpatient sample group (2010ΓÇô2014). ICD-9 codes were used to detect SUD, and logistic regression model was used to evaluate the odds ratio for SUD in hospitalized patients with ADHD.
Results: A higher proportion of ADHD inpatients were ages 12ΓÇô15 years (74.3%), and males had 4-fold higher odds (95% CI 3.73-4.09). Despite the higher prevalence of ADHD in whites (51.9%), black and Hispanic adolescents have 1.3 to 1.4-fold higher odds for ADHD-related hospitalization. Among SUD, cannabis use disorder (12.4%) was most prevalent, followed by tobacco (7.3%) and alcohol (4.8%) use disorders. Cocaine/amphetamine (88%) and opioids (60%) were used in youth ages 16ΓÇô18 years, whereas cannabis use was higher in youth ages 12-15 years (57%). Black adolescents majorly abused cocaine/amphetamine (50%) and cannabis (35.3%), whereas whites abused cocaine/amphetamine and tobacco (72.2% each).
Conclusions: Opioid and cocaine/amphetamine use was predominant in male and older adolescents (ages 16-18 years) with ADHD. Cannabis use was prevalent in youth ages 12-15 years. Cannabis is also known as the gateway drug, making youth vulnerable to experimenting with other substances. Thus, ADHD and SUD need to be explored and require more attention for future studies to improve the postcare quality of life. ADOL, ADHD, SUD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S157.

1.32 PSYCHOPHARMACOLOGIC THERAPY IN 4- AND 5-YEAR-OLD PATIENTS WITH DIAGNOSES OF ADHD AND ADS.

Ochoa-Lubinoff C, Elizabeth AC, Beeson L, et al.

Objectives: This presentation aims to determine the safety, tolerability, and efficacy of psychopharmacological treatment in a sample group of patients ages 4 and 5 years with a diagnosis of both ADHD and ASD.

Methods: Patients 4 and 5 years of age with DSM-5 criteria of diagnoses of ADHD and ASD and who were seen at the Rush University Medical Center Developmental-Behavioral Pediatrics Clinic from 2012 to 2018 were included in this study. Information regarding clinical response and adverse events to methylphenidate and guanfacine treatments administered to patients until they turned age 6 years was collected. Families were offered these 2 drugs as first-line ADHD treatment, and standard doses were prescribed.

Results: Forty-eight patients with ASD + ADHD out of 150 patients with ADHD were included in this study. Of the 48 patients with ASD, 26 received at least one drug to treat ADHD with a total of 31 drug trials (15 guanfacine and 16 methylphenidate). Among those patients receiving at least one drug, 66 percent of the patients receiving guanfacine and 45 percent receiving methylphenidate had a positive response, with improvement in behavior noted in both home and school environments. The rate of positive response to guanfacine in patients with ASD + ADHD (66%) was similar to positive response rate of the patients with ADHD in the general ADHD database (65%). The rate of positive response to methylphenidate in patients with ASD + ADHD (45%) was lower than patients in the ADHD database (63%). According to the general ADHD database listing patients who received guanfacine, 29 percent reported lethargy and 10 percent reported irritability as significant side effects, whereas 20 percent of the patients with ASD + ADHD treated with guanfacine reported lethargy and 40 percent reported irritability. From the general ADHD database listing patients who received methylphenidate, 18 percent reported irritability, 14 percent reported decreased appetite, and 7 percent reported headaches, whereas 31 percent of the patients with ASD + ADHD and treated with methylphenidate reported irritability, 6 percent reported decreased appetite, and 13 percent reported headaches.

Conclusions: Children ages 4 and 5 years with ADHD and a concurrent ASD diagnosis had similar positive responses to guanfacine but a lower positive response rate to methylphenidate. The rate of side effects in children with ADHD was not significantly different from children with ASD + ADHD who were exposed to guanfacine and methylphenidate. Irritability was a more common side effect in children with ASD + ADHD when exposed to these drugs. ADHD, ASD, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S263.

5.54 ADHD MEDICATIONS, BREASTFEEDING, AND INFANT SAFETY: A LITERATURE REVIEW.

Parikh T, Schwab Z.

Objectives: ADHD medications are secreted into breast milk and may affect the clinical decisions of whether the mothers can be prescribed those medications. Maternal mental health is crucial for maternal infant bonding, and mothers may need medications to treat underlying ADHD. This abstract describes the literature review of commonly prescribed ADHD medications and their secretion into breast milk with a goal to identify the effects on infants.

Methods: A thorough literature search using PubMed and TOXicology Data NETwork (TOXNET) was conducted. From informative articles on various ADHD medications published until June 2019 (after excluding irrelevant articles), the search was narrowed to 8 primary studies/articles. We excluded the articles if they pertained to ADHD medication abuse or the nonprescription use of these medications, because our goal is to search literature on the prescribed medication use. We also excluded one report from 1973 on dextroamphetamine use in postpartum depression, which is based on a personal communication with the manufacturer and does not have detailed scientific data.

Results: Relative infant dose (RID) is one of the useful ways to identify potential risk to infants, and 10 percent or lower RID is arbitrarily accepted as a safe range in terms of possible side effects. We identified 5 articles that commented on methylphenidate (n = 6 infants) and breastfeeding, which revealed no infant safety concerns, with the RID range between 0.16ΓÇô0.7 percent; one infant had recurrent pneumonia

secondary to congenital pulmonary airway malformation but no evidence of a relationship with methylphenidate. Three articles were identified that examined amphetamine compounds (n = 6 infants) and found an RID range of 1.9ΓÇô10.6 percent; no side effects or developmental issues were noted for the exposed infants. No information is available for guanfacine or atomoxetine. Because the data remain very limited in terms of the total number of infants reported, further statistical parameters cannot be applied.
Conclusions: The clinical risks versus benefits should be assessed on a case-by-case basis. Clinical caution and monitoring should include the basic infant safety questions. Clinical studies that follow the US FDA guidance on lactation studies are long overdue and warranted, because the data are often derived from case reports. Some have suggested that early morning milk would have the minimum level of medication. Overall, the articles suggest that methylphenidate is excreted less in breast milk and might be safer than amphetamine. Although there were no infant side effects or developmental issues noted for amphetamines in the limited studies, there is more established evidence that amphetamines in large doses may interfere with milk production. ADHD, INF, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S141.

6.5 ADHD DIAGNOSIS AND TREATMENT IN CHILDREN WITH EPILEPSY.

Plioplys S.

Objectives: The goal of this session is to provide practicing clinicians with a comprehensive overview of ADHD prevalence, risk factors, specific clinical features, diagnosis, and treatment in children with epilepsy (CWE) by using current research and evidence-based clinical findings.
Methods: This presentation draws on studies of ADHD in CWE conducted over the past 10 years. A Consensus Paper on ADHD in CWE issued by the International League Against Epilepsy (ILAE) will be reviewed to demonstrate the guiding principles of ADHD clinical care in CWE. A case of ADHD in a child with frontal lobe epilepsy will be presented to illustrate diagnostic and treatment challenges.
Results: ADHD, predominantly the inattentive type, is the most common mental illness comorbidity in CWE, reported in 30–40 percent of patients. Population-based studies show multifactorial variables involved in the development of ADHD in CWE. There is a bidirectional association between ADHD and epilepsy. Compared with control subjects, ADHD occurs 2.5 times more commonly in CWE, and epilepsy occurs 3.9 times more in children with ADHD. Specific associations between ADHD, frontal lobe epilepsy, and subclinical epileptiform discharges will be highlighted. ADHD screening, diagnostic, and treatment approaches will be summarized using ILAE Consensus Paper recommendations, with parallels drawn from the ADHD care in the general population. A differential diagnostic evaluation will be reviewed, with a focus on inattentiveness and absence seizures. Because of concerns of worsening seizures, only a small percentage of CWE receives pharmacological treatment for ADHD. A detailed discussion about the use of medications will be provided to demonstrate that there is no evidence of methylphenidate causing seizure exacerbation. Level B evidence supports efficacy, safety, and tolerability of methylphenidate use in CWE.
Conclusions: A combination of ADHD and epilepsy can have a negative impact on a childΓÇÖs behavior, learning, and social development. The participants will acquire new knowledge and clinical understanding about the accurate ADHD diagnosis and safe pharmacological treatment options, including stimulant medications, for CWE. It will empower child psychiatrists to provide effective ADHD care that will improve the quality of life, reduce cognitive deficits, and assure positive developmental outcomes of CWE in adulthood. ADHD, EP, STIM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S169-S170.

1.70 A PHASE 3, RANDOMIZED, DOUBE-BLIND PLACEBO-CONTROLLED STUDY (P301) ASSESSING THE EFFICACY AND SAFETY OF SPN-812 (EXTENDED-RELEASE VILOXAZINE) 100 AND 200MG FOR THE TREATMENT OF ADHD IN CHILDREN.

Nasser A, Busse GD, Hull J, et al.

Objectives: SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA) under investigation as a treatment for ADHD in children and adolescents. This Phase 3, randomized, double-blind study (P301) evaluated the efficacy and safety of once-daily SPN-812 100 or 200 mg compared to placebo in children ages 6-11 with ADHD.

Methods: Key inclusion criteria included confirmed DSM-5 ADHD diagnosis, ADHD-Rating Scale-5 (ADHD-RS-5) score 28, a Clinical Global Impression-Severity score 4, and free of ADHD medication 1 week before randomization. Subjects (N=477) were randomized 1:1:1 to placebo:100 mg:200 mg SPN-812. The 6-week treatment period included up to 1 week titration and 5 weeks maintenance (intent-to-treat population: N=460; placebo=155, 100 mg=147, 200 mg=158). The primary efficacy endpoint was the change from baseline (CFB) to end of study (EOS) in ADHD-RS-5 total score. Key secondary endpoints included EOS Clinical Global Impression-Improvement (CGI-I) score, and CFB to EOS in Conners 3-Parent Short Form (Conners 3-PS) Composite T-score and in Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P) average score. Safety assessments included adverse events (AEs), laboratory tests, vital signs, physical exams, electrocardiograms, and the Columbia-Suicide Severity Rating Scale.

Results: A statistically significant improvement was observed with 100 mg and 200 mg doses compared to placebo [difference of LS Mean -¦ SE (p-value)] in all endpoints, including CFB at EOS in ADHD-RS-5 total score [-5.8 -¦ 1.61 (0.0004); -6.9 -¦ 1.58 (<0.0001), respectively], CGI score at EOS [-0.4 -¦ 0.14 (0.0020); -0.6 -¦ 0.13 (<0.0001)], Conners 3-PS Composite T-score [-4.2 -¦ 1.16 (0.0003); -4.3 -¦ 1.15(<0.0002] and WFIRS-P average score [-0.14 -¦ 0.047 (0.0019); -0.17 -¦ 0.046 (0.0002)]. Both dose groups had low discontinuations due to AEs (placebo: n=2, 1.3%; 100 mg: n=5, 3.2%; 200 mg: n=2, 1.2%). The most common (ΓëÑ5%) AEs were somnolence, headache, and decreased appetite. Possible limitations include trial duration and sample size.

Conclusions: In this study, SPN-812 at 100 mg and 200 mg doses met the primary and key secondary endpoints with robust statistical significance. The low discontinuation rate indicates that the tested doses were well tolerated

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J Am Acad Child Adolesc Psychiatry. 2019;58:S155-S156.

1.28 ASSESSMENT OF ADHD MEDICATION USE AND ASSOCIATIONS WITH SERIOUS CARDIOVASCULAR EVENTS IN CHILDREN AND ADOLESCENTS WITH ASD IN THE UNITED STATES.

Houghton R, de VF, Loss G.

Objectives: ADHD medication use is prevalent among children and adolescents with ASD. It is currently unclear whether these medications are associated with serious cardiovascular (CV) outcomes in this population. Our study aimed to address this question, using data from a large sample group in the United States.

Methods: Using Market Scan-« insurance claims data (2000-2016), we conducted a nested case-control study within an ASD cohort. The cohort contained individuals with 2 or more claims for ASD and between 3 and 18 years of age, provided that no Rett syndrome or previous history of a CV event was observed. We defined a serious CV event as the first sign of: stroke; myocardial infarction (MI); ventricular arrhythmia; or cardiac arrest. For each case, we matched up to 10 control subjects on calendar time, age, sex, and insurance type. After matching, we checked for current prescription of stimulants and/or atomoxetine (ADHD medications) as the main exposure definition. We conducted a crude (matched) conditional logistic regression analysis, as well as sensitivity analyses controlling for health care use, underlying CV comorbidities, mental illness comorbidities, and other psychotropic medications using adjusted regression models and propensity score weighting approaches.

Results: Of the 326,221 individuals identified with ASD, 48 (0.01%) had a serious CV event. The mean (SD) age for cases was 12.5 (4.42) years, and 79.2 percent were male. All case subjects were matched to 10 control subjects as planned (control group: N = 480). The crude rate of current ADHD medication use for

case subjects was 12.5 percent (n = 6) vs. 22.1 percent (n = 106) for control subjects. This translated to no association of ADHD medication use with CV events in the crude matched analysis (OR = 0.49 [95% CI 0.20-1.20]). Similar results were found after adjusting for all covariates using both a propensity score approach (0.71 [0.28-1.83]) and an adjusted logistic regression model (1.20 [0.33-4.41]).
Conclusions: For children and adolescents with ASD, we found no increased serious CV risk when exposed to ADHD medications. ASD, STIM, CVF

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J Am Acad Child Adolesc Psychiatry. 2019;58:S194.

2.70 USING THE PEERS MIND READ APP TO ASSESS SOCIAL COGNITION IN TWEENS WITH ADHD AND ANXIETY-RELATED DISORDERS.

Loubriel D, Beaumont R, Schild J, et al.

Objectives: A lack of reliable and valid measures of child social cognition can hinder diagnostic and treatment planning and evaluation. This study aimed to evaluate the feasibility and utility of the Mind Read section of a new app (The Pediatric Evaluation of Emotions, Relationships and Socialization [PEERS]) in assessing theory of mind in children. PEERS was developed to assess attention/executive functioning, social cognition, and social communication in individuals aged 4-17.11 years.
Methods: Participants comprised 23 youth ages 8-12 years (mean = 9.59, SD = 1.81) with a primary diagnoses of ADHD (n = 12), anxiety-related disorder (n = 9), or OCD (n = 2). Research assistants administered Mind Read individually to participants. Mind Read consists of 36 video vignettes of common teenage interactions and takes approximately 20 minutes to administer. Vignettes are followed by questions assessing comprehension and the ability to make social inferences and predict socially appropriate behaviors. Children's understanding of socially appropriate behaviors was also assessed using paper-and-pencil story vignettes: James and the Math Test, and Dylan is Being Teased. Children's application of emotion regulation and social skills was examined using parent and teacher-report forms of the Emotion Regulation and Social Skills Questionnaire and the Spence Social Skills Questionnaire. Correlational analyses were conducted to assess the strength of associations between Mind Read scores and paper-and-pencil measures.
Results: Children often struggled to engage with and maintain focus on Mind Read. No significant correlations were found between Mind Read scores and total scores on the James ($rs < 0.38$, $p > 0.13$) and Dylan ($rs < 0.46$, $p > 0.07$) measures. Likewise, there were no significant correlations among Mind Read total correct, total duration, and error scores and parent ($rs < 0.43$, $p > 0.06$) and teacher ($rs < 0.45$, $p > 0.11$) measures of children's emotion regulation and social skills.
Conclusions: The feasibility and use of Mind Read appeared to be limited for our child sample group, possibly because of the app duration, focus and impulse-control issues, and the teenage content of the vignettes being developmentally inappropriate. ADHD, AD, MCS

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J Am Acad Child Adolesc Psychiatry. 2019;58:S148.

1.3 ONLINE PARENT TRAINING FOR DISRUPTIVE BEHAVIORS: INCREASING ACCESS TO CARE.

Diaz-Stransky A, Londono A, Zecher E, et al.

Objectives: Parent-behavior management training is underused, leading to overmedicated and undertreated disruptive behaviors. One-third to one-half of children with disruptive behavior disorders also meet the criteria for ADHD, and comorbidity typically worsens the prognosis. Current online trainings lack an individualized, interactive component. This is an open pilot study of an individualized online parent-training for disruptive behaviors with videoconference integration. The primary objective is to examine the acceptability and feasibility of this training program. A secondary aim is to assess the effect of the program on disruptive behaviors.
Methods: Children between ages 3 and 9 years were enrolled for an 8-week online training of their parents, including 3 videoconferences with a trained clinician. Baseline and endpoint visits were conducted to screen the children and obtain measures of disruptive behaviors. Ten children were included in the study, more than

half of whom have ADHD. The measures collected included a Patient Satisfaction Questionnaire and program completion-monitoring data. In addition, baseline and endpoint measures of disruptive behaviors, including the Disruptive Behavior Rating Scale (DBRS), were compared with a paired t-test.
Results: All participants completed the entire intervention. One participant did not return for an endpoint visit. Seven of 8 participants scored an average of 3 or more in the Patient Satisfaction Questionnaire (a scale from 0 to 4). A statistically significant reduction in the total score of DBRS was noted (p = 0.03).
Conclusions: Interactive online parent training enhanced by video consultation showed high parent satisfaction and a reduction of child disruptive behavior. This program may be an acceptable and feasible strategy to overcome barriers to care. It could minimize unnecessary prescriptions for ADHD and/or disruptive behaviors. DBD, PAT, ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S297.
CLINICAL RESPONSES AND SYMPTOMATIC REMISSIONS ACHIEVED WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD.
Cutler AJ.
Objectives: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) designed to provide treatment effect from the time of waking and throughout the day. A pivotal phase 3 study of DR/ER-MPH in children with ADHD demonstrated significant improvements in ADHD symptoms and functional impairment, with ADHD symptoms measured by the ADHD Rating Scale-IV (ADHD-RS-IV) in the 6-week, open-label, treatment-optimization phase of the study (ClinicalTrial NCT02493777). This post hoc analysis sought to determine the clinical significance of these findings by applying established clinical thresholds of response to the ADHD-RS-IV scores reported in the trial.
Methods: Dose (20, 40, 60, 80, or 100 mg per day; maximum: 3.7 mg/kg per day) and administration time (8:00 PM -¦ 1.5 hours) of DR/ER-MPH were optimized over 6 weeks. ADHD-RS-IV scores were obtained at baseline and at weeks 1-6. Clinical response was defined as a 30-percent reduction in ADHD-RS-IV from baseline. Excellent clinical response was defined as a 50-percent reduction in ADHD-RS-IV from baseline. Symptomatic remission was defined as an ADHD-RS-IV score 18. Proportions of participants meeting each response threshold were compared between weeks.
Results: Mean DR/ER-MPH dose increased from 29.7 mg per day at week 1 to 66.2 mg per day at week 6. Mean ADHD-RS-IV scores decreased (improved) from 42.5 at baseline to 11.0 at week 6. Rates of clinical response, excellent clinical response, and symptomatic remission increased from 62/117 (53%), 39/117 (33%), and 32/117 (27%) participants, respectively, at week 1 to 117/117 (100%), 109/117 (93%), and 104/117 (89%) participants, respectively, at week 6. The proportion of participants who achieved each response threshold increased significantly at each week (p 0.014 for all weeks and thresholds vs. week 1). Participants continued to achieve more stringent response thresholds between weeks 5 and 6, despite the dose remaining constant.
Conclusions: Evening-dosed DR/ER-MPH treatment resulted in high rates of clinical response (93%-100%) and symptomatic remission (89%) in children with ADHD that progressively improved with continued treatment optimization. The treatment optimization strategy used in this trial was effective and may serve as a guide for clinicians to optimize responses when using DR/ER-MPH

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J Am Acad Child Adolesc Psychiatry. 2019;58:S321.
15.1 TRIGEMINAL NERVE STIMULATION FOR ADHD: CORRELATES AND PREDICTORS OF TREATMENT RESPONSE.
Loo SK, McGough JJ.
Objectives: Trigeminal nerve stimulation (TNS) is a noninvasive neuromodulation method with minimal risk that has shown benefits for ADHD in a double-blind, sham-controlled trial, with an estimated effect size (CohenΓÇÖs d) of 0.5. Given the 50-percent response rate, the current study tests whether there are behavioral, cognitive, or EEG characteristics that are associated with ADHD symptom reduction and are predictors of positive response to TNS treatment.

Methods: A total of 62 children ages 8 –12 years, with K-SADS-diagnosed ADHD, were assessed at baseline and after 4 weeks of nightly active or sham TNS treatment. Treatment response was determined based on the week 4 Clinical Global Impression of Severity scale, with scores of 1 or 2 grouped as responders, whereas scores > 2 were grouped as nonresponders. Pearson correlations were used to identify correlates of ADHD symptom reduction and ANOVAs to test for significant baseline differences in TNS treatment responders versus nonresponders.
Results: Improvement in the ADHD Rating Scale (ADHD-RS) score was correlated significantly with improved affect regulation (Conners Emotional Lability Index) (r = 0.42, p = 0.002) and increased resting EEG power in mid- and right-frontal (Fz, F4) theta (4ΓÇô7 Hz), beta (13-25 Hz), and gamma (50-60 Hz) band power (r ranges 0.33 to 0.38, p < 0.05). Within the active treatment group, responders (n = 16) did not differ from nonresponders (n = 14) in age, IQ, gender distribution, socioeconomic status, or baseline ADHD-RS (all p values > 0.2). At baseline, the responders had lower score measures of emotional dysregulation, such as the Child Depression Inventory (CDI Total Score, p = 0.07) and the child (C) and parent (P)-rated Affective Reactivity Index (ARI), compared with the nonresponders (ARI-P, p = 0.01; ARI-C, p = 0.04). During resting-state EEG, treatment responders exhibited lower spectral power in high-frequency bands in frontal electrodes (Fz Beta p = 0.08, Fz Gamma p = 0.09, F4 Beta power p = 0.07) at baseline.
Conclusions: TNS is a promising nonpharmacological treatment for ADHD. Children with positive treatment response had lower baseline levels of emotion dysregulation and lower cortical activity in the frontal regions. Potential mechanisms will be discussed. ADHD, TREAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S288.

6.53 THE RELATIONSHIP BETWEEN ADHD AND ASTHMA IN A PEDIATRIC PSYCHIATRY INPATIENT SAMPLE.

Pritchard CE, Kim D, Dantuluri M, et al.

Objectives: Children with ADHD have a higher risk of allergy-based diseases, such as eczema. A pediatric mental health inpatient sample tests whether ADHD is predictive of asthma while considering potential moderators of the relationship.
Methods: Data on 392 mental health inpatients, ages 5ΓÇô17 years, included the variables age, sex, weight, height, race, household income, asthma diagnosis, ADHD diagnosis, number of mental illness diagnoses (proxy severity mental illness), and parent mental illness history. Univariate analyses predictive of asthma were conducted, and multivariable models were constructed accounting for multicollinearity, as well as moderation by race and sex.
Results: Of 392 inpatients, 81 (21%) had asthma and 168 (43%) had ADHD, whereas 43 (11%) had both. In the entire sample group, slightly more males (23%) had asthma than females (19%). There was a significant association between asthma and the following: 1) ADHD (X2 = 4.36, p =0.037, Cramers V = 0.11); and 2) the number of mental illness diagnoses (OR = 1.23 [95% CI = 1.05, 1.45], p = 0.009). Other predictors were black race (X2 = 12.58, p < 0.001, Cramers V = 0.18) and greater BMI (OR = 1.05 [95% CI = 1.01, 1.09], p = 0.01). Income was marginally associated with asthma (OR = 0.99 [95% CI = 0.99ΓÇô1.0], p = 0.05), but not history of family mental illness (OR = 1.16 [95% CI = 0.84, 1.59], p = 0.365). In a multivariate model, ADHD (p = 0.09), black race (p = 0.002), and BMI (p = 0.009) were predictive of asthma. In females, asthma was strongly associated with ADHD (n = 229; X2 = 9.58, p = 0.002), whereas this relationship was not true in males (n = 163; X2 = 0.327, p = 0.567).
Conclusions: In an inpatient pediatric psychiatry cohort, ADHD is predictive of asthma, whereas mental illness severity, black race, and greater BMI are also associated with asthma. These relationships are stronger in the female-only stratum. Given the past association of ADHD with allergic illnesses, future research should explore the relationship of immunity/inflammation with ADHD. ADHD, PYI

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J Am Acad Child Adolesc Psychiatry. 2019;58:S355.

37.1 ALPHA MODULATION DURING WORKING MEMORY ENCODING PREDICTS NEUROCOGNITIVE IMPAIRMENT IN ADHD.

Lenartowicz A .

Objectives: ADHD is associated with working memory (WM) deficits. However, WM is a multiprocess construct that can be impaired through several pathways, leaving the source of WM impairments in ADHD unresolved. In this study, we aim to replicate, in an independent sample group, previously reported deficits in component processes of WM deficits in ADHD and expand to consider their implications for neurocognitive outcomes.

Methods: In 119 children (ages 7ΓÇô14 years, 85 with ADHD), we used electroencephalography measures to quantify component processes during performance of a spatial working memory task. We quantified stimulus encoding using alpha range (8ΓÇô12 Hz) power, vigilance by the P2 event-related potential to cues, and WM maintenance by occipital-alpha and frontal-theta (4ΓÇô7 Hz) power. These measures were evaluated against metrics of executive function, ADHD symptoms, and academic achievement.

Results: Encoding alpha-power decreases and cue P2 amplitude were attenuated in ADHD, whereas occipital-alpha power during maintenance was significantly greater in ADHD, which is consistent with a compensatory response to weak encoding. Weak alpha modulation during encoding was associated with poorer reading comprehension and executive function, as well as enhanced ADHD symptoms. Previously reported effects in frontal-theta power failed to replicate.

Conclusions: Stimulus encoding, a component process of WM coupled to alpha modulation, is impaired in ADHD, and unlike WM maintenance or vigilance processes, has implications outside of the laboratory through a relationship with executive function and, to a weaker extent, reading comprehension. ADHD, COG, R

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J Am Acad Child Adolesc Psychiatry. 2019;58:S291.

6.62 SYMPTOM-LEVEL ASSOCIATIONS BETWEEN ADHD CRITERIA AND SCHOOL PERFORMANCE.

Rigoni M, Blevins LZ, Rettew DC, et al.

Objectives: The goal of this session is to evaluate the association between specific ADHD symptoms and subtypes and school performance.

Methods: The data for this study come from a follow-up sample group from the National Survey of Children's Health, which is a nationally representative survey performed by the Health Services and Resources Administration/Maternal and Child Health Bureau of Children in the United States under age 18 years. From this sample group, families of children (between the ages of 8 and 17 years), who indicated the presence of a child diagnosed with either ADHD or Tourette's disorder (N = 2782), were contacted by phone as part of the National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome (NS-DATA). Parents were asked about the presence of each individual ADHD symptom, as well as how the child was doing in school. Information on demographics, school services, and other disorders (including learning disorders) was also collected. The children who continued to meet the ADHD criteria were compared with those who no longer met the criteria for ADHD. Regression analyses were used to examine the association between ADHD symptoms (or subtype) and various areas of school performance, controlling for potential confounding variables.

Results: At the subtype level, children with the combined (adjusted OR = 5.84 [95% CI = 3.13-10.91]) and inattentive (adjusted OR = 5.54 [95% CI = 3.05-10.05]) subtype of ADHD were found to show significantly more overall deficits in school performance, controlling for potential confounders, compared with students who no longer met ADHD criteria, whereas no significant differences were found among children with the hyperactive-impulsive subtype. At the symptom level, inattentive ADHD criteria were most strongly associated with reduced school performance in reading, writing, math, and handwriting. It is noteworthy that children with the inattentive subtype, compared with the combined subtype, were more likely to be receiving school services in the form of an intervention educational program or a 504 Plan ($p < 0.05$).

Conclusions: All inattentive ADHD criteria are associated with school impairment. Contrary to other reports, we did not find evidence that children with inattentive ADHD are less likely to be identified for school-based intervention. ADHD, SAC, COG

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J Am Acad Child Adolesc Psychiatry. 2019;58:S95.

66.4 THE ROLE NEUROPSYCHOLOGICAL AND PSYCHOEDUCATIONAL TESTING IN INDIVIDUALS WITH ADHD.

Marks D.

Objectives: The objective of this presentation is to clarify the role of neuropsychological and psychoeducational assessment in the evaluation and management of children with ADHD.

Methods: A comprehensive literature (PubMed) search was conducted examining reviews (including meta-analyses) and empirical studies completed within the past 10 years on the role of psychoeducational and neuropsychological testing in ADHD, including sample groups with comorbid learning disorders.

Results: Recent investigations indicate significant neurocognitive deficiencies that traverse multiple domains; however, effect sizes have been modest, and specificity has been (at best) moderate and markedly variable. In addition, effect sizes for nonexecutive/inhibitory tasks have been found to be comparable to or greater than those for executive indices. A latent class analysis conducted using a preschool sample group showed the predictive utility of neuropsychological indices for school-age diagnoses to be poor, despite initial discriminative capacity. In contrast, a recent prospective (6-year) study of school-aged youth revealed that better working memory predicted lower ADHD severity, whereas diminished reaction time variability predicted improved overall functioning; notably, the findings held even after controlling for baseline behavior. Specific learning disorders, particularly developmental dyslexia (DD), have been found to frequently co-occur with ADHD and may have shared neurocognitive and genetic underpinnings; this includes mechanisms that have been primarily ascribed to DD (eg, rapid automatized naming, phonological awareness).

Conclusions: ADHD is a phenotypically heterogeneous disorder that manifests in variable levels of neurocognitive dysfunction. Such variability likely underlies the limited benefit of cognitive remediation efforts, which are particularly assessed through blind respondents. Neuropsychological and psychoeducational assessments are most productively used to identify individualized learning profile, as well as phenomena (eg, language disorders, specific learning disorders, developmental coordination disorder) that may masquerade as or co-traffic with expressions of ADHD. ADHD, EBP, TREAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S227.

4.24 DO CHILDHOOD SYMPTOMS OF ADHD INFLUENCE THE RISK OF BEING PHYSIVALLY INACTIVE IN ADOLESCENCE?

Selinus EN, Ekblom M, Durbeej N.

Objectives: Physical activity has been documented to influence several aspects of physical and mental health. Growing evidence is showing that physical activity can improve attention. Less is known about how ADHD symptoms in childhood affect physical activity in adolescence. We aimed to explore this relationship further.

Methods: We used a cohort of 3949 Swedish twins with data collected from those ages 9 (or 12) and 15 years. We investigated the influence of ADHD symptoms in childhood at age 9 or 12 years (both ADHD combined, and inattention and hyperactivity/impulsivity separately) on self-rated physical activity at age 15 years, using multiple logistic regression models. We considered potential confounders such as ASD, learning disorder, tic disorder, developmental coordination disorder, sex, and parent education level. The estimated associations are reported as ORs with 95-percent CIs.

Results: Individuals with symptoms over cutoff for ADHD as children (age 9 or 12; n = 246) were less likely to be physically active in adolescence (age = 15 years; OR = 0.56, 95% CI = 0.43 –0.73). More specifically, inattention was associated with less physical activity in adolescence (OR = 0.83, 95% CI = 0.79-0.88), whereas the opposite was true for hyperactivity/impulsivity (OR = 1.09, 95% CI = 1.02-1.16). These associations still remained when taking possible confounders such as sex, parental education level, and neuropsychiatric comorbidity into account. Both lower parental education level (father dropped out of

compulsory school) (OR = 0.6, 95% CI = 0.48-0.78) and female sex (OR = 0.68, 95% CI = 0.59-0.78) were associated with a lower degree of physical activity in adolescence. Learning disorder (OR = 0.62, 95% CI = 0.48-0.79) was the only comorbidity that significantly predicted being physically inactive in adolescence. There was no interaction between sex and ADHD in relation to physical activity.
Conclusions: Higher levels of inattention symptoms in childhood predicted a lower likelihood of being physically active in adolescence. These findings support the importance of helping children and adolescents with inattention symptoms to engage in physical activity. This appears especially important given the vast literature supporting the positive effects of physical activity on physical and mental health. ADHD, EPI, LONG

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J Am Acad Child Adolesc Psychiatry. 2019;58:S222.

4.8 ADMINISTARTION OF YOKUKASAN FOR ADHD IN 20 CHILDREN: A RETROSPECTIVE ANALYSIS.

Iino A.

Objectives: Yokukansan (YKS) is one of the Japanese herbal traditional medicine formulas (Kampo), prescribed for irritation, irritability, mood swing, and agitation, and the third highest selling Kampo for children and adults in Japan. YKS is indicated for neurosis, insomnia, crying baby in the night, delirium of adults, and peripheral symptoms of dementia. Methylphenidate hydrochloride, atomoxetine, and guanfacine hydrochloride are the only current choices under the Japanese health insurance system for ADHD in children. This time, the sole or combined administration of YKS for ADHD in 20 children was investigated retrospectively. The aim of this presentation is to determine the effect of YKS for children with ADHD.
Methods: This retrospective case series report was conducted in children with ADHD who received YKS. The 20 eligible children had the diagnoses of ADHD or suspected ADHD from January 2017 through March 2018 at our child psychiatric outpatient facility. These children were from ages 6 to 14 years. The following were researched: age, gender, IQ test (Wechsler Intelligence Scale for Children-Fourth Edition [WISC-4], Tanaka-Benet-5 test), the severity that DSM-5 defines at their family and school on the initial examination and 2 years later (0, mild [1], moderate [2], severe [3]), dropout of outpatient, and medication comorbidities.
Results: The average age was 9.75 years. The ratio of male to female was 19:1. The average IQ was 88.2 (range = 54-125). There were no side effects after administration. Eleven children had a blood test, which showed that 2 (10%) had a food allergy; 4 (20%) had febrile convulsion, an abnormal EEG, or epilepsy; and 2 (10%) had any severe physical disabilities. The diagnoses of comorbidity were 3 (15%) pervasive developmental disorders and ASD, 4 (20%) ODD, and 5 (25%) intellectual disability. Fourteen children (70%) had continued YKS more than a year, and 5 (25%) had dropped out of child psychiatric outpatient. There was sole administration of YKS for 13 cases (65%), whereas 7 (35%) had the combined administration. The average dose per day was 3.0 g (1 package is 2.5 g). The price of methylphenidate (27 mg) was $3.40, atomoxetine (25 mg) was $3.80, guanfacine (3 mg) was $5, and YKS was <source.27. Their ADHD severity at their family and school on the initial examination was 1.85 (average, range 0-3). Two years later, the average severity was 0.85 (0-2, n = 13).
Conclusions: The anti-stress effect of YKS might improve the severity of ADHD symptoms in children. ADHD, CAM, RCR

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J Am Acad Child Adolesc Psychiatry. 2019;58:S355-S356.

37.2 MULTI-METHOD EVIDENCE FOR IMPAIRING EFFECTS OF EMOTIONAL AROUSAL ON COGNITIVE CONTROL IN ADHD.

Karalunas S.

Objectives: Emotional dysregulation (ED) is of interest in ADHD, because wide variation predicts individual differences in impairment. Nonetheless, the mechanisms of ED remain unclear. ADHD-related impairments in cognitive control are hypothesized to underlie ED. However, simple relationships between cognitive control and ED have not been found consistently. An improved model is needed that considers how emotional context affects cognitive control in ADHD. This could help clarify mechanisms of ED in the disorder.

Methods: A total of 130 well-characterized adolescents (nADHD = 61, mean age = 13.8 years) completed an emotional go/no-go task while a 32-channel EEG data were recorded. Reaction time and accuracy were analyzed using a linear ballistic accumulator (LBA) model, which separately quantifies efficiency of evidence accumulation (ie, drift rate) and the location of the response threshold (ie, boundary height). Event-related potentials quantified the following: 1) reactive responses to emotional stimuli (P1); 2) regulatory processing (LPP); and 3) effects of emotion on cognitive control (No-go N2).
Results: LBA identified decisive Bayesian evidence for group x emotion interactions in drift rate (Go OR = 11.94) and boundary height (Go OR = 24.88; No-go OR = 24.93). Drift rates increased for positive versus neutral stimuli. The effect was largest in ADHD and was consistent with increased emotional arousal in that group. Only typically developing adolescents made strategic-boundary height adjustments to improve performance in the positive condition, which was consistent with emotion interfering with cognitive control in ADHD. Neurophysiological results converged with behavioral findings. The effects of emotion on P1 were larger in ADHD than in control subjects (interaction p = 0.016), which was consistent with greater emotional arousal. Adolescents with ADHD had smaller no-go N2s overall, with the largest difference in the positive condition (interaction p = 0.029), which was consistent with cognitive weaknesses exacerbated by emotional context.
Conclusions: Findings provide convergent cognitive and neurophysiological evidence that reactive overarousal in positive-valence contexts exacerbates ADHD-related impairments in cognitive control. Distinguishing reactive and regulatory contributions to ED can spur the development of novel interventions in ADHD. ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S291-S292.

6.64 CHILDREN AND ADOLESCENT WITH ADHD: A MET5A-ANALYSIS OF THE PREVALENCE OF BONE FRACTURES.

Seens H, Modarresi S, MacDermid JC, et al.

Objectives: Among children and adolescents, ADHD is a significant neurodevelopmental disorder with 5-percent prevalence. Bone fractures account for 25 percent of accidents and injuries among all children and adolescents. Considering the characteristics of inattention, hyperactivity, and impulsivity in ADHD, it is critical to analyze the prevalence of bone fractures among children and adolescents with ADHD.
Methods: A systematic review and meta-analysis were completed using an electronic search of the following databases: CINAHL, Embase, PsycINFO, PubMed, and Scopus. The search terms used were: attention deficit hyperactivity disorder OR attention deficit disorder and bone fracture. Studies examining patients ages 18 years or younger who received a diagnosis of ADHD and were tracked (prospectively or retrospectively) for 5 or more years were included. Effect sizes, using a random-effects model, were calculated.
Results: The database search resulted in 445 records, which were assessed for duplicates and inclusion criteria based on their abstracts. This led to the examination of 31 full-text articles, of which 5 met the inclusion criteria for meta-analysis. The summary revealed that the prevalence of bone fractures among children and adolescents with ADHD was 4.83 percent (95% CI = 3.07%-6.58%). Using a subset of data, the distribution of fractures in the upper limbs, lower limbs, and other anatomical regions was found to be 69.62 percent, 22.85 percent, and 7.53 percent, respectively. Another subset of studies determined that children and adolescents with ADHD have a 2.55-fold increase in the prevalence of fractures than their counterparts.
Conclusions: The results of this analysis revealed the prevalence, distribution, and fold-increase of fractures among children and adolescents with ADHD. This knowledge is critical to psychiatrists, physicians, parents, and policymakers in their endeavors to create safe environments in which children and adolescents can thrive and optimize their health. ADHD, PYI, EPI

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J Am Acad Child Adolesc Psychiatry. 2019;58:S289.

6.56 THHE RELATIONSHIP BETWEEN BRAIN-DERIVED NEUROTROPIC FACTOR (BDNF), POLYMORPHISM, AND QUANTITATIVE EEG SUBSTRATES OF ADHD IN CHILDREN AND ADOLESCENT.

Jhung K, Park Y-J, Young PJ.

Objectives: Because of its role in neuronal survival, proliferation, and synaptic plasticity during development, brain-derived neurotropic factor (BDNF) has been hypothesized to be associated with susceptibility to ADHD. The BDNF 196 G/A polymorphism, causing a valine-to-methionine substitution at codon 66, results in reduced cell surface expression of BDNF. This study aimed to investigate the association between BDNF polymorphism and neurophysiological characteristics in Korean children and adolescents with ADHD.

Methods: A total of 79 subjects (mean age 9.41 -¦ 3.30 years) with ADHD participated in the study. EEG with eyes closed and eyes open conditions were recorded. Relative powers were estimated for delta (1-4 Hz), theta (4ΓÇô8 Hz), alpha (8-12 Hz), beta (12-25 Hz), and gamma (30-40 Hz) bands. The single-nucleotide polymorphism (SNP) rs6265 of BDNF was genotyped to examine the association with power of frequency bands. Ratio coefficients were calculated between frequency bands. The Kruskal-Wallis Test was used for statistical analyses.

Results: The BDNF genotype comprised 33 homozygotes (GG, AA) and 46 heterozygotes (GA). There were significant differences of quantitative EEG among BDNF genotypes. In eyes closed and open state, the homozygote genotype of the BDNF showed significantly higher theta power in frontal, central, and posterior and lower alpha power in frontal, central, and posterior regions compared with the heterozygote genotypes. Moreover, homozygotes showed greater levels of slow wave activity in frontal and central regions. For theta/alpha, theta/beta, and delta/alpha ratios, homozygotes showed greater slow wave activity in the posterior regions.

Conclusions: The findings support the association of BDNF polymorphism and neurophysiological markers of ADHD. A heterozygote advantage, referring to situations in which heterozygotes show a greater or weaker effect for a trait than the homozygotes, is suggested. Underexpression or overexpression of BDNF, produced by the polymorphism, may cause disruption of normal neural functioning. Because of the limited sample group size, further investigation by larger and other ethnic groups will be needed for the future. ADHD, GS, NEURODEV

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J Am Acad Child Adolesc Psychiatry. 2019;58:S296.

DURATION OF EFFECT OF A NOVEL, HOME-BASED, DIGITAL TREATMENT FOR PEDIATRIC ADHD.

Kollins SH.

Objectives: AKL-T01 is an investigational digital treatment delivered through a video game-like interface, targeting neural networks involved in attention and cognitive control. As previously reported (Software Treatment for Actively Reducing Severity of ADHD: STARS-ADHD), AKL-T01 showed statistically significant improvement over an active digital control in an objective measure of attention [The Test of Variables of Attention (TOVA®) Attention Performance Index (API)], from baseline to posttreatment. Secondary endpoints improved in both groups but did not separate between groups. AKL-T01 was well tolerated with few and mild adverse events. The duration of effect of AKL-T01 after treatment cessation is unknown. In this study, we assessed sustained effects from end-of-treatment (FU-0) to 28 days posttreatment (FU-28).

Methods: The STARS-ADHD-Follow-Up (FU) was a 12-week double-blind, parallel group, observational study, conducted in patients (n = 175) who completed the STARS-ADHD trial. Primary outcomes were within-group differences in the AKL-T01 group in API, ADHD Rating Scale (ADHD-RS), Impulsivity Rating Scale (IRS), Behavior Rating Inventory of Executive Function (BRIEF)-Parent Version, and Cambridge Neuropsychological Test Automated Battery Spatial Working Memory (CANTAB SWM) from FU-0 to FU-28. Secondary outcomes were between-group differences for these variables at FU-28. Post-hoc responders for these measures were assessed.

Results: Twenty-eight days after AKL-T01 cessation, no significant difference was found compared to FU-0 in any of the primary outcome variables. Furthermore, AKL-T01 did not significantly differ from the active control in any of the measures. Comparison of responder rates for AKL-T01 at FU-0 as compared to FU-28 revealed that of responders with an API change >1.4 (40%), half remained responders at FU-28 (20%). Responders with an API score 0 decreased from 13.9 percent to 4.6 percent. There was a decrease of

ADHD-RS responders (those with at least 30% improvement) from 30.1 percent to 17.8 percent. The percentage of IRS responders decreased (48.7% to 27%).
Conclusions: AKL-T01 outcomes did not differ significantly after one month of treatment cessation. Responder analyses suggest that for most outcomes approximately half of the responders exhibited a sustained response after one-month treatment cessation. More rigorously controlled, future follow-up studies should investigate the stability of treatment outcomes for specific patient populations

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J Am Acad Child Adolesc Psychiatry. 2019;58:S356.

37.4 COMPURE-BASED AND PARENT-REPORTED ASSESSMENT OF EXECUTIVE FUNCTIONING: METHOD VARIANCE AND IMPLICATIONS FOR INTERPRETING FINDINGS FROM ADHD EFFICACY TRIALS.

Kollins SH.

Objectives: The objectives of this presentation are to assess the relationship among various measures of executive functioning, ADHD symptomatology, and impairment in a sample group of youth with ADHD enrolled in an RCT for a novel digital therapeutic (AKL-T01).
Methods: Post hoc analysis on data from 345 children between 8 and 12 years of age, with a verified diagnosis of ADHD, were conducted. The relationships among baseline (before randomization) scores from parent-reported measures (Behavior Rating Inventory of Executive Function [BRIEF], ADHD-Rating Scale [RS], Impairment Rating Scale) and computer-based measures (Test Of Variables of Attention [TOVA], Cambridge Neuropsychological Test Automated Battery [CANTAB]) were evaluated. In addition, the patterns of change after treatment across the measures were also assessed for children randomized to the digital treatment condition (n = 179).
Results: In general, correlations between parent-reported and computer-based measures of functioning were low at baseline, although within parent-reported or computer-based measures, the associations across different indices were generally somewhat higher. For example, the correlations between subscales (Inattention and Hyperactivity-Impulsivity) of the ADHD-RS and subscales of the TOVA and CANTAB ranged from r = 0.09 to 0.18, whereas the ADHD-RS subscale correlations with subscales of BRIEF (r = 0.02 to 0.59) and Impairment Rating Scale (r = 0.0-0.33) were higher but still small. Even within domains purporting to measure similar constructs, correlations between parent-reported and computer-based measures were small. For example, measures of working memory performance from the CANTAB were virtually unrelated to parent-reported measurement of working memory on the BRIEF (baseline correlations: 0.02 to 0.04). The pattern of associations between change scores for children receiving active treatment tended to be different for those children who showed improvement after the digital treatment compared with those who did not exhibit improvement.
Conclusions: Findings suggest that, overall, the relationship between computer-based measures of executive functioning and related outcomes are not strongly associated with parent-report measures of symptoms and impairment. Results will be discussed in the context of interpreting findings from ADHD efficacy studies using parent-report measures, as well as understanding the clinical meaningfulness of traditional clinical trial outcome measures. ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S244.

4.72 DIFFERENTIOA QUANTITATIVE ELECTROENEPHALOGRAPHY (QEEG) SUBSTRATES ASSOCIATED WITH SUBTYPES OF ADHD CHILDREN AND ADOLESCENTS.

Jhung K, Park Y-J, Young PJ.

Objectives: ADHD is classified by the DSM-5 into 3 subtypes that can be distinguished from each other on various characteristics. Developing a reliable neural marker to distinguish the illness and the subtypes will provide further insights underlying this heterogeneous illness and aid in making a precise diagnosis. This study aimed to investigate the neurophysiological markers associated with the predominantly inattentive type and the combined type of ADHD children and adolescents.

Methods: Eighty ADHD subjects (mean age 9.90 -¦ 3.1 years; 48 ADHD-Combined type [ADHD-C], 32 ADHD-Inattentive type [ADHD-I]) and 30 healthy control subjects (mean age, 9.10 -¦ 2.9 years) participated. Resting-state EEG with eyes-closed and eyes-open condition was recorded. Relative powers were estimated for delta (1-4 Hz), theta (4-8 Hz), alpha (8ΓÇô12 Hz), beta (12-25 Hz), and gamma (30ΓÇô40 Hz) bands. Ratio coefficients were calculated between frequency bands. The Kruskal-Wallis test was used for statistical analyses.
Results: There were significant differences of frequency bands among the groups. The ADHD-C subtype showed significantly higher levels of delta power in the frontal and central regions and lower alpha power in the frontal regions compared with the ADHD-I (all, $p < 0.05$). Moreover, ADHD-C showed greater levels of slow wave activity in the delta/beta and delta/alpha ratios in the frontal and central regions compared with the ADHD-I (all, $p < 0.05$). Compared with control subjects, ADHD-C showed greater levels of slow-wave activity in delta/theta ratios in the frontal and central regions (all, $p < 0.05$).
Conclusions: The findings show that the combined type (ADHD-C) has different neurophysiological characteristics than the inattentive type and control subjects. More specifically, higher levels of slow waves of ADHD-C more closely implicate the hypothesized maturational lag group in ADHD. In future studies, heterogeneity should be fully considered for exploring neurobiological mechanisms of ADHD. ADHD, ND

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J Am Acad Child Adolesc Psychiatry. 2019;58:S312.

8.3 MINDFULNESS-BASED ADHD TREATMENT FOR CHILDREN: A PILOT FEASIBILITY STUDY.

Saunders DC.

Objectives: ADHD is a neurodevelopmental disorder associated with a myriad of adverse outcomes. Medication is known to be effective but is limited by side effects. Mindfulness improves attention in healthy adults, as well as adults with ADHD, and 2 small studies in teenagers with ADHD have shown preliminary evidence of efficacy. To our knowledge, however, there are no standardized mindfulness interventions for children with ADHD, nor has it been studied in a rigorous research setting in children.
Methods: We developed a novel mindfulness-based intervention for children with ADHD Mindfulness-Based ADHD Treatment for Children (MBAT-C)ΓÇöand conducted a single-arm pilot study (N = 10) with the following aims: 1) refine the MBAT-C manual for a subsequent randomized controlled trial; 2) evaluate acceptability and feasibility of MBAT-C, as measured by attendance, retention, homework completion, and engagement; and 3) test for preliminary efficacy on multiple objective and subjective indices of ADHD symptoms, including attention, behavior, executive function, and clinical severity by self-report and parent report and neuropsychiatric assessment.
Results: In aim 1, the MBAT-C manual was finalized through focus groups and feedback from participants and parents. The ideal sequence of meditation practices, discussion topics, and logistical considerations were identified. In aim 2, multiple indices of feasibility and acceptability exceeded pretrial benchmarks, including attendance (65.9%), retention (75%), homework completion (66.1%), and engagement. In aim 3, multiple subjective and objective indices of ADHD symptoms showed improvement, including ADHD symptoms measured by the ADHD Rating Scale; attention, problem behaviors, and anxiety measured by the Child Behavior Checklist; and working memory as assessed on the NIH Toolbox List Sorting Working Memory test.
Conclusions: These data suggest that MBAT-C is a feasible and acceptable intervention for children with ADHD and that it may be efficacious. Further study is warranted to assess efficacy. The next phase, funded by the National Institutes of Health, is a 3-arm, randomized controlled trial comparing MBAT-C to medication and a combined intervention. CAM, ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S283.

6.38 CROSS-SECTIONAL AGE ANALYSIS OF SLEEP PROBLEMS IN 25- TO 17-YEAR-OLD CHILDREN WITH ADHD-COMBINED, ADHD-INATTENTIVE, OR ASD.

Mayes S, Puzino K, DiGiovanni C, et al.

Objectives: Sleep problems are common in ASD and ADHD, but no study has compared the frequency and type of sleep problems as a function of age in children ages 2-17 years with ASD, ADHD-Combined (C), and ADHD-Inattentive (I). This study determined the frequency of 10 sleep problems at successive ages; examined when specific sleep problems were likely to occur, peak, decline, or remain stable; and compared age-related patterns between diagnostic groups.

Methods: Participants comprised 2456 children rigorously diagnosed with ASD, ADHD-C, or ADHD-I. Mothers rated their children from not at all to very often a problem on 10 Pediatric Behavior Scale sleep items (difficulty falling asleep, restless during sleep, wakes during the night, nightmares, talks/walks in sleep, wets bed, wakes early, sleeps less than normal, sleeps more than normal, and daytime sleepiness). ANCOVA and partial correlations (controlling for medication status) determined differences in sleep problems between diagnostic and age groups (2-5, 6-8, 9-12, and 13–17 years) and the linear relationship between age and sleep problems. Frequency percentages by severity for the 10 sleep problems for each age and diagnostic group were graphed.

Results: Children with ASD had more sleep problems than children with ADHD-C, who had more sleep problems than children with ADHD-I. Nighttime sleep problems were more often severe in ASD and ADHD-C and mild in ADHD-I. The most common problems were difficulty falling asleep, restless during sleep, and wakes up during the night. All 7 nighttime sleep problems were negatively correlated with age in ASD and ADHD-C, and most were in ADHD-I. Sleeping more than normal and daytime sleepiness were positively correlated with age in all groups (adolescents were the sleepiest) and were strongly correlated with each other (children who slept more at night were sleepier during the day).

Conclusions: Even though nighttime sleep problems tended to decline with age, correlations were small. Difficulty falling asleep (at least sometimes) was a problem for more than half of the adolescents with ASD, ADHD-C, and ADHD-I, and waking up during the night was a problem for almost half of those with ASD and ADHD-C. Given that sleep problems are unlikely to resolve with age for the majority of youth, developmentally appropriate, tailored interventions are needed to address sleep difficulties and to limit their potential adverse effects. SLP, ADHD, ASD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S125.

1.2 DOUBLE-BLIND, SHAM-CONTROLLED, PILOT STUDY OF TRIGEMINAL NERVE STIMULATION (TNS) FOR ADHD.

McGough JJ.

Objectives: Trigeminal nerve stimulation (TNS)ΓÇöa minimal risk, noninvasive neuromodulation method ΓÇöhas shown potential benefits for ADHD in an unblinded open study. This blinded sham-controlled trial was conducted to assess the efficacy and safety of TNS for ADHD and the potential changes in brain spectral power using resting-state quantitative electroencephalography (qEEG).

Methods: A total of 62 children aged 8-12 years, with full-scale IQ 85 and K-SADS-diagnosed ADHD, were randomized to 4 weeks nightly treatment with active or sham TNS, followed by 1 week without intervention. Assessments included weekly clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales, as well as qEEG at baseline and at week 4.

Results: ADHD-RS totals showed significant group-by-time interactions (F = 8.12, df = 1/228, p = 0.005); at week 4, Cohen's d = 0.5. CGI-Improvement also favored active treatment (+º2 = 8.75, df = 1/168, p = 0.003); number-needed-to-treat (NNT) = 3. Resting-state qEEG showed increased spectral power in right frontal and frontal midline frequency bands with active TNS. Neither group had clinically meaningful adverse events.

Conclusions: This study demonstrates TNS efficacy for ADHD in a blinded sham-controlled trial, with the estimated treatment effect size similar to nonstimulants. TNS is well-tolerated and a minimal risk. Additional research should examine treatment response durability and the potential impact on brain development with sustained use. ADHD, NM, RCT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S247-S248.

5.9 SYMPTOM PROFILES AND MEDICATION TREATMENT PATTERNS IN A CLINICAL SAMPLE OF CHILDREN WITH ADHD VERSUS ASD.

Mayes S, Baweja R, Waxmonsky JG, et al.

Objectives: Studies show that the vast majority of children with ASD have ADHD, and children with both ADHD-Combined (ADHD-C) and ASD have high rates of oppositional, aggressive, and irritable behavior. Despite the similarity of symptoms that are the target of common treatment, the levels of impairment and prescribing practices may differ between the groups, although this has not been examined systematically in children with ADHD-C, ADHD-Inattentive (ADHD-I), and ASD.

Methods: A total of 1407 children with ASD and 1036 children with ADHD without ASD (ages 2ΓÇô17 years) underwent comprehensive evaluations in a psychiatry diagnostic clinic and were compared with 186 of their typical peers. Symptom profiles were derived from maternal ratings on the Pediatric Behavior Scale in 8 areas (ADHD, oppositional/aggressive, irritable/angry, anxious, depressed, and social, writing, and learning problems).

Results: Psychotropic drugs were prescribed to 38.0 percent with ADHD-C, 33.3 percent with ASD, and 20.2 percent with ADHD-I. These drugs included 24.0 percent ADHD medication (22.1% stimulant, 2.3% atomoxetine), 7.8 percent antipsychotic drug, 5.5 percent SSRI, and 4.9 percent +¦2 agonist. Less frequent were an anticonvulsant, non-SSRI antidepressant, lithium, and anxiolytic drugs. ADHD severity ratings did not differ between the sample groups of total ADHD and ASD ($F = 0.1$, $p > 0.05$) but were higher for ADHD-C than ASD and ADHD-I and were higher for ASD than ADHD-I ($F = 240.0$, $p < 0.05$). Children with ASD were more irritable/angry and anxious than children with ADHD-C, but ratings did not differ in oppositional/aggressive behavior. Compared with ASD, children with ADHD-C were more likely to be on an ADHD medication (¤ç2 = 33.7, $p < 0.0001$), whereas antipsychotic drugs and SSRIs were more common in ASD (¤ç2 = 22.9, 16.8, $p < 0.0001$). Children with ADHD-I were least impaired and least likely to use medication ($p < 0.0001$). For the groups with ADHD and ASD, medicated children were more impaired than children not treated in all 8 symptom areas ($p = 0.004$). Symptom scores were far worse for treated and untreated children with ADHD and ASD than they were for typical untreated children.

Conclusions: Medication did not come close to normalizing symptoms in treated children. Given the nonsignificant difference in ADHD severity ratings between the sample groups with ASD and total ADHD, it is important to recognize and treat ADHD in ASD and to assess for possible ASD in children diagnosed with ADHD so that evidence-based ASD intervention is provided. ADHD, ASD, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S252.

5.21 EVALUATION OF EFFICACY AND SAFETY OF SHP465 MIXED AMPHETAMINE SALTS ATA LOW DOSE IN CHILDREN WITH ADHD: RESULTS FROM A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY.

Mattingly G, Arnold V, Yan B, et al.

Objectives: The goal of this session is to evaluate the efficacy, safety, and tolerability of a once-daily regimen of 6.25 mg SHP465 mixed amphetamine salts (MAS) extended-release, a dose lower than the approved doses, versus placebo (Pbo) in children with ADHD.

Methods: Children (ages 6-12 years) with DSM-5ΓÇôdefined ADHD, baseline ADHD-Rating Scale-5 total scores (ADHD-RS-5-TS) 28, and Clinical Global Impression-Severity (CGI-S) scores 4 were eligible. Participants were randomized 1:1 to 6.25 mg SHP465 MAS or Pbo for 4 weeks. The ADHD-RS-5-TS change from baseline at week 4 (the primary endpoint) and CGI-Improvement (CGIΓÇôI) score at week 4 (the key secondary endpoint) were assessed in the full analysis set (safety set participants with a baseline and 1 postdose ADHD-RS-5-TS assessment) using linear mixed-effects models for repeated measures. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and vital sign changes in the safety set (randomized participants with 1 study drug dose).

Results: Of the 89 randomized participants (Pbo, n = 44; SHP465 MAS, n = 45), 83 completed the study (Pbo, n = 41; SHP465 MAS, n = 42). At week 4, least squares (LS) mean (95% CI) scores were as follows: 1) ADHD-RS-5-TS changes from baseline were 9.7 (13.2, 6.2) with Pbo and 11.6 (15.0, 8.2) with SHP465 MAS; and 2) CGI-I scores were 3.3 (3.0, 3.6) with Pbo and 3.2 (2.9, 3.5) with SHP465 MAS. The LS mean (95% CI) treatment differences (SHP465 MAS Pbo) were not statistically significant for ADHD-RS-5-TS

change (1.9 [6.8, 3.1], p = 0.451; effect size [ES] = 0.17) or CGI-I score (0.1 [0.5, 0.3], p = 0.597; ES = 0.12). The frequency of TEAEs was greater with SHP465 MAS (24.4%) than Pbo (16.3%); no serious or severe TEAEs were reported. The most frequently reported TEAEs (Pbo vs. SHP465 MAS) were headache (7.0% vs. 4.4%) and decreased appetite (4.7% vs. 2.2%). Mean -¦ SD changes from baseline (Pbo vs. SHP465 MAS) at the final on-treatment assessment were as follows: 1) 1.8 -¦ 10.02 versus 0.5 -¦ 9.87 beats per minute for pulse; 2) 0.8 -¦ 6.23 versus 1.8 -¦ 6.52 mm Hg for systolic blood pressure; and 3) 0.3 -¦ 6.61 versus 3.1 -¦ 7.24 mm Hg for diastolic blood pressure.
Conclusions: At a low dose of 6.25 mg, SHP465 MAS was not statistically superior to Pbo in reducing ADHD symptoms in children aged 6-12 years with ADHD. This dose of SHP465 MAS was generally well-tolerated. ADHD, PPC, RCT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S143-S144.

7.5 Assessment and management of ADHD in youth with ASD.

McCracken JT.

Objectives: The presentation will provide an overall, clinically oriented review of the nature of the overlap of ADHD with ASD, and the clinical impact, assessment, and treatment approaches, guided by a major review of best available clinical evidence.
Methods: Summaries of research (RCTs, clinical phenotyping studies of ASD, clinical guidelines) from the following key areas of research will be presented: 1) frequency of overlap of ADHD symptoms and categorical diagnoses in those with an ASD diagnosis; 2) parents and other adults confirm significance of these behaviors in impeding developmental progress among the top 5 parental concerns; 3) recommended approaches for assessment of ADHD in those with ASD; and 4) ranked options, based on published evidence of recommended treatment approaches, monitoring, and other clinical features, of medical and behavioral intervention approaches for significant ADHD features in those with ASD.
Results: ADHD behaviors and categorical ADHD diagnoses are very common in children, adolescents, and adults with ASD, approaching 30 to 50 percent of all those diagnosed. This overlap is believed to partially reflect the impact of overlapping/shared risk genes for ASD and ADHD. Careful assessment and differential diagnoses will be shared and presented, but many familiar assessment tools perform well to assess ADHD. Recently, data from well-controlled RCTs confirm the largely positive performance of methylphenidate and guanfacine. Other options also will be discussed. Setting appropriate goals also will be reviewed.
Conclusions: ADHD in ASD is a major and impairing common co-occurring disorder with ASD. Assessment and treatment can be straightforward and of major positive impact if recognized. ASD, ADHD, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S186.

2.48 Clinical characteristics associated with receipt of behavioral helth care embedded in pediatric primary care versus autside of the practice for teens stimulant-treated for ADHD.

Joseph HM, Lindstrom RA, Kipp HL, et al.

Objectives: Pediatricians often manage ADHD, and AACAP provides recommendations for when to refer to behavioral health care (BH). Although BH providers are increasingly embedded in primary care, little research has examined their use. This study of adolescents stimulant-treated for ADHD in pediatric offices provided an opportunity to examine BH use and associated clinical characteristics as a function of embedded versus outside BH.
Methods: Participants (N = 338) ages 13–18 years (mean = 14.98 years; SD = 1.53), treated with stimulants for ADHD in 1 of 7 pediatric practices, and one parent each, were enrolled into a randomized controlled trial aimed at decreasing stimulant misuse and diversion. Each participant completed an electronic survey about the following: demographics; the adolescent's symptoms of mental illness; academic, social, and global functioning; and current medical and behavioral treatments. T-tests and chi-squares examined the demographic and clinical characteristics as a function of BH services.

Results: A total of 140 (41.4%) adolescents reported BHΓÇö27.5 percent (n = 93) embedded and 13.9 percent (n = 47) outside. Adolescents with embedded BH, compared with those without BH, had greater ODD (t = 1.96 [289], p = 0.05, anxiety, t = ΓêÆ2.58 [285], p = 0.01) and marginally greater depression symptoms (t = ΓêÆ1.91 [285], p = 0.06). They were also more likely to receive multiple psychotropic medications (t = 3.93 [289], p < 0.01) and have poorer social functioning (t = 2.11 [289], p = 0.04) and lower parental education (X2 = 12.00 [3], p < 0.01). Compared with adolescents receiving embedded BH, adolescents receiving outside BH had more severe symptoms of ADHD (X2 = 10.52 [1], p < 0.01, ODD, t = 2.435 [336], p = 0.02), anxiety (t = 2.51 [332], p = 0.02), and depression (t = 2.70 [332], p < 0.01). They also had greater impairment from ADHD (t = 3.86 [336], p < 0.001), ODD (t = ΓêÆ2.79 [336], p < 0.01), lower general functioning (t = 3.36 [336], p < 0.001), and lower grades (t = ΓêÆ2.08 [329], p = 0.04).
Conclusions: Although <50 percent of stimulant-medicated teenagers received BH services, adolescents with a higher clinical need (mood, anxiety, and ODD symptoms, impairment, and/or polypharmacy) were more likely to use these services. Adolescents under the care of outside BH providers reported the highest levels of impairment, suggesting a limit to the severity of cases managed in-house and appropriate referral to resources. ADHD, STIM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S286.

6.46 SINGLE-DOSE PHARMACOKINETICS OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN CHILDREN WITH ADHD.

King TR, Herman BK, Pardo A, et al.

Objectives: The objective of this study was to evaluate the pharmacokinetics (PK) of fasting conditions with a single dose of 10 mg of amphetamine extended-release oral suspension (AMPH EROS; 2.5 mg/ml) in pediatric patients with ADHD (ages 6-12 years). AMPH EROS comprises a 3.2:1 ratio of d- and l-amphetamine delivered using the LiquiXR drug technology.
Methods: This phase 1, open-label, single-dose, one-period, one-treatment PK study enrolled 12 children ages 6ΓÇô12 years with ADHD. PK parameters for d- and l-amphetamine in plasma (Cmax, tmax, AUC0-Γê×, and t1/2) were calculated and expressed as means, geometric means, and standard deviations. The primary endpoint was all objective PK measurements at 28 hours postdose. PK was evaluated for 2 cohorts (6 patients ages 6-9 years and 6 patients ages 10-12 years). Safety was monitored continuously and assessed based on the occurrence of adverse events.
Results: The Cmax was 54.9 ng/mL and 17.1 ng/mL for d- and l-amphetamine, respectively. The Tmax was reached at 3.4 hours for d-amphetamine and at 4.1 hours for l-amphetamine. The mean plasma AUC0-Γê× was 1061.3 for d-amphetamine and 380.5 for l-amphetamine. The mean t1/2 was 10.4 for d-amphetamine and 12.1 for l-amphetamine. The apparent elimination half-life was 10.6 hours for d-amphetamine and 12.5 hours for l-amphetamine. Overall, AMPH EROS Tmax in the 6ΓÇô9-year cohort was 4.6 hours and that for the 10ΓÇô12 age group was 2.93 hours. The corresponding Cmax measurements were 62.6 ng/mL in patients ages 6ΓÇô9 years and 43.3 ng/mL in patients ages 10ΓÇô12 years. The study drug was well-tolerated by the subjects in this study. Two treatment-emergent adverse events (TEAEs) were reported in one subject, and the TEAEs (rash on legs and diarrhea) occurred approximately 12 hours postdose.
Conclusions: In conclusion, this study confirmed that the PK profile of AMPH EROS was different for some parameters between youth ages 6ΓÇô9 years and those ages 10ΓÇô12 years, and overall, the PK profile for those ages 6-12 years was comparable to other amphetamine formulations. ADHD, PKS, SAC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S291.

6.63 DOES THE DIAGNOSIS OF ODD COMORBID WITH ADHD AFFECT BEHAVIOR IN CHILDREN?

Satodiya R, Spring L, Carlson GA.

Objectives: Impulsivity and mood dysregulation characterize children with ADHD. However, often loses temper and easily annoyed are symptoms of ODD. Children with serious problems of anger and explosive behavior account for many psychiatric hospitalizations with higher needs for medications. This study

hypothesized that ODD, in addition to ADHD, accounts for the frequency and severity of outbursts in hospitalized children.
Methods: Parents completed rating scales (SNAP, Strength and Difficulties Questionnaire, Affective Reactivity Scale, and Irritability Inventory) for children hospitalized in a 10-bed psychiatric inpatient unit. Nurses completed the Behavior Activity Rating Scale (BARS) on outburst episodes of children getting PRN medication (PRN), seclusion, restraint, or therapeutic holds (S/R/H). The BARS quantifies why a child gets agitated (anger or distress), duration of outbursts in 15-minute intervals, type of PRN given, and any other restrictive needed. Diagnoses were made at an interdisciplinary team meeting held for each child. We performed a group comparison controlling for admission from aggression.
Results: A total of 113 children (ADHD = 17 [15%], ADHD+ODD = 58 [51.3%]) were admitted between November 2017 and April 2018. There were 570 incidents requiring PRN and/or S/R/H intervention in these children significantly more in ADHD+ODD children (463 [81.2%]) than ADHD only (107 [18.8%]). Compared with ADHD only, children with ADHD+ODD were significantly more likely to be admitted for aggression (79.3% vs. 29.4%), and to have higher parent-rated ODD (p = 0.04) and conduct disorder symptoms (p = 0.009), resulting in worse behavioral outbursts at home (p = 0.023). During hospitalization, the children required more S/R/H (74.1% vs. 35.3%) and received more neuroleptic PRNs (60.7% vs. 48.1%). The duration of outbursts did not differ by diagnosis, and 55 percent of outbursts lasted more than 45 minutes.
Conclusions: Comorbid ODD worsens the behavior of children with ADHD, leading to more aggression that requires hospitalization and higher levels of care than children with ADHD only. Further examination of aggression symptomatology and treatment interventions are needed to understand the phenomenology underlying their behavior and to design appropriate management protocols in these children. ADHD, ODD, ICP

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J Am Acad Child Adolesc Psychiatry. 2019;58:S289.

6.57 PREDICTORS OF STIMULANT MEDICATION CONTINUITY IN CHILDREN WITH ADHD.

Kamimura-Nishimura KI, Brinkman WB, Epstein JN, et al.

Objectives: Pediatric ADHD medication continuity is suboptimal. Although some predictors of ADHD medication continuity have been delineated, prior studies have not investigated models that simultaneously combine child and family factors. The purpose of this study was to examine the impact of sociodemographic, clinical, and parent attitudinal predictors of medication continuity in the first year after ADHD diagnosis.
Methods: Stimulant-na+»ve children (N = 144, mean age = 8 years, 71% male) with ADHD completed an individualized methylphenidate (MPH) dose-finding RCT and were followed for 1 year after RCT completion and return to community care. We investigated predictors of having at least 1 filled ADHD prescription versus none in the year after the RCT via a multivariable analysis using the least absolute shrinkage and selection operator (LASSO) method. Among participants with at least 1 filled prescription, we determined predictors of having more days covered with medicine using LASSO regression models. Predictors examined included race, age, sex, income, baseline ADHD symptom severity, experience with MPH during the RCT, child and family mental health conditions, and family beliefs about ADHD, ADHD medications, and their clinical therapeutic alliance.
Results: A total of 121 (84%) children had at least 1 day of medication coverage (mean = 178 days) in the year after returning to community care. Multivariable models identified only one factorΓÇöhaving a lower family-reported clinical working alliance as a predictor of not filling any ADHD prescriptions. Among those who filled at least 1 prescription, factors linked to fewer days of medication coverage included nonwhite race, older age, female sex, lower income, comorbid ODD, less improvement of ADHD symptoms during the RCT, caregiver diagnosis of ADHD, lower caregiver beliefs that the child's ADHD affects their lives, and higher caregiver beliefs that medication is harmful.
Conclusions: Some children based on sociodemographic and clinical characteristics, caregiver mental health diagnosis, and caregiver perceptions are less likely to continue ADHD medication treatment. These findings may facilitate the development of effective strategies to improve ADHD medication continuity. ADHD, STIM, SAC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S94.

66.3 WORKING WITH FAMILIES AND SCHOOLS IN TREATING ADHD: ESSENTIAL COLLABORATIONS.

Diaz Y.

Objectives: The objective of this presentation is to review current research related to collaborative consultation models for working with parents and school staff when developing school-based intervention plans.

Methods: Children and adolescents with ADHD often display significant functional impairment in both home and school settings, underscoring the need to implement empirically supported treatments in both settings. Although many effective behavioral strategies and accommodations have been developed and are detailed in the literature, they can be time consuming and appear burdensome to parents and teachers, leading to inconsistent implementation. Moreover, both developing and problem-solving the plan require communication and collaboration among parents, teachers, and mental health professionals. This presentation will review important factors that may serve as barriers to effective collaboration between these key players and describe strategies for reducing these barriers. Within a collaborative framework, specific considerations for developing effective school-based interventions for children and adolescents with ADHD and disruptive behavior problems will also be discussed, including research findings to date.

Results: Behavioral interventions for children and adolescents with ADHD are an essential component of treatment. However, there are many barriers that can impede consistent implementation of behavioral interventions. More specifically, barriers related to parent-teacher communication, perceptions of behavior and problem identification, acceptability of recommended interventions, and a lack of collaborative problem solving after an intervention is implemented each affect intervention compliance and outcomes. Current research supports the need for a collaborative framework that facilitates communication between parents and teachers to approach treatment from a more ecological perspective.

Conclusions: Mental health professionals can serve an important role in both developing effective behavioral interventions and increasing collaboration between parents and teachers when working with children with ADHD and disruptive behavior problems. Moreover, research indicates that the use of a collaborative problem-solving approach to develop behavioral interventions can significantly enhance treatment acceptability, compliance, and outcomes. ADHD, EBP, TREAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S153.

1.20 PSYCHIATRIC COMORBIDITIES IN CHILDREN WITH ADHD AND ADS ON THE US-MEXICO BORDER.

Ghumman U, Muniz J, Kirkham C, et al.

Objectives: ASD and ADHD are of growing importance in research because of the high prevalence and significant morbidity among children in the United States. One study found increased rates of mental illness comorbidities in children who were found to have both ADHD and ASD compared with either one of these disorders alone. In another study of predominantly white children, the severity of ADHD correlated with increased severity of ASD and increased likelihood of other comorbid mental health conditions. This study aims to determine the relationship of additional mental illness comorbidities in children with ADHD and ASD in the predominantly Hispanic population at the US-Mexico Border.

Methods: This study used a retrospective chart review in which we extracted data from electronic medical records from January 2015 to December 2017 at the Texas Tech Health Sciences Center El Paso Child and Adolescent Psychiatric Clinic. The patients included in the study were under the age of 18 years and had a diagnosis of ADHD and ASD using validated measures. Social Communication Questionnaire (SCQ), Autism Diagnostic Observation Schedule (ADOS-2) assessment, Vanderbilt scores, and the initial mental health evaluation were used to determine the diagnosis and severity of ASD and ADHD. The mental health evaluation and the subsequent visits were used to determine whether the patients had other mental health comorbidities.

Results: Our sample group had 37 patients with a mean age of 7.57 years (SD = 3.13) and was 70 percent Hispanic. Lower SCQ and ADOS scores were associated with more mental illness comorbidities ($p = 0.05$ and 0.048, respectively). The data illustrated no significant relationship between higher severity of ADHD in children with ASD and increased prevalence of other mental illness comorbidities.

Conclusions: It is noteworthy that the data illustrated lower SCQ and ADOS scores were associated with a higher number of mental illness comorbidities. In addition, the data showed increased prevalence of mental illness comorbidities in the female population. These findings could have been skewed because of the size of our small sample group. Further research should explore these topics in larger sample groups to determine trends in gender and other racial and ethnic minorities. ASD, ADHD, CM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S284.

6.40 RELATIONSHIP BETWEEN CHRONOTYPE, SLEEP, AND SCREEN EXPOSURE IN ADOLESCENTS WITH ADHD.

Budagova G, Tugba BA.

Objectives: Sleep problems and related factors in ADHD have been interesting subjects to explore. The aim of this study was to compare chronotype, sleep problems, and screen exposure in adolescents with ADHD and normal control subjects and to investigate the relationship between these concepts within the group with ADHD.

Methods: Patients (N = 60; ages 11ΓÇô17 years) diagnosed with ADHD from Marmara University Pendik Education and Research Hospital Child Psychiatry Outpatient Clinic in Istanbul, Turkey and 48 normal control subjects were included in this study. Clinical assessments were performed by K-SADSΓÇôPresent and Lifetime Version. Four subtests of WISC-R were implemented to the participants, and a Screen Exposure Questionnaire (SEQ) was completed. Parents completed the Children's Chronotype Questionnaire (CCQ), Pediatric Sleep Questionnaire (PSQ), Conners Parent Rating Scale (CPRS), and SNAP-IV Parent Rating Scale.

Results: The following were significantly higher in the group with ADHD compared with the control subjects: eveningness score according to the CCQ (p = 0.028) and CCQ total score (p = 0.01); PSQ total score (p < 0.001); Behavioral Problems subscale score (p < 0.001) of PSQ; the duration of daily screen exposure (p < 0.001), daily computer exposure (p = 0.005), and daily cell phone exposure (p = 0.015); the duration of violent content broadcasting (p = 0.003); and the duration of exposure to cell phone (p = 0.002) and TV (0.028) before sleep/in the dark according to the SEQ. Four separate multivariate linear regression models within the ADHD group revealed the following: 1) PSQ total sleep problems score (adjusted [adj.]R2 = 0.130, +¦ = 0.381, p = 0.003) was associated with CCQ total score; 2) CPRS psychosomatic subscale score (adj.R2 = 0.069, +¦ = 0.291, p = 0.024) was associated with CCQ total score; 3) SNAP-IV Parent Rating Scale inattention score (adj.R2 = 0.049, +¦ = 0.256, p = 0.048) was associated with daily screen exposure time; and 4) daily violent content broadcast monitoring time (adj.R2 = 0.093, +¦ = 0.334, p = 0.017) was associated with daily computer monitoring time.

Conclusions: Eveningness, sleep problems, and total screen exposure time were higher in the group with ADHD. A significant relationship was found between sleep problems and chronotype within the group with ADHD. ADHD, SLP

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J Am Acad Child Adolesc Psychiatry. 2019;58:S172.

2.4 MODIFIED COMPREHENSIVE BEHAVIOR INTERVENTION FOR TICS: TREATING CHILDREN WITH TIC DISORDERS, CO-OCCURING ADHD, AND PSYCHOSOCIAL IMPAIRMENT.

Greenberg E, Wilhelm S, Sprich S, et al.

Objectives: Chronic (persistent) tic disorders (including Tourette's disorder) (further referred to as CTD) are developmental neuropsychiatric conditions affecting up to 2 percent of the population. In individuals with CTD, Γê+50 percent have co-occurring ADHD. The comorbidity of CTD and ADHD is associated with greater psychosocial impairment than a CTD without ADHD. Comprehensive behavioral intervention for tics (CBIT) is a first-line behavioral treatment for those with CTD. However, it is tic-specific with certain studies showing limited impact on quality-of-life measures and has been shown to be less effective in those with co-occurring ADHD. As such, we were interested in developing a modified CBIT treatment protocol that would additionally target ADHD and quality-of-life symptoms.

Methods: The present pilot study sought to assess the feasibility and acceptability of this modified CBIT treatment, and secondarily, the preliminary treatment responses regarding tics, ADHD, quality-of-life symptoms, and other clinical factors.
Results: Seventeen individuals with co-occurring CTD and ADHD between the ages of 10 and 17 years were randomized and enrolled into the study. Nine were in the modified CBIT (MCBIT) group, and 8 were in the standard CBIT group. Sixteen of the 17 participants completed the study, which included 10 weeks of weekly hour-long sessions and 2 booster sessions and assessments at the midpoint, endpoint, and 3 months post-active treatment. Satisfaction ratings were high, with 15 completers rating excellent or good quality of treatment. Both groups showed trends toward reductions in tics, ADHD symptoms, and quality-of-life symptoms but without significant differences between groups.
Conclusions: The modified treatment was found to be acceptable and feasible to almost all participants. The findings provide guidance for future modifications to the MCBIT protocol. ADHD, TD, CBT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S290.
6.60 CLINICAL AND FAMILY CHARACTERISTICS OF SIBLINCS OF PATIENTS WITH ADHD.
Gomez-Alzate AM, Hidalgo-Lopez C, Garcia-Valencia J, et al.
Objectives: This poster presentation aims to determine the clinical and family characteristics in a group of siblings of patients with ADHD.
Methods: A total of 74 ADHD index siblings (AIS), 74 high-risk siblings (HRS), and one of their parents were evaluated. Participants were between the ages 8 and 19 years. The ADHD Rating Scale-IV (ADHD-RS-IV); the Children's Global Assessment Scale (C-GAS); the Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) test; and the Brief Psychiatric Rating Scale were applied to the sibling couple. The Mini-International Neuropsychiatric Interview (MINI), Beck Depression and Anxiety Inventories, and a sociodemographic and psychosocial adversity data questionnaire were carried out with their mothers. Rutter indicators of adversity (RIA) were used: low social class, severe marital discord, large family size, paternal criminality, and maternal mental disorder.
Results: In the AIS group, 79.7 percent were men, and they had an average C-GAS score of 54.0 (SD = 14.8). One-third of parents reported a history of childhood ADHD, and 14.9 percent had 3 or more mental health disorders. One-third of all families had family dysfunction, with the most frequent factors being verbal discussions (44.6%) followed by separated parents, single-parent family, and a low APGAR score. In addition, 28.3 percent of the families had high scores in the RIA. Among HRS, 24.3% had an ADHD diagnosis, and the majority had the ADHD combined presentation. With respect to other mental health disorders, ODD was the most common in the HRS group, regardless of whether or not the youth had ADHD. In comparison with HRS without ADHD, the HRS group with ADHD had more adversity factors such as having a mother with 2 or more mental health disorders (61.1% vs. 32.1%), family dysfunction (38.8% vs. 26.7%), and also any parent with childhood history of ADHD (88.8% vs. 19.6%).
Conclusions: HRS have a high prevalence of ADHD and other mental disorders. In addition, it seems that this prevalence is not only determined by genetics but also by the presence of other environmental and psychosocial factors. ADHD, RF, FAM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S294.
6.70 PREDICTION OF SLEEP SIDE EFFECTS FOLLOWING METHYLPHENIDATE TREATMENT IN ADHD YOUTH.
Yoo JH, Sharma V, Kim J-W, et al.
Objectives: Sleep problem is a common side effect of methylphenidate (MPH) treatment in youth with ADHD and may negatively affect long-term self-regulatory functioning. This study aimed to examine whether applying machine-learning approaches to pretreatment through a demographics and clinical questionnaire, as well as environmental, neuropsychological, genetic, and neuroimaging features, can predict sleep side effects after MPH treatment.

Methods: The present study included 83 subjects with ADHD (9.5 -¦ 2.6, 18 girls) as a training dataset. The participants were enrolled in an 8-week, open-label trial of MPH. The Barkley Stimulant Side Effects Rating Scale was used to determine the presence/absence of sleep problems during the second week of treatment. Prediction of sleep side effects were performed with stepwise addition of variables measured at baseline; demographics (age, gender, IQ, height/weight) and clinical variables (ADHD Rating Scale-IV [ADHD-RS] and Disruptive Behavior Disorder rating scale) at stage 1; neuropsychological tests (continuous performance test [CPT], Stroop color word test) and genetic/environmental variables (candidate genetic polymorphisms [DAT1, DRD4, ADRA2A, and SLC6A2], blood lead, and urine cotinine levels) at stage 2; and structural connectivities of frontostriatal circuits at stage 3. Three different machine-learning algorithms (Logistic Ridge Regression [LR], support vector machine [SVM], and J48) were used for analysis. Robustness of classifier model was validated in the independent dataset of 36 subjects with ADHD (8.5 -¦ 2.5, 4 girls).
Results: Classification accuracy of LR was 95.5 percent (area under receiver operating characteristic curve [AUC] = 0.99), followed by SVM (91.0%, AUC = 0.85) and J48 (90.0%, AUC = 0.87) at stage 3 for predicting sleep problems. The inattention symptoms of ADHD-RS, CPT response time variability, the DAT1, ADRA2A DraI, and SLC6A2 A-3081T polymorphisms, and the structural connectivities of frontostriatal regions, were identified as the most differentiating subset of features. Validation analysis achieved accuracy of 86.1 percent (AUC = 0.92) at stage 3 with J48.
Conclusions: Our results provide preliminary support to the combination of a multimodal classifier, in particular, neuroimaging features, as an informative method that can assist in predicting MPH side effects in ADHD. ADHD, PPC, IMAGS

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J Am Acad Child Adolesc Psychiatry. 2019;58:S293.

6.68 IMPROVEMENT IN INATTENTION AND IMPULSIVE/HYPERACTIVITY AFTER CONSUMING PHOSPHATIDYLSERINE-CONTAINING OMEGA-3 SUPPLEMENTS IN MILTI-ETHNIC ASIAN CHILDREN WITH ADHD.

Cheryl Chang WL, Ying Tee CJ, Fong ZH, et al.

Objectives: ADHD is characterized by behaviors that can result in issues in social settings, family relationships, and education. Phosphatidylserine-containing omega 3 supplements (PSO3) were reported to improve ADHD symptoms. Previous studies that have examined this possible effect largely used white populations, with little to no reports focusing on the Asian population. We aim to evaluate whether improvements are seen in a multiethnic Asian population.
Methods: This review is a prospective open-label pilot study, with 20 primary school boys aged 6ΓÇô13 years, diagnosed with ADHD, and taking PSO3 for 6 months. The boys were evaluated for mean T-score improvement (TSI) in symptoms using Conners' Third Edition Parents Rating Scale (Conner-3P) before intervention (T0), 3 months after intervention (T3), and 6 months after intervention (T6). Those with no improvement at T3 will have their dosage doubled (from 2 capsules to 4 capsules per day) and symptoms re-evaluated at T6. If improvements are seen, subjects will continue to take 2 capsules per day for the next 3 months.
Results: Our preliminary analysis of N = 20 showed improvements in Conner-3P ratings for inattention (IN) and DSM-IV-TR inattention (AN) (mean TSI of IN = 11.7, AN = 8.8; p Γëñ 0.001) and impulsivity/hyperactivity (HY) and DSM-IV-TR hyperactivity/impulsivity (AH) (mean TSI of HY = 10.5, AH = 8.2, p Γëñ 0.003) between T0 and T3. The improvements in these domains were sustained until T6 (mean TSI between T0 and T6 of IN = 12.9, AN = 14.1, HY = 14.2, AH = 11.2, p < 0.001) with large effect sizes seen (d = 0.94ΓÇô1.63).
Conclusions: Our study shows that PSO3 helps with inattention and impulsivity/hyperactivity in boys diagnosed with ADHD. Improvements were sustained until the end of the study at T6. PSO3 may help to improve family relationships through reduced symptoms of inattention and hyperactivity, which are major factors that result in a tense parent-child dynamic. These findings may allow PSO3 to be considered as an alternative therapy to stimulants in the Asian population. The relatively small sample group size means that results may not apply to the general population. Further research using the Asian population will need to be

conducted to confirm the effectiveness, efficacy, and safety of PSO3. Because the ethnicity of our sample group is varied, this prompts future ethnicity-targeted studies to assess whether the efficacy of PSO3 differs among ethnicities. ADHD, SAC, OLT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S285-S286.

6.45 EFFICACY STUDY OF AN OMEGA-3/6 COMBINATION FOR MILD- TO MODERATE-INATENTIVE ADHD: A RANDOMIZED, DOUBLE-VLIND, PLACEBO-CONTROLLED TRIAL IN ITALIAN CHILDREN.

Carucci S, Romaniello R, Balia C, et al.

Objectives: ADHD treatment is based on a multimodal approach that combines behavioral and pharmacological treatment. Recently, there has been a growing interest in dietary supplementation of polyunsaturated fatty acids (PUFAs), such as omega-3 and omega-6 that showed that they are possibly effective in the control of inattentive symptoms. A specific omega-3/6 combination dietary supplement therefore was administered to a sample group of Italian children with ADHD-Inattentive (ADHD-I) presentation to evaluate its clinical efficacy and effects on essential fatty acid (EFA) plasma levels.

Methods: A randomized, double-blind, multicenter, placebo-controlled efficacy trial was conducted; the trial studied omega-3/6 combination in children aged 6 to 12 years who were diagnosed with mild/moderate ADHD-I. The study included a phase 1 evaluation of omega-3/6 supplement versus placebo (6 months) and a further 6-month phase 2 open-label treatment with omega-3/6 in all patients. Clinical effects and EFA plasma profiles (omega-3, omega-6, and omega-3/6 ratio) were assessed at 5 time points: baseline, 1 month, 3 months, 6 months, and 12 months.

Results: A total of 160 patients (118 boys and 42 girls) were enrolled from 4 Italian sites. A significant change in the total and inattention score was found from baseline to the end of the study within each group with no significant differences between omega-3/6 and placebo groups. At baseline, EFA levels did not show a statistically significant correlation with clinical severity. After 12 months, a slight (not statistically significant) reduction in omega-6/3 ratio was measured in the group taking active treatment only during phase 2. Dietary supplementation was well-tolerated, and no subjects reported severe adverse effects.

Conclusions: In our sample group, the plasma omega-6/3 ratio was not related to ADHD clinical severity or to clinical improvement. To evaluate the real effectiveness of omega supplementation in reducing the core symptoms of ADHD, it would be essential to establish the target characteristics of potential responder subjects in terms of the basal level of the fatty acid and possible individual variables (clinical symptoms, diet, optimal age and duration of PUFA treatment, and ethnicity). ADHD, RCT, TREAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S294.

6.71 ATTENTION IS PREDICTED BY ALZHEIMER'S DISEAS4E POLYGENIC RISK SCORE IN TYPICALLY DEVELOPING CHILDREN MORE THAN IN CHILDREN WITH ADHD.

Yoon W, Zayats T, Park KJ, et al.

Objectives: We aimed to investigate the association between the genetic risks for Alzheimer's disease (AD) and cognitive function in children with ADHD and typically developing children (TC).

Methods: The polygenic risk score of AD was calculated in 324 Korean children (208 case subjects and 116 control subjects) using the PRSise software and summary statistics from the International Genomics of Alzheimer's Project (IGAP) Study. ADHD was diagnosed based on DSM-IV and confirmed with K-SADS-Present and Lifetime Version (PL). The Korean Wechsler Intelligence Scales for Children, Fourth Edition (K-WISC-IV) and a neurocognitive battery consisting of the continuous performance test (CPT), the ChildrenΓÇÖs Color Trails Test (CCTT), the Stroop Color–Word Test, the Auditory Verbal Learning Test, and the Complex Figure Test (CFT) were administered. Permutation was applied to correct for multiple testing. Empirical p value (pemp) of 0.05 was considered statistically significant.

Results: The Working Memory Index on the K-WISC-IV was associated significantly with AD polygenic risk in TC (r2 = 0.393, pemp = 0.007). The commission errors on visual (r2 = 0.064, Pemp=0.040) and auditory (r2 = 0.172, Pemp=0.019) CPTs and the Response Time Variability (r2 = 0.145, pemp = 0.024) on visual

CPT showed significant association with AD polygenic risk in TC, but not in ADHD. The AD polygenic risk score significantly explained the omission errors on the CPT in ADHD (r2 = 0.256, pemp = 0.031), but not in TC. The copy score on the Kiddie-CFT was affected significantly by the AD polygenic risk in ADHD (r2 = 0.312, pemp = 0.028). Difference Inference Index in the CCTT was predicted significantly by the AD polygenic risk in TC (r2 = 0.111, pemp = 0.044), but not in ADHD.
Conclusions: Our results suggest some genetic overlap between AD and cognitive function, especially attention, in typically developing children. Our results also indicate that biological processes underlying ADHD and AD may be different. ADHD, GS, ND

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J Am Acad Child Adolesc Psychiatry. 2019;58:S286-S287.

6.48 CLINICAL RESPONSE AND SYMPTOMATIC REMISSIONS ACHIEVED WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD.

Childress AC, Wigal SB, Marraffino A, et al.

Objectives: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) designed to provide treatment effect from the time of waking and throughout the day. A pivotal phase 3 study of DR/ER-MPH in children with ADHD demonstrated significant improvements in ADHD symptoms and functional impairment, with ADHD symptoms measured by the ADHD Rating Scale-IV (ADHD-RS-IV) in the 6-week, open-label, treatment-optimization phase of the study (ClinicalTrial NCT02493777). This post hoc analysis sought to determine the clinical significance of these findings by applying established clinical thresholds of response to the ADHD-RS-IV scores reported in the trial.
Methods: Dose (20, 40, 60, 80, or 100 mg per day; maximum: 3.7 mg/kg per day) and administration time (8:00 PM -¦ 1.5 h) of DR/ER-MPH were optimized over 6 weeks. ADHD-RS-IV scores were obtained at baseline and at weeks 1-6. Clinical response was defined as a 30-percent reduction in ADHD-RS-IV from baseline. Excellent clinical response was defined as a 50-percent reduction in ADHD-RS-IV from baseline. Symptomatic remission was defined as an ADHD-RS-IV 18. Proportions of participants meeting each response threshold were compared between weeks.
Results: Mean DR/ER-MPH dose increased from 29.7 mg per day at week 1 to 66.2 mg per day at week 6. Mean ADHD-RS-IV scores decreased (improved) from 42.5 at baseline to 11.0 at week 6. Rates of clinical response, excellent clinical response, and symptomatic remission increased from 62/117 (53%), 39/117 (33%), and 32/117 (27%) participants, respectively, at week 1 to 117/117 (100%), 109/117 (93%), and 104/117 (89%) participants, respectively, at week 6. The proportion of participants who achieved each response threshold increased significantly at each week (p 0.014 for all weeks and thresholds vs. week 1). Participants continued to achieve more stringent response thresholds between weeks 5 and 6, despite the dose remaining constant.
Conclusions: Evening-dosed DR/ER-MPH treatment resulted in high rates of clinical response (93%-100%) and symptomatic remission (89%) in children with ADHD that progressively improved with continued treatment optimization. The treatment optimization strategy used in this trial was effective and may serve as a guide for clinicians to optimize responses when using DR/ER-MPH. ADHD, STIM, RCT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S312.

NEW FEEDING FROM THE MULTIMODAL TREATMENT OF ADHD (MTA) STUDY FOLLOW-UP

Hechtman L, Pliszka SR.

Objectives: This Symposium presents new findings from the Multimodal Treatment Study of ADHD (MTA) 16-year prospective follow-up study.
Methods: The MTA initially was a 14-month treatment study of 579 children aged 7-10 years with DSM-IV ADHD combined presentation randomized to medication alone (Med Mgt), behavioral treatment (Beh), their combination, or routine community care (CC). Follow-up assessments monitored treatment as usual in the community of the group with ADHD and a local normal control group (LNCG) matched for age and gender

(N = 258). Follow-up occurred in childhood (2 and 3 years), adolescence (6, 8, and 10 years), and adulthood (12, 14, and 16 years) after baseline.
Results: G. P. Algorta, PhD, will present on how Maternal Personality Traits Moderate ADHD Treatment Response in the MTA. Biological mothers (N = 437) of the children with ADHD completed the NEO Personality Inventory measuring neuroticism and conscientiousness. Children of mothers with high neuroticism and low conscientiousness benefited more from behavioral treatments (Beh ΓÇô Comb) relative to Med Mgt or CC. J. Swanson, PhD, will present on the Patterns and Predictors of Stimulant Medication Use from Childhood to Adulthood in the Prospective Long-Term Follow-up of the Multimodal Treatment Study of ADHD (MTA). Self-selected use of medication decreased with age. The duration of continued treatment was not affected by baseline risk factors for adverse outcome or persistence of ADHD. L. Hechtman, MD, will present on Adolescent Predictors of Adult Outcome in ADHD: Results From the Multimodal Treatment Study of ADHD (MTA). In general, adolescent predictors of adult outcome were similar for both the ADHD and LNCG groups. Important adolescent predictors included increased ADHD and ODD symptoms, low household income, and low academic achievements, particularly in math. Various combinations of these factors affected adult emotional, educational, occupational, and sexual functioning.
Conclusions: 1) Evaluation of maternal personality may aid the treatment selection for children and adolescents with ADHD. 2) There is a marked decrease in medication use from childhood to adulthood, for which the reasons need to be explained. 3) Addressing ongoing ADHD and ODD symptoms, low family income, and low academic achievement is important to improve adult functional outcomes. ADHD, LONG

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J Am Acad Child Adolesc Psychiatry. 2019;58:S287-S288.

6.51 ACHIEVEMENT AND MAINTENANCE OF NORMALIZED LEVELS OF EARLY MORNING AND LATE AFTERNNON/EVENING FUNCTIONAL IMPAIRMENT WITH DELAYED-RELEASE METHYLPHENIDATE (DP/ER-MPH) IN CHILDREN WITH ADHD: POST HOC ANALYSES OF BEFORE-SCHOOL FUNCTIONING.

Faraone SV, Wilens T, Childress AC, et al.

Objectives: In a pivotal phase 3 trial in children (ages 6ΓÇô12 years) with ADHD, 1 week of double-blind (DB) treatment with evening-dosed HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), resulted in significant improvements in early morning and late afternoon/evening functional impairment versus placebo (PBO), as measured by the validated Parent Rating of Evening and Morning Behavior Scale-Revised (PREMB-R), morning (AM) and evening (PM) subscales, respectively. Substantial improvements in functional impairment over the preceding 6-week, open-label (OL) treatment-optimization phase also were noted by PREMB-R AM/PM and the validated Before School Functioning Questionnaire (BSFQ). In this post hoc analysis, age-adjusted, norm-referenced cutoffs, determined from a representative sample group of 1200 US youth (ages 6-17 years), were applied to BSFQ, PREMB-R AM, and PREMB-R PM scores to interpret changes in functional impairment severity levels (screening risk: mild, moderate, and severe) following OL and DB phases of the pivotal phase 3 trial (ClinicalTrial NCT02493777).
Methods: The age-adjusted, norm-referenced cutoffs were applied to total BSFQ, PREMB-R AM, and PREMB-R PM scores at baseline, after the 6-week OL phase (randomization) and 1 week of DB DR/ER-MPH or PBO treatment (end point) to calculate the proportions of participants meeting each norm-referenced cutoff.
Results: Most participants at baseline were at or above screening risk for functional impairment by norm-referenced cutoffs (BSFQ: 96%, PREMB-R AM: 80%, PREMB-R PM: 98%). Of the participants with any level of functional impairment at baseline, the vast majority ΓÇ£normalizedΓÇØ (ie, score below screening risk) after 6 weeks of OL DR/ER-MPH (BSFQ: 93%, PREMB-R AM: 98%, PREMB-R PM: 81%). Of the participants normalized at randomization, fewer DR/ER-MPH versus PBO participants reverted to some level of functional impairment after 1 week of DB treatment (PREMB-R AM: 0% vs. 18%; PREMB-R PM: 9% vs. 26%).
Conclusions: In this post hoc analysis, 6 weeks of OL DR/ER-MPH treatment resulted in high rates of normalization on measures of early morning and late afternoon/evening functional impairment. After 1 week of DB treatment, DR/ER-MPH maintained normalization at higher rates than PBO. STIM, ADHD, RCT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S313.

9.3 ADOLESCENT PREDICTORS OF ADULT OUTCOME IN ADHD: RESULTS FROM THE MULTIMODAL TREATMENT STUDY OF ADHD (MTA).

Hechtman L.

Objectives: The goal of this session is to explore the importance of adolescent functioning in predicting adult functioning in participants with and without ADHD.

Methods: In the Multimodal Treatment Study of ADHD (MTA), 576 participants with and 258 without ADHD were followed prospectively for 16 years to the mean age of 25 years. Occupational, educational, emotional functioning, sexual behavior, and justice involvement were assessed in adulthood. Adolescent predictors explored and included: household incomes; parental job loss; public assistance; parental separation/divorce; academic abilities (reading, spelling, and math); ADHD symptom severity; and comorbidity (ODD/conduct disorder).

Results: Occupational functioning in adulthood was measured by total job losses, public assistance or not, and income levels. Higher adolescent ADHD severity was associated with higher adult job losses. Lower household income and lower academic abilities (math) in adolescence were related to the receipt of public assistance in adulthood. Receipt of public assistance and lower academic abilities (math) in adolescence were associated with lower income levels in adulthood. Adolescents with lower academic abilities (math) were less likely to obtain a Bachelor's degree in adulthood. Emotional functioning was measured by emotional lability in adulthood and associated with higher ADHD symptom severity and higher ODD symptom, as well as lower academic abilities (math) in adolescence. Risky sexual behavior was measured by the age of first sexual contact and the number of sexual partners. Younger age of the first sexual contact and higher number of sexual partners were associated with lower household income and higher ODD symptoms in adolescence. Justice involvement in adulthood (number of police contacts) was associated with poor academic abilities (math) in adolescence. Generally, the predictive associations were similar for participants with and without ADHD.

Conclusions: Important adolescent predictors of adult functional outcomes include the following: severity of ADHD; comorbidity (eg, severity of ODD); low household income or low socioeconomic status; and low academic abilities, which may reflect lower IQ. Thus, intervening in these areas in adolescence is important to promote more positive adult outcome. ADHD, LONG, ADOL

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J Am Acad Child Adolesc Psychiatry. 2019;58:S162.

1.48 WECHSLER INTELLIGENCE SCALE FOR CHILDREN, FOURTH EDITION (WISC-IV) INTELLECTUAL PROFILES IN KEREAN CHILDREN AND ADOLESCENTS WITH ADHD.

Shon S-H, Kim Y, Kyoung KM, et al.

Objectives: The study aimed to compare the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) profiles of children with ADHD and typically developing children (TC) in Korea.

Methods: The 377 children and adolescentsΓÇö224 with ADHD (age 8.2 -¦ 2.1 years, 182 boys) and 153 TC (age 8.7 -¦ 2.4 years, 68 boys) were administered the Korean version of WISC-IV and the Advanced Test of Attention (ATA). Partial correlation and ANCOVA were used to investigate the relationship between the scores of the WISC-IV and ATA.

Results: The mean score of the Full-Scale IQ (FSIQ) was lower in children with ADHD than TC children ($p < 0.001$). Controlling gender and FSIQ as a covariate, working memory index (WMI) ($p < 0.001$) and its subtest digit span ($p = 0.001$) of the WISC-IV were lower in the ADHD group compared with TC. WMI ($r = 0.26$, $p < 0.001$) and its subtest arithmetic scores ($r = 0.25$, $p < 0.001$) showed a negative correlation with commission errors on the auditory ATA.

Conclusions: Children with ADHD showed significantly lower scores in WMI, which were clinically correlated with commission errors on the auditory task of ATA scores. Through the results of this study, WMI can be used as an indicator of attention deficit in children with ADHD. ADHD, RCR, DEV

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J Am Acad Child Adolesc Psychiatry. 2019;58:S288-S289.

6.54 SINGLE-DOSE PHARMACOKINETICS OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN 4 TO 5 YEARS-OLD CHILDREN WITH ADHD.

Herman BK, Marraffino A, Kando JC, et al.

Objectives: The primary objective of this pharmacokinetic (PK) study was to evaluate the primary PK of amphetamine extended-release oral suspension (AMPH EROS) in preschool-age children (ages 4-5 years) after a single dose of 2.5 mg/mL. The data from the present study are intended to guide appropriate dosing for future safety and efficacy studies with AMPH EROS in the preschool-aged patient population (ages 4-5 years).

Methods: This open-label, single-dose, single-period, single-treatment study was designed to evaluate the PK profile of AMPH EROS in male and female subjects (ages 4-5 years) with weight ΓëÑ28 pounds at screening. Eligible subjects were diagnosed with ADHD by an appropriately credentialed health care professional. All subjects provided written informed consent by both parents or legal guardians and verbal assent prior to the administration of the study procedures. Demographics included descriptive statistics for age, sex, race, weight, and height. PK parameters for d- and l-amphetamine in plasma (Cmax, tmax, AUC0-t, AUC0-, and t1/2) were calculated and expressed as means, geometric means, and standard deviations. The primary endpoint was all objective PK measurements at 28 hours postdose. Safety was monitored continuously and assessed based on the occurrence of adverse events, as well as on measurements of vital signs and ECG.

Results: Five subjects (2 females and 3 males) completed the study. The mean age of the enrolled subjects was 4 years, with a mean (SD) BMI of 16.2 (1.1). For d-amphetamine, the mean (SD) Cmax, area under the curve (AUC)0-t, and AUC0-Γê× were 20.920 (2.292) ng/mL, 288.327 (48.096) hours*ng/mL, and 311.847 (46.287) hours*ng/mL, respectively. The median (range) tmax was 2.98 (2.97-3.98) hours, and the mean (SD) t1/2 was 6.81 (1.27) hours. For l-amphetamine, the mean (SD) Cmax, AUC0-t, and AUC0- were 6.550 (0.739) ng/mL, 96.481 (15.702) hours*ng/mL, and 106.842 (14.369) hours*ng/mL, respectively. The median (range) tmax was 3.98 (2.97-4.02) hours, and the mean (SD) t1/2 was 7.56 (1.56) hours. The study drug was well-tolerated by the subjects in this study. No adverse events, serious adverse events, or significant findings for vital signs or ECGs were reported.

Conclusions: The PK parameters for AMPH EROS in children ages 4-5 years measured and assessed in this PK study were consistent with those observed in children ages 6 to 12 years and in adults. ADHD, PKS, PSC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S293.

6.69 TREATING MOTHER AND FATHERS WITH ADHD WITH STIMULANT MEDICATION AND PARENT TRAINING: EFFECTS ON PARENTING AND GLOBAL IMPROVEMENT.

French WP, Chronis-Tuscano A, Whitock K, et al.

Objectives: Evidence-based interventions require parents to obtain, administer, and implement treatment. Parents with ADHD demonstrate parenting behavior characterized by disorganization, negativity, and inconsistency. We sought to examine parenting practices of mothers and fathers with ADHD, and parent and child ADHD symptom improvement in response to parent stimulant medication or behavioral parent training (BPT).

Methods: Mother-child (N = 34) and father-child dyads (N = 8) were randomized to 8 weeks of either lisdexamfetamine (LDX) or BPT. The Alabama Parenting Questionnaire (APQ) and parent-child interaction during child-initiated play, homework, and cleanup periods (Dyadic Parent-Child Interaction Coding System [DPICS]) were used to evaluate baseline mother and father parenting practices and compared via ANOVA without covariate adjustment (APQ) or adjusted for child deviance (DPICS). Improvement of parent and child impairment (Clinical Global Impression-Improvement [CGI-I]) was assessed by a blind rater at 8 weeks, and LDX and BPT were compared using Fisher exact test.

Results: On the APQ, fathers rated themselves as less involved ($p < 0.05$) and as using less corporal punishment compared with mothers with ADHD. Mothers displayed higher rates of both positive and negative parenting behaviors ($p < 0.05$) during cleanup, but there were no observed differences during child-initiated play and homework. After 8 weeks, 59 percent (10/17) of the mothers treated with stimulant medication and

50 percent (2/4) of the fathers were much or very much improved. Of the children whose mothers were treated with stimulant medication, 6 percent (1/17) were much or very much improved compared with 35 percent (6/17) of those treated with BPT (p = 0.09). None of the children whose fathers were treated with stimulant medication were much or very much improved after LDX treatment, whereas 50 percent of the fathers treated with BPT (2/4) were positive responders based on CGI-I.
Conclusions: Parenting practices of parents with ADHD are similar, although fathers report less baseline involvement in parenting. Stimulant medication directly improves parental global functioning in parents with ADHD but not child ADHD outcomes, whereas BPT modestly improves parenting and ADHD severity in their children. In multiplex families where both the parent and child have ADHD, brief monotherapy targeting parents with either parental stimulant medication or BPT provides some, but generally insufficient, improvement to their child's ADHD symptoms and functioning. ADHD, IMP, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S288.

6.52 THE RELATIONSHOP BETWEEN INTERNALIZING SYMPTOMS AND DECISION-MAKING INVOLVEMENT IN ADOLESCENTS WITH ADHD.

Folker AE, Brinkman WB, Becker SP, et al.

Objectives: Despite persistence of ADHD symptoms, medication use declines as children enter adolescence, which can negatively affect functional outcomes. Increased adolescent involvement in decision making not only increases autonomy and self-efficacy but also has been related to increased adherence in the context of other chronic conditions. Further, adolescents with ADHD and their parents are more likely to exhibit anxiety and depression, which can negatively affect family communication. Because individuals with internalizing symptoms may be less willing to engage in conversations or seek new information, we hypothesized that parent- and adolescent-internalizing symptoms would be inversely related to adolescent decision-making involvement related to management of their ADHD.
Methods: A total of 150 adolescents diagnosed with ADHD (based on DSM-5 criteria) completed the Revised Child Anxiety and Depression Scale (RCADS), and the parents completed the Depression, Anxiety, and Stress Scale (DASS-21). Parents and adolescents completed the Decision-Making Involvement Scale (DMIS), which has 5 subscales: parent express (ie, parent makes a suggestion, expresses an opinion, gives information); parent seek (ie, parent asks for childΓÇÖs opinion); child express (ie, child gives information to parent); child seek (ie, child asks for advice); and joint/options (ie, parent and child negotiating/brainstorming together). Pearson correlations were used to determine the associations between teenager- and parent-internalizing symptoms and the DMIS subscales.
Results: There was a significant negative association between parent-internalizing symptoms and teenage report of DMIS subscales parent express (r = ΓêÆ0.23, p < 0.01) and teenage report of joint/options (r = ΓêÆ0.16, p < 0.05). AdolescentsΓÇÖ reported internalizing symptoms were unassociated with DMIS subscales.
Conclusions: ParentsΓÇÖ own internalizing symptoms may affect the extent to which adolescents with ADHD are involved in decision making. Pediatricians should encourage these discussions and support adolescents assuming a greater role in the management of their ADHD as they mature. Limitations of the study include the cross-sectional design of this study. Future studies should consider the directionality of the relationship. ADOL, ADHD, FAM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S292-S293.

6.67 PREDICTORS ADHD DIAGNOSIS AMOING SCHOOL-AGE CHILDREN WITH ATTENTION PROBLEMS IN PRIMARY CARE.

Sikov J, Baul TD, Garg A, et al.

Objectives: ADHD is one of the most common pediatric conditions. Although the widely used Pediatric Symptom Checklist (PSC-17) can be used to accurately screen for ADHD in primary care, with a positive predictive value of 70 percent, disparities persist in ADHD diagnosis and treatment. Our primary goal was to

measure the prevalence of ADHD diagnosis among school-age children screening positive for attention problems at well-pediatric visits, and to identify demographic and clinical predictors of diagnosis following positive screens.
Methods: We conducted a cross-sectional retrospective electronic medical record (EMR) study in an urban safety net hospital-based pediatric clinic of children ages 6-11 years, who arrived for a well-child visit between September 1, 2016 and August 31, 2017 and screened positive for attention problems (ΓëÑ7) on the PSC-17. Information extracted from the EMR included PSC-17 scores, medical and mental health diagnoses, age, gender, race/ethnicity, and language. We conducted multivariate logistic regression analysis to analyze our data.
Results: A total of 253 children (10.9%) had a positive PSC-17 attention subscale score. Most of these children identified as non-Hispanic black (55.3%), followed by Hispanic (22.9%), non-Hispanic white (6.3%), and other (15.4%). ADHD was the most common mental health or development diagnosis (43%), followed by developmental and learning disorders including ASD (37.6%) and disruptive behavior disorder (21.0%). In the multivariable logistic regression, predictors of ADHD diagnosis among children with attention problems were older age (ages 9-11 vs. 6-8 years, Wald X2 = 10.6; adjusted [a]OR 2.6 [95% CI 1.5-4.5]; p value = 0.0012), EMR language listed as English (Wald X2 = 5.1; aOR 2.6 [95% CI 1.1-5.9]; p value = 0.02); completed parent or teacher Vanderbilt questionnaire (Wald X2 = 8.7; aOR 3.3 [95% CI 1.5-7.1]; p value = 0.003), and asthma diagnosis (Wald X2 = 9.6; aOR 2.7 [95% CI 1.4-5.1]; p value = 0.0019).
Conclusions: Based on our data, ADHD is underdiagnosed in this population, and diagnostic disparities could be reduced by increasing the rate of diagnostic questionnaire completion following positive screens and working to reduce language and cultural barriers to diagnosis. ADHD, SAC, RCR

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J Am Acad Child Adolesc Psychiatry. 2019;58:S94.
66.2 PSYCOTHERAPEUTIC INTERVENTIONS FOR ADHD: LESSIONS FROM THE SUMMER PROGRAM FOR KIDS (SPK).
Fleiss K.
Objectives: The objectives of this presentation are: 1) to review the literature on behavioral interventions, including parent training, for the treatment of ADHD; 2) to describe a specific comprehensive behavioral treatment intervention strategy, a summer camp the Summer Program for Kids (SPK) that addresses ADHD symptoms; and 3) to extrapolate findings from the SPK to general clinical practice with children with ADHD and their families.
Methods: During the presentation, a review of the literature on behavioral management and specifically of summer treatment programs for children with ADHD will be provided. The design and implementation of the New York University (NYU) SPK will be delineated, highlighting key components of the program that are effective in bringing about change in children's (and in their parents) behaviors. The outcomes of the measures and the questionnaires used in the program to assess the effectiveness of behavioral treatment strategies will be discussed.
Results: The NYU SPK is an effective, evidence-based day program that uses behavioral methods to improve prosocial behavior and reduce negative behaviors. Specific social skills are modeled, role-played, and targeted for change. Furthermore, the parent training sessions are effective in improving the parent-child relationship.
Conclusions: Children with ADHD benefit from a full-day, intensive social-immersion therapeutic program that uses behavioral and cognitive-behavioral treatment methods, along with a complementary parent training component to improve behavior across home, school, and recreational settings. The continuous clinical monitoring of each child's behavioral and social goals, through the collection and evaluation of data from the daily point system, enables the shaping of positive, prosocial behavior and the reduction of negative behavior over the 5-week period. Parents benefit from learning effective parent management strategies that help reduce conflict at home and improve parent-child relationships. Children's self-esteem is improved, and parents feel more effective and competent in their understanding and parenting of their children. These findings suggest that implementing behavioral strategies across the various milieus in which children engage can have an appreciable impact. ADHD, EBP, TREAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S340.

27.2 DISENTANGLING THE ROLES OF THREAT AND DEPRIVATION IN ASSOCIATIONS WITH EARLY CHILDHOOD PSYCOPATHOLOGY

Stein CR, Sheridan MA, Copeland WE, et al.

Objectives: The risk for psychopathology increases with the number of adverse childhood experiences. Summing a number of experiences, however, assumes that all adversity equitably confers risk and operates through complementary mechanisms. To disentangle neurobiological pathways between disparate events and mental health, we examined how threat and deprivation-2 common dimensions of adversity-relate to early childhood psychopathology. Threat or the presence of experiences involving harm or threat of harm affects emotional control. Deprivation or absence of expected environmental inputs affects higher-order cognitive function. If threat and deprivation differentially affect brain development, then they may differentially relate to psychopathology, especially among young children.

Methods: To examine these patterns, we used the Duke Preschool Anxiety Study, a cross-sectional study of youth ages 2-6 years enrolled through primary care from 2007 to 2011, weighted to reflect a screened population of 3433. Threat and deprivation were operationalized using questions from the Conflict Tactics Scale-2, Conflict Tactics Scale for Parent and Child, and Preschool Age Psychiatric Assessment. Threat measured physical or sexual abuse, domestic violence, and violent neighborhood. Deprivation measured neglect and lack of cognitive stimulation. Poisson regression with robust standard errors estimated adjusted prevalence ratios (PR) jointly for deprivation and threat in relation to counts for total symptoms and symptoms for specific disorders, such as anxiety, depression, and ADHD, in 760 children.

Results: Threat (47%) and deprivation (18%) were common; 36 percent of children had at least one disorder, and the total number of symptoms ranged from 0 to 46. Threat-exposed children had 40 percent more total symptoms (95% CI 1.2-1.6) than unexposed children after adjusting for deprivation and demographic covariates. Deprivation was not meaningfully associated with total symptom count (PR 1.1, 95% CI 0.9ΓÇô1.5) after adjusting for threat and demographic covariates.

Conclusions: These disparate associations among threat, deprivation, and mental health symptomatology may reflect the young age of these children or our approach designed to distinguish the unique contributions of deprivation and threat, lending support to the dimensional model of adversity and psychopathology. CAN, PSP, PSC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S285.

6.44 PSYCOPHARMACOLOGIC THERAPY IN 4 AND 5-YEAR-OLD PATIRNTS WITH ADHD.

Elizabeth AC, Ochoa-Lubinoff C, Beeson L.

Objectives: This presentation aims to determine the safety, tolerability, and efficacy of psychopharmacological treatment in a patient sample group of children ages 4 and 5 years with a diagnosis of ADHD.

Methods: Patients ages 4 and 5 years with a DSM-5 criteria diagnosis of ADHD and who were seen at the Rush University Medical Center developmental-behavioral pediatrics clinic from 2012 to 2018 were included in this study. Assessment for developmental, behavioral, and emotional comorbidities was performed. Information regarding clinical response, length of treatment, and adverse events to the different psychopharmacological treatments provided to patients until they turned age 6 years was collected. Families were offered methylphenidate or guanfacine as first-line ADHD treatment, and the medications were dosed in the standard recommended fashion.

Results: A total of 150 patients were included in this study, 93 of whom received at least one drug to treat ADHD. We had 144 medication trials, including 57 with methylphenidate and 51 with guanfacine. Sixty-five percent of the patients who received methylphenidate and 63 percent of patients who received guanfacine had a positive response, with improvement in behavior noted in both home and school environments after 1ΓÇô2 months of starting medication. Of the patients who received guanfacine, 29 percent reported lethargy and 10 percent reported irritability as significant side effects. Of the patients who received methylphenidate, 18 percent reported irritability, 14 percent reported decreased appetite, and 7 percent reported headaches as notable side effects. The rate of positive response and adverse events was not different across age subgroups.

Conclusions: Methylphenidate and guanfacine are effective psychopharmacologic agents in the treatment of ADHD in children under 6 years of age, and both psychopharmacologic interventions have similar efficacy and adverse events rates regardless of age subgroups. ADHD, EC, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S171.

2.3 COHORT ANALYSIS OF ANTIPSYCHOTIC TREATMENT IN ADHD.

Sultan R, Olfson M.

Objectives: Significant concern exists over treating youth with ADHD with antipsychotic medications, yet little is known about the factors that promote antipsychotic treatment. This presentation aims to describe the percentage of youth who fill antipsychotic prescriptions in the year after a new diagnosis of ADHD and to characterize the clinical and demographic factors associated with antipsychotic initiation.

Methods: We performed a retrospective longitudinal cohort analysis of antipsychotic treatment among 187,563 youth, ages 3 to 24 years, with a new diagnosis of ADHD (without recent diagnosis of any US FDA-indicated conditions for antipsychotic treatment). The sample group was derived from the 2010ΓÇô2015 MarketScan Commercial Database, with the analysis completed between November 2018 and May 2019.

Results: The main outcomes and measures include: the percentage of youth prescribed an antipsychotic drug in the first year after receiving a new diagnosis of ADHD; among those prescribed antipsychotic medications, the percentage of those that received a diagnosis of conduct disorder, ODD, or a disorder for which ΓëÑ1 antipsychotic medication has received a youth indication from the US FDA (schizophrenia, bipolar disorder, and Tourette's disorder); and the percentage of youth that filled an antipsychotic prescription before filling a stimulant prescription.

Conclusions: Approximately half of youth with a new ADHD diagnosis had an evidence-supported indication for an antipsychotic medication, and only about half of these youth received stimulants before initiating the antipsychotic drug. The use of antipsychotic drug prescriptions was associated with high levels of mental illness comorbidity. APS, ADHD, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S313.

9.2 PATTERNS AND PREDICTORS OF STIMULANT MEDICATION USE FROM CHILDHOOD TO ADULTHOOD IN THE PROSPECTIVE LONG-TERM FOLLOW-UP OF THE MULTIMODAL TREATMENT STUDY OF ADHD (MTA).

Swanson JM.

Objectives: Most children diagnosed with ADHD are treated with stimulant medication. The AACAP Practice Parameter for the assessment and treatment of ADHD (recommendation number 12) advises treatment for as long as symptoms persist, but information on duration of medication use (treatment as usual in clinical practices) is limited. The main objective is to use the data from long-term follow-up of the MTA to address this important gap in the literature.

Methods: After the 14-month RCT phase, follow-up assessments monitored treatment as usual in community settings during childhood (2 and 3 years); adolescence (6, 8, and 10 years); and adulthood (12, 14, and 16 years after baseline) when approximately 50 percent of the cases met criteria for persistent ADHD. The percentage of days of treatment between assessments was calculated, and a 50-percent cutoff was used to define minimally adequate treatment with medication for each year. Longitudinal sequences of self-selected use (and non-use) were used to form rule-based subgroups defined by duration of continued use before stopping or by continued non-use before starting stimulant medication from the 2-year assessment up to each year of the follow-up. Duration-related biases were evaluated, and characteristics of treatment regimens were documented.

Results: In the MTA follow-up, 308 cases (56%) had self-selected use immediately after the end of the 14-month randomized trial that continued up to 2 years (55 cases), 3 years (117 cases), 6 years (69 cases), 8 years (46 cases), and 10 years or more (21 cases) after baseline; 95 cases (17%) had delayed self-selected use (that started between 3 and 16 years after baseline); and 146 cases (27%) had no self-selected use. The duration of continued treatment was not confounded with baseline risk factors for adverse outcome or

with persistence of ADHD symptoms into adulthood. Although treatment was continued (or when it was started), adherence was high (medication was taken on about 90% of the days per year), and the daily dose was related to age (with increases by about 2 mg per year).
Conclusions: Common patterns of self-selected use of medication emerged in the MTA observational follow-up, but they were not confounded with risk factors for adverse outcome (as often suggested) or with persistence of symptoms in adulthood (as recommended by professional guidelines). STIM, ADHD, LONG

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J Am Acad Child Adolesc Psychiatry. 2019;58:S292.

6.65 ESTIMATING THE HERIRABILITY OF THE BRAIN'S STRUCTURAL CONNECTICVITY AND ITS ASSOCIATION WITH CHANGING SYMPTOMS OF ADHD.

Sudre GP, Sharp W, Shaw P.

Objectives: Using longitudinal data, we estimated the heritability of developmental change in the microstructural properties of white matter tracts. We further determined associations with changes in ADHD symptoms.
Methods: Participants were 133 children drawn from 51 nuclear families; 34 (26%) had a diagnosis of ADHD, and 84 were male. Our goal is to attain longitudinal analyses on 200 siblings. All children had 2 assessments (age at baseline [BL]: 9.2 -¦ 3.1 years; age of follow-up [FU]: 11 -¦3.3), from which the annual rate of change in clinician-determined ADHD symptoms was determined. Diffusion tensor imaging (3T scanner; 60 noncollinear directions) estimated 2 microstructural properties on approximately 14,000 voxels: axial diffusivity (AD, which reflects diffusion along axons) and radial diffusivity (RD, which reflects diffusion perpendicular to the axon). Voxel-wise total additive genetic heritability (h2r) of the annual rate of change in white matter microstructural properties was calculated using Sequential Oligogenic Linkage Analysis Routines. This uses a variance component method to estimate the proportion of phenotypic variance because of additive genetic factors. Permutation tests were used to correct for multiple comparisons by assessing cluster-size significance over the white matter skeleton.
Results: In these preliminary analyses, rates of change in microstructural properties emerged as significantly heritable in 2 separate clusters of voxels: the left uncinate fasciculus (AD: h2r = 0.48 -¦ 0.09, p = 0.004) and the forceps minor (RD: h2r = 0.52 -¦ 0.12, p = 0.01). Improvement with age in inattentive symptoms was associated with AD change in the left uncinate (t = 3.41, p = 0.003), and there was a trend for association with RD change the forceps minor cluster (t = 2.05, p = 0.06). Only the uncinate cluster was associated with improvements in symptoms of hyperactivity/impulsivity (t = 3.39, p = 0.003).
Conclusions: We provide the first demonstration of significant heritability in the development of microstructural properties of white matter tracts. We further highlight the heritable tract properties that are also associated with age-related change in ADHD symptoms. These estimates will be refined by our continued collection of longitudinal imaging data in siblings. Our ultimate goal is to use this relatively small number of developing white matter tracts properties-both heritable and associated with symptom changeΓÇöas phenotypes in large-scale, collaborative genome-wide association study (GWAS). ADHD, IMAGS

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J Am Acad Child Adolesc Psychiatry. 2019;58:S130.

1.5 PHARMACOLOGICAL STRATEGIES IN ADHD.

Wilens T.

Objectives: Increasingly complex cases of children with ADHD are presenting to child and adolescent psychiatrists requiring practitioners to learn new strategies for sequencing treatment, management of refractory core ADHD symptoms, and treatment of comorbidity(ies). Longer-term outcomes remain unclear.
Methods: A systematic review of the literature from historic, recently completed, and ongoing trials was reviewed to elucidate data on stimulant and nonstimulant treatments for ADHD. The data on longer-term outcomes of medication treatment of ADHD were reviewed.

Results: The literature combined with the clinical experience indicates that alterations in the use of traditional stimulants in existing and novel release forms, atomoxetine, +¦ agonists, the use of alternative agents, and combinations of medications can enhance a patient's ADHD response. Longer-term outcomes generally show positive results, with some adverse effects that can be monitored.
Conclusions: Pharmacological strategies will be reported for those who: 1) have not responded to traditional agents; and 2) present with comorbidity(ies). Both empirically derived data and illustrative cases will be used in the presentation. ADHD, STIM, ATA

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J Am Acad Child Adolesc Psychiatry. 2019;58:S296.

SAFETY OF EXTENDED-RELEASE METHYLPHENIDATE IN PRESCHOOL CHILDREN WITH ADHD.

Childress AC.

Objectives: The goal of this session is to present the safety profile of methylphenidate extended-release (MPH-MLR, Aptensio XR-«) for treatment of ADHD in preschool-aged children 4 and < 6 years, as derived from 2 phase 4 studies.
Methods: Study 1 (RCT) was a multiphase, prospective, randomized, double-blind, placebo-controlled study (ClinicalTrial NCT02683265); study 2 (open label, OL) was a follow-on 12-month, prospective, open-label, multicenter safety study (ClinicalTrial NCT02677519). After adjustments on a weekly basis in the RCT dose optimization phase, MPH-MLR dosing in the double-blind phase ranged from 10 to 40 mg. In the OL study, the MPH-MLR dose ranged from 10 to 60 mg after additional adjustments, as needed, to the RCT optimum dose.
Results: The safety population included children who received MPH-MLR in RCT (n = 119) and OL study (n = 89). The median optimized dose in RCT was 30 mg, and the median final dose in OL was 40 mg. Efficacy in all subgroups was statistically significant in favor of MPH-MLR versus placebo (p 0.05) in the RCT. Safety data from both studies demonstrated good correlation with published results in children with ADHD ΓëÑ 6 years of age. One serious treatment-emergent adverse event (TEAE) was reported in each study: RCT, campylobacter infection; OL, suicidal ideation; neither was considered related by the investigator. Severe TEAEs were reported by 6.7 percent and 10.1 percent of children in the RCT and OL study, respectively. The most common TEAEs (>10%) reported in RCT were decreased appetite (20.2%) and weight (17.6%), insomnia (15.1%), irritability (14.3%), hypertension (11.8%), emotional disorder (10.9%), and affect liability (10.1%). The most common TEAEs (>10%) reported in OL were decreased appetite and weight (18.0% for each) and nasopharyngitis (11.2%).
Conclusions: MPH-MLR was well tolerated in preschool-aged children and in doses that were higher (when needed) than in previous studies. These data contribute to the collective understanding of the safety of long-acting methylphenidate formulations for treatment of ADHD in preschool-aged children

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J Am Acad Child Adolesc Psychiatry. 2019;58:S196.

3.5 THE IMPACT EXERCISE ON IMPROVING EXECUTIVE DYSFUNCTION IN CHILDREN AND ADOLESCENTS WITH ADHD, ASD, AND FETAL ALCOHOL SPECTRUM DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE LITERATURE.

Varigonda A, Edgcomb J, Zima B.

Objectives: The goal of this work was to perform a systematic review and meta-analysis evaluating the role of exercise in improving executive function among children and adolescents with ADHD, ASD, and fetal alcohol spectrum disorders (FASD).
Methods: A systematic literature search was conducted in PubMed Central and PsycINFO from October 1, 2018 through January 30, 2019, for original peer-reviewed articles investigating the relationship between exercise interventions and improvements in 3 domains of executive function (working memory, attention/set shifting, and response inhibition) among children and adolescents with ADHD, ASD, and FASD. Effect sizes (ES; HedgesΓÇÖ g) were extracted and combined with random-effects meta-analytic methods. Covariates and moderators were subsequently analyzed using meta-regression and subgroup analyses.

Results: A total of 28 studies met the inclusion criteria, containing information on 1277 children and adolescents (N = 1193 ADHD, N = 54 ASD, N = 30 FASD). For ADHD, exercise interventions were associated with improvements in attention/set-shifting (ES = 0.38, 95% CI 0.01-0.75, k = 14) and approached significance for working memory (ES = 0.35, 95% CI 0.17 to 0.88, k = 5) and response inhibition (ES = 0.39, 95% CI 0.02 to 0.80, k = 12). For ASD and FASD, exercise interventions were associated with improvements in working memory (ES = 1.36, 95% CI 1.08-1.64) and response inhibition (ES = 0.78, 95% CI 0.21-1.35) and approached significance for attention/set-shifting (ES = 0.69, 95% CI 0.28 to 1.66). There was evidence of high methodologic and substantive heterogeneity among studies. Sample group size, mean age, study design, and the number or duration of intervention sessions were investigated as moderators of the relationship between exercise and executive function.
Conclusions: Exercise interventions among children and adolescents with neurodevelopmental disorders were associated with moderate improvements in executive function domains. Of note, studies of youth with ASD and FASD tended to report higher effect sizes compared with studies of youth with ADHD, although there were just a few existing studies. Exercise may be a potentially cost-effective and readily implementable intervention to improve executive function in these populations. Standardization of methods and control of confounding variables are critical to ascertaining the quality and efficacy of exercise interventions for children and adolescents with neurodevelopmental disorders. ND, COG, ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:S286.

6.47 COMPARISON OF PARENT-REPORTED PROVIDER DIAGNOSIS OF ADHD WITH STANDARDIZED PARENT AND TEACHER REPORTS OF CHILD SYMPTOMS.

Cree R, Bitsko R, Danielson M, et al.

Objectives: The purpose of this analysis was to compare the parent report of child ADHD ever diagnosis (DX) from a health care provider, a question commonly used to obtain national ADHD prevalence estimates, with ADHD diagnostic criteria based on combined parent and teacher report of symptoms (SX). Our second objective was to assess the concordance of DX and SX by child and family characteristics to identify demographic subgroups for whom there may be gaps in appropriate DX or treatment of SX.
Methods: Using data from a community-based study (N = 533), we calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of parent-reported child ADHD DX against diagnostic criteria based on current SX (combined report from parents [DISC-IV] and at least 2 ADHD symptoms endorsed by teachers). We assessed the concordance of DX and SX by parent-reported demographic characteristics and child treatment (ie, behavioral therapy or ADHD medication use), using weighted percentages and Wald Chi-squared tests.
Results: Comparing parent-reported ADHD DX with parent- and teacher-reported current ADHD SX, specificity and NPV were high (80% and 96%) and sensitivity and PPV were low (65% and 22%). Most children (65%) with a DX without SX (DX+/SX) were receiving treatment compared with 10 percent without a DX with SX (DX/SX+). Children with discordant DX and SX were more often male (66.7% DX+/SX and 78.1% DX/SX+) compared with those who were concordant (48%; $p < 0.01$). Children DX+/SX were more often in families receiving public insurance and living at <200 percent of the federal poverty level (54% and 70%) compared with those DX/SX+ (26% and 39%) and those who were concordant (43% and 37%; $p < 0.05$).
Conclusions: Children with an ever ADHD DX did not always meet SX criteria, and not all children with current SX had received a DX. Nearly 2 of 3 children DX+/SXΓêÆ were receiving treatment, potentially suggesting effective treatment. Nine of 10 children DXΓêÆ/SX+ were not receiving treatment, which may indicate children with unidentified ADHD. Differences in concordance of DX and SX by demographic characteristics revealed an area for possible future research. Researchers may wish to consider how the identified differences in parent-reported DX of ADHD and SX-based criteria may influence study results. ADHD, EPI

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J Am Acad Child Adolesc Psychiatry. 2019;58:S283-S284.

6.39 VITAMIN D INSUFFICIENCY/DEFICIENCY IN ADOLESCENTS WITH ADHD IN THE APPALACHIAN REGION.

Amin S.

Objectives: The American Psychiatric Association has reported socioeconomic challenges and health disparities that significantly affect the mental health of children in the Appalachian region. The insufficient/deficient level of vitamin D (Vit. D) is known to be significantly correlated with mental health from prenatal care to adulthood. We examined the level of Vit. D in 50 adolescents affected by ADHD (mean age 13.2 -¦ 4.6 years) at Carilion Clinic in the Appalachian region of Virginia.

Methods: From the EPIC medical records, 27 males (M) and 23 females (F) of the adolescents affected by ADHD from our outpatient patient pools were available. The subjects were grouped into 3 cohorts based on the levels of serum Vit. D: 1) Cohort A-Vit. D deficiency (20 ng/L), n = 32; 2) Cohort B-Vit. D insufficiency (21ΓÇô29 ng/L), n = 13; and 3) Cohort C, normal levels of Vit. D (30 ng/L), n = 5. Data are represented as the mean -¦ SD (with Student's t-test and p values as required) using.

Results: There was no significant (p Γëñ 0.1) difference in the average age of M (12.6 -¦ 3.6) and F (14.1 -¦ 2.7) or in the levels of their Vit. D (p Γëñ 0.09) in all M (20.4 -¦ 7.3 ng/L) or F (17.7 -¦ 6.6 ng/L). However, there was a very significant (p Γëñ 1.02E-09) difference in the Vit. D levels in Cohort A (14.9 -¦ 3.9 ng/L) versus Cohort B (24.3 -¦ 2.7 ng/L); or in Cohort A (p Γëñ 1.02E-11) or B (p 1.02E-06) versus Cohort C (33.0 -¦ 1.7 ng/L), in which each cohort contained both M and F.

Conclusions: This study shows that 90 percent of adolescents affected by ADHD from the Appalachian region of Virginia exhibited an insufficient/deficient level of Vit. D irrespective of their sex or age. Our observation suggests that there may be an epidemic of Vit. D insufficiency in adolescents affected by ADHD in this region. The small sample group size, dietary habits, and cross-section of subjects across the Appalachian region are the main limitations of this preliminary study. Nevertheless, the initial investigation raises a red flag for more controlled, extensive evidence-based studies across the country in the future. ADHD, SP, RCR

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J Am Acad Child Adolesc Psychiatry. 2019;58:S312-S313.

9.1 MATERNAL PERSONALITY TRAITS MODERATE ADHD TREATMET RESPONSE IN THE MULTIMODAL STUDY OF ADHD (MTA).

Algorta GP.

Objectives: The goal of this session is to evaluate the moderating effect of maternal personality traits (neuroticism, conscientiousness) on treatment response in the Multimodal Treatment Study of ADHD (MTA).

Methods: A total of 579 children (ages 7ΓÇô10 years) with DSM-IV ADHD-Combined were randomized to medication alone (MedMgt), behavioral treatment (Beh), their combination (Comb), or routine community care (CC) for 14 months. The analyses included children whose biological mothers completed the NEO Personality Inventory (N = 437). Latent class analyses estimated subgroups of mothers with different levels of neuroticism and conscientiousness. Linear-mixed models included: time, treatment, and NEO latent classes as fixed effects; ADHD symptoms (measured via parent and teacher SNAP) as dependent variables; and slope. Predetermined orthogonal contrasts were Comb and MedMgt versus Beh and CC, Comb versus MedMgt, and Beh versus CC.

Results: A 3-class (C) solution demonstrated the best fit for the NEO: C1) moderate neuroticism and conscientiousness; C2) high neuroticism and low conscientiousness; and C3) low neuroticism and high conscientiousness. Parent-rated SNAP showed 2 significant 3-way interactions. The biggest effect was for Beh versus CC (b = 0.13, SE = 0.05, CI = 0.22 to 0.03, p = 0.009). Children of mothers in C2 receiving Beh improved more (b = 0.31, SE = 0.04, CI = 0.39 to 0.24) than children of mothers in C2 receiving CC (b = 0.18, SE = 0.04, CI = 0.26 to 0.11). There was also a moderating effect for Comb and MedMgt versus Beh and CC (b = 0.05, SE = 0.03, CI = ΓêÆ0.11 to ΓêÆ0.0006, p = 0.04). Children of mothers in C1 (but not other classes) receiving Comb and Med (b = ΓêÆ0.37, SE = 0.02, CI = 0.40 to 0.33) improved more than children of mothers in C1 receiving Beh and CC (b = 0.15, SE = 0.02, CI = 0.18 to 0.12). Teacher SNAP showed 1 significant 3-way interaction (b = 0.13, SE = 0.06, CI = 0.24 to 0.02, p = 0.02). Children of mothers

in C2 receiving Comb (b = 0.39, SE = 0.05, CI = 0.49 to 0.30) improved more than children of C2 mothers receiving MedMgt (b = 0.22, SE = 0.05, CI = 0.31 to 0.13).
Conclusions: Children of mothers with high neuroticism and low conscientiousness benefited more from behavioral treatments (Beh, Comb) relative to MedMgt or CC than did children of other mothers. Evaluation of maternal personality may aid the treatment selection for children with ADHD. ADHD, TREAT, PAT

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J Am Acad Child Adolesc Psychiatry. 2019;58:S187.
2.50 DIAGNOSTIC INTERVIEW SCHEDULE FOR CHILDREN, VERSION 5 (DISC-5): DEVELOPMENT AND VALUATION OF ADHD AND TIC DISORDER MODULES.
Bitsko R, Adams HR, Holbrook J, et al.
Objectives: The Diagnostic Interview Schedule for Children (DISC) has been used in research and clinical settings to assess DSM-5 criteria of mental disorders in children. DISC-5 was recently developed, and it included updates to both the ADHD and tic disorder modules to reflect changes in DSM-5 criteria. The DISC-5 tic module differed substantially from DISC-IV in response to previous research showing poor agreement between the DISC-IV and expert clinical assessment of tic disorders. This study was conducted to determine sensitivity and specificity of the DISC-5 parent- and youth-report ADHD and tic disorder modules.
Methods: As part of a tic disorder measure validation study, the DISC-5 parent-report modules for ADHD (a common comorbidity of tic disorders) and tic disorders were completed for 100 children (aged 6-17 years), including 55 children with an established tic disorder diagnosis and 45 community control subjects with no known tic diagnosis history. Children aged 9 years and older (n = 78 total) completed the respective DISC-5 youth-report modules. All children also received a comprehensive clinician assessment for ADHD and tic disorders. DISC-5 and clinical assessors were blinded to each other's assessment results. Sensitivity and specificity were calculated to compare DISC-5 diagnoses to clinical assessment (gold standard).
Results: The clinical assessment identified 26 children with ADHD and 57 (including 2 control subjects) with a tic disorder. For parent report on the DISC-5 of past-year ADHD, sensitivity was 80.8 percent and specificity was 71.6 percent; for youth report, sensitivity was 64.7 percent and specificity was 82.0 percent. For parent report on the DISC-5 for any tic disorder in the past year, sensitivity was 98.3 percent and specificity was 97.7 percent; for youth report, sensitivity was 73.9 percent and specificity was 100 percent.
Conclusions: Parent report on the DISC-5 ADHD and tic modules had good sensitivity and specificity. For youth report, specificity exceeded sensitivity on both modules. The sensitivity and specificity of DISC-5 s tic module were improved compared with a previous study that used DISC-IV. Additional validation of all DISC-5 modules is needed to determine its utility in a general population setting; however, it is encouraging that both the ADHD and tic disorder modules perform well in identifying children with these disorders, specifically based on parent report. ADHD, TD, SII

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J Am Acad Child Adolesc Psychiatry. 2019;58:S316-S317.
12.3 ONE-YEAR FOLLO-UP OF DOUBLE-BLIND RCT OF NEUROFEEDBACK FOR ADHD.
Arnold LE, deBeus R, Kerson C, et al.
Objectives: The goal of this session is to determine whether neurofeedback (NF) has a delayed specific benefit for ADHD beyond a nonspecific benefit, such as placebo response and a benefit of 30+ sessions, with coaching and encouragement to focus on a screen. Unblinded RCTs have shown encouraging results, but small blinded, flawed RCTs have not. Some of those have shown delayed benefit in follow-up (FU) reports. Despite wide variation in its quality, NF has the potential to be an alternative or adjunct to medication with a more enduring effect.
Methods: Children ages 7-10 years (N = 142) at 2 sites were assigned randomly in a 3:2 ratio to 38 sessions of active NF (3 times a week) using the Lubar-Monastra method to downtrain theta-beta ratio (TBR) versus sham NF of equal duration, frequency, and intensity. Active and sham NF was programmed into a central server by an unblinded offsite investigator who never met the family, using de-artifacted recordings of active NF for sham on which the real-time artifacts of the child were superimposed. The duration of treatment was

3 to 4 months, with follow-up at 13 months after baseline. The primary outcome is analyzed by a linear mixed model with repeated measures and site, and site X treatment interaction is entered.
Results: Adherence to treatment was good, with 7 dropouts (5%). End-of-treatment blind guesses with regard to treatment assignment were not more accurate than expected by chance. Primary outcome (improvement in parent- and teacher-rated ADHD symptoms) was not significantly different between active NF and sham NF at the end of treatment, but 13-month FU from three-fourths of the sample group suggests divergence, with the NF group showing further improvement (d = 0.4) and the control group merely sustaining end-of-treatment improvement. Complete 13-month data will be presented.
Conclusions: Although primary clinical results of this NIMH-funded 2-site double-blind RCT of NF were comparable at the end of treatment for NF and control subjects, there appears to be a delayed benefit from the NF not observed in the control subjects. This is compatible with FU results from other NF studies. ADHD, CAM, NM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S330-S331.
21.1 PREDICTIVE UTILITY OF AUTISTIC TRAITS IN YOUTH WITH ADHD: A CONTROLLED 10-YEAR LONGITUDINAL FOLLOW-UP STUDY.
Biederman J.
Objectives: The goal of this session is to investigate the stability and predictive use of autistic traits (AT) in youth with ADHD.
Methods: Participants were referred youth with and without ADHD, who were without a diagnosis of ASD, and their siblings derived from identically designed longitudinal case-control family studies of boys and girls with ADHD. The subjects were assessed with structured diagnostic interviews and measures of social, cognitive, and educational functioning. The presence of ATs at baseline was operationalized using a unique profile of the Child Behavior Checklist (CBCL) consisting of an aggregate T-score of 195 on the Withdrawn, Social, and Thought Problems subscales (a CBCL-AT profile).
Results: At the follow-up, 83 percent of the ADHD youth with a positive AT profile at baseline continued to have a positive CBCL-AT profile. The presence of a positive CBCL-AT profile at baseline in youth with ADHD heralded a more compromised course characterized by higher levels of psychopathology and adverse interpersonal, educational, and neurocognitive outcomes compared with other youth with ADHD and control subjects.
Conclusions: The findings indicate a high level of persisting ATs in youth with ADHD over time, as indexed through the CBCL-AT profile, and its presence prognosticates a compromised course in adult life in multiple domains of functioning. ADHD, IMP, CM

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J Am Acad Child Adolesc Psychiatry. 2019;58:S331.
21.2 PHARMACOTHERAPY OF ADHD IN INTELLECTUALLY CAPABLE YOUTH WITH ASD: A REVIEW OF LITERATURE.
Wilens T.
Objectives: Empirical evidence for the treatment of ADHD in populations with high-functioning (HF)-ASD is limited. This presentation summarizes findings from an up-to-date review of empirical evidence on the treatment of ADHD in youth with HF-ASD.
Methods: A systemic PubMed search of peer-reviewed literature was conducted. Controlled trials, published in English, examining the safety and efficacy of anti-ADHD medication in youth with ASD and ADHD were included in the review. A minimum of 3 investigators reviewed full texts of all relevant articles, extracting variables with demographic information that covered associated psychopathology, anti-ADHD medication dose, and efficacy and tolerability response.
Results: Twelve trials met the inclusion criteria. A majority had a small-to-medium sample size (N = 9-24), with the exception of a methylphenidate (MPH) RCT (N = 66), 2 atomoxetine RCTs (N = 128, 97), and 1 guanfacine RCT (N = 62). The sample groups generally consisted of children with intellectual disability (ID) suffering from hyperactivity. No RCT excluded participants with ASD suffering from anxiety and mood

dysregulation. A substantial number of RCTs did not expose participants to the typically tolerated maximum dose of an anti-ADHD agent. Stimulant trials are conspicuous for a lack of controlled trials on mixed-amphetamine salts. The largest MPH RCT suggests poor tolerability and a response of hyperactivity in children ASD who also have an ID. Two large RCTs of atomoxetine in youth with ASD and ADHD reported tolerability similar to youth with only ADHD but with an anti-ADHD response rate poorer than typically expected from youth with only ADHD. Anti-ADHD response in one large RCT of guanfacine mirrors that of youth with only ADHD. Two small trials of clonidine reported poor tolerability with marginal anti-ADHD efficacy in youth with ASD and ADHD.
Conclusions: There is a lack of controlled trials examining anti-ADHD treatments in populations with ASD but with no ID. Atypical responses to MPH and atomoxetine may be confounded by the presence of ID and the lack of exclusion of anxiety and mood dysregulation. Conclusions of this review thus call for anti-ADHD treatment trials in HF-ASD populations that exclude participants suffering from significant anxiety and/or mood dysregulation. ADHD, ASD, PPC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S287.
6.50 SEX AND MEDICATION PRESCRIPTION PATTNERS IN CHILDREN WITH ADHD.
El SE, Kamimura-Nishimura KI, Epstein JN, et al.
Objectives: Prior epidemiological studies have shown that boys who are diagnosed with ADHD are more likely to receive ADHD medication than girls. However, it is unclear whether this gender disparity is attributed to underprescribing or underrecognition, because epidemiological studies use representative sample groups irrespective of whether the child was ever referred for an ADHD concern. The purpose of this study was to determine whether this gender disparity in medication prescribing rates exists among children presenting to pediatricians for ADHD.
Methods: The charts of 367 elementary school-aged children who presented to a pediatrician with ADHD concerns were reviewed. Parents and teachers of the participants completed the Vanderbilt ADHD Parent Rating Scale (VAPRS) and Vanderbilt ADHD Teacher Rating Scale (VATRS). A multivariable regression then was conducted examining the effect of patient sex, study-derived ADHD diagnosis, and their interaction on receipt of medication.
Results: Of the 367 participants (107 girls, 260 boys), 69 percent of the girls and 76 percent of the boys met ADHD diagnostic criteria based on ADHD symptom, pervasiveness, and impairment criteria derived from the rating scales. Patient sex (OR = 0.51; $p < 0.05$) and study-derived ADHD diagnosis (OR = 2.13; $p < 0.0001$) predicted ADHD medication prescription. There was also a sex x ADHD diagnosis interaction (OR = 1.99, $p < 0.05$). Boys and girls who met diagnosis criteria for ADHD were prescribed medication at equal rates (77% prescribed medication). However, boys who did not meet the ADHD diagnosis criteria were prescribed medication at nearly twice the rate (56% prescribed medications) as girls who did not meet the ADHD diagnostic criteria (30%).
Conclusions: There seems to be a gender disparity in medication prescribing, in which boys who do not meet the diagnostic criteria for ADHD are more likely to be prescribed medication than girls who do not meet ADHD diagnostic criteria. We were unable to ascertain why boys received ADHD medication at higher rates than girls when their ADHD rating scale results did not meet the ADHD diagnostic thresholds. Further study is needed to better understand the reasons why treatment choices may in some cases be discrepant from apparent diagnostic status both in research studies and in real-world clinical settings. STIM, ADHD, CC

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J Am Acad Child Adolesc Psychiatry. 2019;58:S273.
6.8 IMPULSIVITY AND PREDICTION ERROR CIRCUITS IN CHILDREN WITH ADHD.
Bernanke J, Luna A, van den Bos W, et al.
Objectives: ADHD is a common condition that has been associated with poor educational, economic, and social outcomes, even in adults who no longer meet the diagnostic criteria. These poor outcomes might be related to impulsive decision making, which is thought to involve abnormalities in valuing anticipated rewards.

Appropriate valuation of a reward requires the neural encoding of the difference between the received and expected reward. This difference is called ΓÇ£prediction errorΓÇØ (PE) and is likely encoded by the activity of dopaminergic neurons originating in the midbrain. In an ongoing study, we aim to compare the encoding of PE in children (ages 6-12 years) with ADHD (n = 18) and healthy control (HC; n = 18) subjects using a previously validated, probabilistic rewarded decision task during fMRI data acquisition.
Methods: We will compare summative measures of task performance (win-stay/lose-switch, accuracy) between subjects with ADHD and HC subjects. We will also compare and select (based on Bayesian information criteria) the most appropriate computational reinforcement-learning model (decay, tremble, 2-learning parameter, 1-learning parameter, or Bayesian) for each group and use the selected model to estimate the PE for each subject on a trial-by-trial basis. For each trial in each subject, the fMRI signal will be regressed on the calculated PE. Finally, contrast maps, modulated by PE, will be used for group-level comparisons of children with and without ADHD.
Results: Enrollment is ongoing. However, we completed a preliminary analysis with 16 children (4 with ADHD, 12 HCs). We have found that models with fewer parameters (ie, 2 learning parameters but not the decay or tremble models) fit the individual data better in almost all cases. Bayesian model fitting remains underway. Group comparisons and fMRI analyses are incomplete, pending a larger, more balanced sample grouping.
Conclusions: Computational models of PE with fewer model parameters might be more parsimonious and accurate than more highly parameterized models. Bayesian models might be more stable and allow for more direct group-level comparisons of model parameters. ADHD, IMAGS

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J Am Acad Child Adolesc Psychiatry. 2019;58:S307.

5.3 SYSTEMATIC REVIEW OF POLYPHARMACY STUDIES IN CHILD AND ADOLESCENT PSYCHIATRY: FOCUS ON ADHD.
Baker M, Hilt RJ.

Objectives: The goals of this session are to conduct a systematic review of psychiatric medication combination studies for youth with ADHD and to examine the evidence that supports the use of more than one concurrent psychotropic medication.
Methods: A literature search was conducted as described in the overall Proceedings abstract and then limited to populations with ADHD, including ADHD plus additional symptoms or comorbidities.
Results: A total of 30 articles were identified. Seventeen articles investigated an +¦-2 agonist plus a stimulant, of which 16 focused on ADHD care, 7 included ODD/conduct disorder comorbidities, and 1 study included TourretteΓÇÖs disorder plus ADHD. Seven of these articles were alternative analyses of the same 2 large RCTs combining guanfacine and a stimulant to treat ADHD. Overall, the combination of an +¦-2 agonist and a stimulant yielded greater treatment effects for stimulant partial responders, despite side-effect increases and a high rate of discontinuation in a community care claims review. We identified 5 articles on combining a stimulant and atomoxetine-2 of which were prospective, 1 was a continuation, and 2 were retrospective reviews. In summary, the combination linked to more side effects, mixed at best reports of additive benefit, and 1 suggested that partial responders first try atomoxetine for more than 4 weeks. Eight articles examined treatment with a stimulant and any other medication besides an +¦-2 agonist or atomoxetine. Of them, 5 added an antipsychotic drug to a stimulant, 2 small trials added an SSRI, 1 added a mood stabilizer, and 1 added either a mood stabilizer or an antipsychotic drug in populations with ADHD and disruptive behavior disorder or aggression. As a group, these studies are heterogeneous in method, outcome measures, and results, leading to a limited ability to draw overarching conclusions about effectiveness.
Conclusions: The best-studied ADHD medication combination was a stimulant plus alpha-2 agonist, with benefits of monotherapy frequently reported for stimulant partial responders. Other articles on medication combinations for ADHD, with or without comorbid conditions, showed less consistent benefits of monotherapy and more heterogeneous research methods limiting firm conclusions. ADHD medication combinations frequently yielded more side effects, leaving monotherapy trials as preferred if a sufficient treatment response could be achieved. ADHD, PPC, DAM

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J Can Acad Child Adolesc Psychiatry. 2019;28:66-71.

ATTENTION DEFICIT HYPERACTIVITY DISORDER PRESENTATIONS TO THCHILD AND ADOLESCENT MENTAL HEALTH URGENT CONSULT CLINIC.

Martins J, Roberts N, Nesdole R, et al.

Objective: The objective of the present study is to compare and contrast demographic and clinical characteristics of patients diagnosed with and without ADHD referred to the Child and Adolescent Mental Health Urgent Consult Clinic (CAMHUCC) in order to identify any differences between the patient groups and potentially improve care of these patients in the community.

Methods: This is retrospective cohort study of all children and adolescents, who were referred to the CAMHUCC between 2012 and 2014. Using data routinely collected at the clinic, individuals with ADHD were compared to individuals without ADHD. Data analysis was conducted using frequencies, percentages, means and standard deviations to describe participant demographic and clinical information, and comparisons between individuals with and without ADHD was made using Mann-Whitney U statistics.

Results: Of the 803 urgent assessments at the clinic, 367 (45.7%) were diagnosed with ADHD. Individuals with ADHD were statistically significantly more likely to be younger, male, referred for aggression, and not living with both parents. Individuals with ADHD were also more likely to be referred for follow-up than those without ADHD, and were more likely to have had at least one previous admission to the CAMHUCC.

Conclusions: Individuals with ADHD account for a significant proportion of child and adolescent presentations to CAMHUCC. Provision ourgent psychiatric care to young people with ADHD represents a significant utilization of resources on health care in terms of initial assessment, higher rates of follow up care, need for risk assessment and referral to CMHA

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Korean J Pediatr. 2019;62:360-66.

EFFECT OF OMEGA-3 PLUS METHYLPHENIDATE AS AN ALTERNATIVE THERAPY TO REDUCE ATTENTION DEFICIT-HYPERACTIVITY DISORDER IN CHILDREN.

Mohammadzadeh S, Baghi N, Yousefi F, et al.

Background: Attention deficit-hyperactivit y disorder (ADHD) is one of the most common chronic behavioral disorders in school-aged children. Purpose: This study aimed to evaluate the effect of omega-3 supplementation as an alternative therapy for ADHD, which can be caused by vitamin and mineral deficiencies.

Methods: This was a double-blinded clinical trial study. Sixty-six children with ADHD (aged 6-12 years) referred to our child and adolescent psychiatric educational and therapeutic clinic were selected based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria. Instruments including the Parent ADHD Rating Scale were used to assess ADHD at 0, 2, 4, and 8 weeks during the study.

Results: The results showed no statistically significant difference between the methylphenidate with omega-3 group and methylphenidate with placebo group based on the Parents ADHD Rating Scale between week 0 (P-0.96) and week 8 (P-0.75). There were no significant intergroup differences between the Inattention (P-0.48) and hyperactivity/impulsivity (P-0.80) subscale scores on the Parents ADHD Rating Scale. The most common drug complications in the methylphenidate with placebo and methylphenidate with omega-3 groups were anorexia (27 [54%] vs. 41 [60.29%], respectively) and diarrhea (10 [20%] vs. 8 [11.76%], respectively), but the differences were not statistically significant (P> 0.05).

Conclusion: Our results demonstrate that a specific dose of omega-3 for 8 weeks had no effect on ADHD

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Lancet Psychiatry. 2019 Aug;6:651-58.

METHYLPHENIDATE AND THE RISK OF PSYCHOSIS IN ADOLESCENTS AND YOUNG ADULTS: A POPULATION-BASED COHORT STUDY.

Hollis C, Chen Q, Chang Z, et al.

BACKGROUND: There is a clinical concern that prescribing methylphenidate, the most common pharmacological treatment for attention-deficit hyperactivity disorder (ADHD), might increase the risk of psychotic events, particularly in young people with a history of psychosis. We aimed to determine whether the risk of psychotic events increases immediately after initiation of methylphenidate treatment or, in the longer term, 1 year after treatment initiation in adolescents and young adults with and without a previously diagnosed psychotic disorder.

METHODS: In this cohort study, we used population-based observational data from the Swedish Prescribed Drug Register, the National Patient Register, and the Total Population Register, three population-based registers containing data on all individuals in Sweden, to attain data on sex, birth, death, migration, medication use, and psychotic events for all eligible participants. We screened individuals on these registers to identify those receiving methylphenidate treatment, and who were aged 12-30 years at the start of treatment, for their inclusion in the study. We used a within-individual design to compare the incidence of psychotic events in these individuals during the 12-week periods immediately before and after methylphenidate initiation. Longer term risk was assessed by comparing the incidence of psychotic events 12 weeks before methylphenidate initiation and during a 12-week period one calendar year before the initiation of methylphenidate with the incidence of these events during the 12-week period one calendar year after methylphenidate initiation. We estimated the incidence rate ratios (IRR) and 95% CIs of psychotic events after the initation of methylphenidate treatment, relative to the events before treatment, which were defined as any hospital visit (inpatient admission or outpatient attendance, based on data from the National Patient Register) because of psychosis, using the International Classification of Diseases version 10 definition. Analyses were stratified by whether the individual had a history of psychosis.

FINDINGS: We searched the Swedish Prescribed Drug Register to find eligible individuals who had received methylphenidate between Jan 1, 2007 and June 30, 2012. 61 814 individuals were screened, of whom 23 898 (38.7%) individuals were assessed and 37 916 (61.3%) were excluded from the study because they were outside of the age criteria at the start of treatment, they had immigrated, emigrated, or died during the study period, or because they were administered other ADHD medications. The median age at methylphenidate initiation was 17 years, and a history of psychosis was reported in 479 (2.0%) participants. The IRR of psychotic events in the 12-week period after initiation of methylphenidate treatment relative to that in the 12-week period before treatment start was 1.04 (95% CI 0.80-1.34) in adolescents and young adults without a history of psychosis and 0.95 (0.69-1.30) among those with a history of psychosis.

INTERPRETATION: Contrary to clinical concerns, we found no evidence that initiation of methylphenidate treatment increases the risk of psychotic events in adolescents and young adults, including in those individuals with a history of psychosis. Our study should reassure clinicians considering initiating methylphenidate treatment for ADHD in adolescents and young adults, and it challenges the widely held view in clinical practice that methylphenidate should be avoided, or its use restricted, in individuals with a history of psychosis.

FUNDING: Swedish Research Council, National Institute of Mental Health, UK National Institute of Health Research Nottingham Biomedical Research Centre

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Medicina (B Aires). 2019;79 Suppl 3:33-36.

SLEEP IN NEURODEVELOPMENTAL DISORDERS.

Mulas F, Rojas M, Gandia R.

The development and establishment of the normal sleep patterns are very important processes in the final anatomical and physiological architecture of the central nervous system. The relationship between sleep disturbances during childhood with neurodevelopmental disorders is complex and potentially synergistic. Sleep patterns are present since the fetal period but their structure and physiology is modified according with the maturation of the central nervous system. Sleep disorders and their relationship with attention deficit hyperactivity disorders(ADHD), autism spectrum disorders(ASD) and other neurodevelopmental disorders

(TDN) are not well understood yet, but significant progresses have been made in understanding associations and potential etiological correlations. We reviewed sleep disturbances in NDT, in ADHD and in ASD. A greater understanding of the pleiotropic functions of the genes involved in sleepwake cycle disorders and deviations from neurological developme nt could lead to new diagnostic and therapeut ic strategies in an early stage in order to improve the quality of life of the patient, relatives and caregivers

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Neurochirurgie. 2019.

NEUROPSYCHOLOGICAL CONSEQUENCES OF CRANIOSYNOSTOSIS: NON-SYNDROMIC SCAPHOCEPHALY.

Verlut I, Mottolese C, Szathmari A, et al.

Background: Scaphocephaly increases the rate of some modifications of cognitive and mood profile in a manner that remains to be elucidated.

Objective: We aimed to describe the impact of scaphocephaly on neuropsychological profile and more particularly on the executive functions.

Patients and methods: An experimental group of 19 children older than 5 years, operated on for scaphocephaly, was compared with a control group of 10 children operated on for trigonocephaly, using IQ tasks, attention tasks and mood scales. A group of 6 children from 2 to 4 years old, operated on for scaphocephaly, and a group of 6 children with non-operated scaphocephaly are also described.

Results: Both the experimental group and the control group showed unchanged IQ, whereas attention deficit and anxiety disorder were more frequent in the experimental group. Cognitive profiles differed between groups, with a higher rate of impaired inhibitory control of visual processing in the scaphocephaly group, contrasting with a higher rate of impaired auditory verbal working memory in the trigonocephaly group. Comparable profiles were also found in groups of younger or non-operated children with scaphocephaly.

Conclusions: Many children with scaphocephaly must cope with a specific neuropsychological profile throughout development. This study suggests the interest for these children and their families of specific follow-up in reference centers

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Neurology. 2019;92.

METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) C677T POLYMORPHISM STATUS DOES NOT PREDICT SERUM FOLATE AND B12 IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Silverstein S, Junger A, Pecor K, et al.

Objective: To contrast serum folate and B12 levels among MTHFR C677T polymorphisms in a cohort of children with ADHD.

Background: Polymorphisms in the methylenetetrahydrofolate reductase enzyme (MTHFR), which allows for the metabolism of homocysteine to methionine, have been extensively investigated for a contributing role in a variety of neurologic diseases, including ADHD. The homozygous C677T (TT) polymorphism has been correlated with serum folate and B12 deficiency, which has been hypothesized to contribute to disease pathogenesis. Furthermore, several studies of healthy populations found that TT status was associated with decreased folate levels despite adequate folate intake. As such, TT status is often used as a rationale to treat patients with folate and B12 supplementation.

Design/Methods: Serum folate and B12 levels as well as MTHFR C677T gene status (wild type (CC), heterozygous (CT), or homozygous (TT) polymorphism) were determined for 45 children with ADHD. ANOVA was used to contrast serum folate and B12 levels among MTHFR C677T genotypes.

Results: Neither serum vitamin B12 [F2,42 = 0.46; p=0.63; n= (CC 14; CT 20; TT 11)] nor folate levels [F = 2.72; p=0.09; n= (CC 9; CT 12; TT 6)] were significantly different among MTHFR genotypes.

Conclusions: The association of ADHD with C677T polymorphisms is controversial and as yet unsettled. Similarly, the role of vitamin B12 and folate have been debated. Our data suggest that the role of MTHFR C677T status in children with ADHD may not be directly coupled to vitamin B12 and folate levels. As such, further studies on the aforementioned questions should be careful to entertain the possibility that the MTHFR C677T gene status and vitamin B12 and folate levels are at least partially, if not entirely, independent

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Neurology. 2019;92.

METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) C677T POLYMORPHISM AND ASSOCIATED VITAMIN D LEVELS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Silverstein S, Pecor K, Junger A, et al.

Objective: To contrast vitamin D25-OH levels among MTHFR C677T genotypes in children with ADHD.

Background: Vitamin D deficiency in ADHD patients has been well documented in the literature, but there is no consensus as to the explanation for this association. There has also been conflicting evidence regarding the association between MTHFR C677T gene status and ADHD. Given recent reports of a correlation between low MTHFR C677T prevalence and regions with high ultraviolet radiation (UVR), we sought to examine MTHFR status and vitamin D25-OH levels, which themselves are directly influenced by UVR exposure.

Design/Methods: Serum vitamin D25-OH levels and MTHFR C677T genotype (wild type (CC), heterozygous (CT), and homozygous (TT) polymorphisms) were determined for 50 children with ADHD. ANOVA was used to contrast vitamin D25-OH levels among MTHFR C677T genotypes.

Results: Serum vitamin D25-OH differed significantly among the three genotypes [F = 5.02; p=0.01; n= (CC 18; CT 21; TT 11)]. The CC variant had lower vitamin D levels than the TT variant, and the CT variant had intermediate levels that did not differ from the other two genotypes.

Conclusions: Existing literature does not suggest a genetic predilection for vitamin D deficiency in children with ADHD. However, an interaction between folate and vitamin D levels regulated by UVR intensity as a mechanism that preserves both nutrients has been suggested. The TT variant of MTHFR is thermolabile and unable to process folic acid efficiently at high UVR exposure, which is typically necessary for vitamin D formation. As such, individuals with MTHFR TT may manufacture and/or maintain vitamin D more efficiently due to their genetic need to avoid prolonged UVR exposure. Hence, vitamin D levels may be higher at baseline in children with MTHFR TT status. In either case, our findings suggest a possible yet unelucidated interaction between MTHFR C677T status and vitamin D and children with ADHD

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Neurology. 2019;92.

NOVEL MUTATION IN ACSL4 GENE LEADING TO X-LINKED INTELLECTUAL DISABILITY, AUTISM AND ADHD.

Gupta S, Toor F, You B, et al.

Objective: In this case report and literature review, we report a novel mutation in the ACSL4 gene leading to X-linked intellectual disability (XLID), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) Background: Intellectual disability (ID) has prevalence of 1-3% with a male predominance. Isolated cases of ACSL4-associated XLID are rare in the literature. ACSL4(Xq22.3-q23) encodes FACL4 (long-chain-fatty-acid-CoA ligase 4), an enzyme that is part of the long-chain fatty acid coenzyme A ligase family. FACL4 is expressed in various tissues, including the brain and liver, and functions in lipid metabolism, signal transduction, and apoptosis

Design/Methods: Case report and literature review

Results: A 5-year old boy presented with intellectual disability as well as symptoms consistent with both an ASD and ADHD. Initial genetic work-up included Fragile X gene repeat testing, chromosome karyotype, and comparative genomic hybridization (CGH) microarray, all of which were normal. Next Generation Sequencing on 454 genes associated with diseases which are inherited in an autosomal recessive pattern (Inherited Recessive Disease Panel) was then sent. Sequencing reveled a possibly pathogenic hemizygous frameshift mutation in the ACSL4 gene: NP-075266.1:p. Ala490HisfsTer10. Sanger sequencing was then performed in

the patient and his sister, mother and father. Sanger sequencing revealed that the patient's mother and sister were carriers of the same ACSL4 mutation, while his father did not carry the mutation. Mother had mild symptoms of inattention in school whereas the sister fulfilled criteria for ADHD predominantly hyperactive/impulsive type. Both the mother and sister were of normal intelligence
Conclusions: We report a novel mutation in ACSL4 gene causing XLID, ASD, and ADHD in a 5-year-old boy. The patient's mother and sister are mildly affected carriers of the same ACSL4 gene mutation

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Neuropsychiatr Dis Treat. 2019;15:2213-19.
COMPARISON OF SERUM B12, FOLATE AND HOMOCYSTEINE CONCENTRATIONS IN CHILDREN WITH AUTISM SPECTRUM DISORDER OR ATTENTION DEFICIT HYPERACTIVITY DISORDER AND HEALTHY CONTROLS.
Yektaş Ç, Alpay M, Tufan AE.
Objective: We aimed to investigate the serum concentrations of vitamin B12, folate and homocysteine in children diagnosed with attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) and healthy controls.
Materials and methods: Serum vitamin B12, folate and homocysteine concentrations were measured in 118 children (48 children diagnosed with ADHD, 35 children diagnosed with ASD and 35 healthy controls). Symptom severity in the ADHD and ASD groups was evaluated by the Childhood Autism Rating Scale and Turgay-DSM-IV-Based Screening and Assessment Scale for Disruptive Behavior Disorders. Multivariate analysis of covariance was used to evaluate the effects of diagnosis and gender on biochemical parameters.
Results: The ADHD and ASD groups and the healthy controls differed significantly regarding vitamin B12 and homocysteine concentrations, but not folate levels. Patients with ASD had the lowest vitamin B12 and the highest homocysteine levels. Vitamin B12 levels correlated negatively with hyperactivity and/orimpulsivity and oppositionality symptoms in children with ADHD. There were no relationships between psychometric evaluations and laboratory measurements in children with ASD. Gender did not affect vitamin concentrations.
Conclusion: Previous studies found that vitamin B12 was reduced while homocysteine was elevated among patients with ADHD and ASDs. Our results also support those reported previously. Oppositionality and hyperactivity and/orimpulsivity may be related to vitamin B12 and homocysteine levels in children with ADHD. Further studies are required to define the role of these parameters and effects on the etiology and clinical manifestations of ASD and ADHD

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Neuropsychology. 2019.
WORKING MEMORY AND INFORMATION PROCESSING IN ADHD: EVIDENCE FOR DIRECTIONALITY OF EFFECTS.
Kofler MJ, Soto EF, Fosco WD, et al.
Objective: Children with ADHD demonstrate impaired performance on a wide range of neuropsychological tests. It is unclear, however, whether ADHD is associated with many neurocognitive deficits or whether a small number of impairment(s) broadly influence test performance. The current study tests competing model predictions regarding two candidate causal mechanisms in ADHD: information processing speed and working memory.
Method: A well-characterized sample of 86 children (Mage = 10.52, SDage = 1.54; 34 girls; 64% Caucasian/Non-Hispanic) with ADHD (n = 45) and without ADHD (n = 41) completed eight fully crossed experimental tasks that systematically manipulated working memory (BF10 = 1.80 +ù 1093) and information processing speed (drift rate; BF10 = 7.61 +ù 106).
Results: Bayesian mixed-model ANOVAs indicated that increasing working memory demands produced significant reductions in information processing speed (drift rate; BF10 = 5.82 +ù 1096). In contrast, experimentally reducing children's information processing speed did not significantly change their working memory performance (BF10 = 1.31). ADHD status interacted with the working memory manipulation, such that the ADHD and non-ADHD groups showed equivalently high accuracy under the encoding-only conditions (BF011 = 3.45) but differed significantly under high working memory conditions (encoding + recall; BF10 = 19.58). Importantly, however, ADHD status failed to interact with (a) the working memory manipulation to

differentially affect information processing speed and (b) the information processing speed manipulation to differentially affect working memory performance (all BF011 > 4.25).
Conclusions: These findings indicate that top-down executive control exerts significant effects on children's ability to quickly process information, but that working memory deficits and slowed information processing speed appear to be relatively independent impairments in ADHD

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Neuropsychology. 2019 May;33:445-61.

FACE PROCESSING IN AUTISM SPECTRUM DISORDER RE-EVALUATED THROUGH DIFFUSION MODELS.

Powell G, Jones CRG, Hedge C, et al.

OBJECTIVE: Research using cognitive or perceptual tasks in autism spectrum disorder (ASD) often relies on mean reaction time (RT) and accuracy derived from alternative-forced choice paradigms. However, these measures can confound differences in task-related processing efficiency with caution (i.e., preference for speed or accuracy). We examined whether computational models of decision-making allow these components to be isolated.
METHOD: Using data from two face-processing tasks (face recognition and egocentric eye-gaze discrimination), we explored whether adolescents with ASD and wide-ranging intellectual ability differed from an age and IQ matched comparison group on model parameters that are thought to represent processing efficiency, caution, and perceptual encoding/motor output speed.
RESULTS: We found evidence that autistic adolescents had lower processing efficiency and caution but did not differ from nonautistic adolescents in the time devoted to perceptual encoding/motor output. These results were more consistent across tasks when we only analyzed participants with IQ above 85. Cross-task correlations suggested that processing efficiency and caution parameters were relatively stable across individuals and tasks. Furthermore, logistic classification with model parameters improved discrimination between individuals with and without ASD relative to classification using mean RT and accuracy. Finally, previous research has found that ADHD symptoms are associated with lower processing efficiency, and we observed a similar relationship in our sample, but only for autistic adolescents.
CONCLUSIONS: Together, these results suggest that models of decision-making could provide both better discriminability between autistic and nonautistic individuals on cognitive tasks and also a more specific understanding of the underlying mechanisms driving these differences

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Neuropsychopharmacology. 2019.

THE EFFECT OF METHYLPHENIDATE ON SOCIAL COGNITION AND OXYTOCIN IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Levi-Sachar O, Gvirts HZ, Goldwin Y, et al.

The current study aimed to explore the possible effect of stimulants on oxytocin (OT), a neuropeptide which regulates social behavior, as a mediator of the pro-social effect of methylphenidate (MPH) in children with attention deficit hyperactivity disorder (ADHD) compared to healthy controls (HCs). Utilizing a double-blind placebo-controlled design, we compared the performance of 50 children with ADHD and 40 HCs in ΓÇ£theory of mindΓÇØ (ToM) tasks and examined the effect of a single dose of MPH/placebo on ToM and salivary OT levels in children with ADHD at baseline and following an interpersonal interaction. Children with ADHD displayed significantly poorer ToM performance; however, following MPH administration, their performance normalized and differences between children with ADHD and HC were no longer found. Salivary OT levels at baseline did not differ between children with ADHD and HCs. However, after a parentΓÇôchild interaction, OT levels were significantly higher in the HC group compared to children with ADHD. Administration of MPH attenuated this difference such that after parentΓÇôchild interaction differences in OT levels between children with ADHD and HC were no longer found. In the ADHD group, OT levels decreased from administration of placebo to the parentΓÇôchild interaction. However, the administration of MPH to children with ADHD was associated with an increase in OT levels after the parentΓÇôchild interaction. We conclude that OT might play a role as a mediator of social deficits in children with ADHD and that the reactivity

of the OT system to social interaction in children with ADHD might be impaired. Stimulants may improve ToM and social functions in children with ADHD via its impact on the OT system. PRS: OT and Social Cognition in Children with ADHD: Impact of MPH

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Nutrients. 2019;11.

ASSOCIATION BETWEEN FATTY ACIDS PROFILE AND CEREBRAL BLOOD FLOW: AN EXPLORATORY FNIRS STUDY ON CHILDREN WITH AND WITHOUT ADHD.

Grazioli S, Crippa A, Mauri M, et al.

Polyunsaturated fatty acids (PUFAs) biostatus has been proposed as possible attention deficit hyperactivity disorder (ADHD) diagnosis biomarker. The present exploratory study aimed to investigate the association between PUFAs biostatus and cerebral cortex metabolism measured by functional Near Infrared Spectroscopy (fNIRS) in a sample of children with and without ADHD. 24 children with ADHD and 22 typically developing (TD) peers, aged 8ΓÇô14, were recruited. Linoleic, arachidonic, docosahexaenoic and eicosapentaenoic acids levels were evaluated in whole blood. All children underwent fNIRS while performing an n-back working memory task. Between groups comparisons revealed lower levels of arachidonic acid in children with ADHD and stronger NIRS signal in TD participants, especially when completing more difficult tasks. Correlations conducted between fNIRS activation and PUFA biostatus revealed several associations between hemodynamic changes in the frontoparietal regions and fatty acids profile across participants. This result was also confirmed by the multiple hierarchical regression analyses that remarked an inverse effect of eicosapentaenoic acid levels on oxyhemoglobin values in right frontoparietal region. Such preliminary findings, if confirmed, would suggest that PUFAs could play a role in atypical neurodevelopment

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Pediatrics. 2019;144.

SCHOOL READINESS IN PRESCHOOLERS WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Perrin HT, Heller NA, Loe IM.

OBJECTIVE: To compare school readiness in preschoolers with and without attention-deficit/hyperactivity disorder (ADHD) symptoms using a comprehensive framework. We hypothesized that preschoolers with ADHD symptoms have higher odds of school readiness impairment.

METHODS: Children ages 4 to 5 years (n = 93) were divided into 2 groups on the basis of presence of ADHD symptoms (ADHD group, n = 45; comparison group, n = 48). School readiness was assessed through 10 component measures, including direct assessments and standardized questionnaires, regarding 5 school readiness domains: physical well-being and motor development, social and emotional development, approaches to learning, language, and cognition and general knowledge. Analysis of covariance compared group mean scores on component measures. Domain impairment was defined as score 1 SD from the test population mean in the unfavorable direction on 1 measure in the domain. School readiness impairment was defined as impairment in 2 of 5 domains. Logistic regression predicted impairment within domains and overall readiness.

RESULTS: The ADHD group demonstrated significantly worse mean scores on 8 of 10 component measures and greater odds of impairment in all domains except for cognition and general knowledge. Overall, 79% of the ADHD group and 13% of the comparison group had school readiness impairment (odds ratio 21, 95% confidence interval 5.67-77.77, P < .001).

CONCLUSIONS: Preschoolers with ADHD symptoms are likely to have impaired school readiness. We recommend early identification of school readiness impairment by using a comprehensive 5-domain framework in children with ADHD symptoms paired with targeted intervention to improve outcomes

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Pediatr Neonatol. 2019;60:581-83.

GENDER-DIFFERENTIAL ASSOCIATIONS BETWEEN ATTENTION DEFICIT AND HYPERACTIVITY SYMPTOMS AND YOUTH HEALTH RISK BEHAVIORS.

Jhang K-J, Lin Y-F, Tsai M-C, et al.

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PLoS ONE. 2019;14.

NO EVIDENCE OF ASSOCIATIONS BETWEEN ADHD AND EVENT-RELATED BRAIN POTENTIALS FROM A CONTINUOUS PERFORMANCE TASK IN A POPULATIONBASED SAMPLE OF ADOLESCENT TWINS.

Lau-Zhu A, Tye C, Rijsdijk F, et al.

We investigated key event-related brain potential markers (ERPs) derived from a flanked continuous performance task (CPT) and whether these would show phenotypic associations with ADHD (attention-deficit/hyperactivity disorder) in a population-based sample. We further explored whether there was preliminary evidence that such ERPs could also index genetic risk for ADHD (depending on finding phenotypic associations). Sixty-seven maleonly twin pairs (N = 134; aged 12-15) from a subsample of the Twins' Early Development Study, concordant and discordant for ADHD symptoms, performed the flanked CPT (or CPT-OX) while electroencephalography (EEG) was recorded. ERPs were obtained for cue (P3, CNV or contingency negative variation), go (P3, N2) and nogo trials (P3, N2). We found no phenotypic associations between CPT-derived ERPs and ADHDΓÇöthe sizes of the estimated phenotypic correlations were nonsignificant and very small (r's = -.11 to .04). Twinmodel fitting analyses using structural equation modelling provided preliminary evidence that some of the ERPs were heritable (with the most robust effect for go-P3 latency), but there was limited evidence of any genetic associations between ERPs and ADHD, although with the caveat that our sample was small and hence had limited power. Overall, unlike in previous research, there was no evidence of phenotypic (nor preliminary evidence for genetic) associations between ADHD and CPT-derived ERPs in this study. Hence, it may be currently premature for genetic analyses of ADHD to be guided by CPT-derived ERP parameters (unlike alternative cognitive-neurophysiological approaches which may be more promising). Further research with better-powered, population-based, genetically-informative and cross-disorder samples are required, which could be facilitated by emerging mobile EEG technologies

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Postgrad Med. 2019 Sep;131:445-52.

DEVELOPMENT OF A MULTIDISCIPLINARY CLINIC OF NEUROFIBROMATOSIS TYPE 1 AND OTHER NEUROCUTANEOUS DISORDERS IN GREECE. A 3-YEAR EXPERIENCE.

Kokkinou E, Roka K, Alexopoulos A, et al.

Given the complexity of neurocutaneous syndromes, a multidisciplinary approach has been advocated in order to provide optimum care. Subjects and Methods: Retrospective analysis of a cohort of 157 patients during a 3-year period, seen at a newly developed neurocutaneous clinic in a pediatric tertiary care hospital in Athens (Greece); and systematic chart review of the patients diagnosed with neurofibromatosis type 1 during this time period. Results: The most frequent neurocutaneous syndromes were neurofibromatosis type 1 (NF1) in 89 patients and tuberous sclerosis complex in 17. In 20.38% of patients a neurocutaneous syndrome was not confirmed. Approximately 2/3 of the NF1 patients underwent genetic analysis, and for 76.67% of them, a pathogenic mutation on the NF1 gene was revealed. Eighty-one patients manifested with generalized NF1 and eight with mosaic NF1. Dermatological manifestations included cafe-au-lait macules in all patients, followed by axillary and/or inguinal freckling (n = 57), external plexiform neurofibromas (n = 17), and cutaneous and subcutaneous neurofibromas (n = 11). Approximately half of patients had learning disabilities and attention deficit hyperactivity disorder, followed by mental retardation (n = 9), autistic spectrum disorders (n = 4), headaches (n = 3) and seizures (n = 2). Neuroimaging showed characteristic areas of hyperintensity on T2-weighted images in 74.07% of patients and optic pathway glioma in 19.75%. Two patients developed malignant peripheral sheath nerve tumor. Conclusions: Neurocutaneous syndromes are clinically heterogeneous and the surveillance of potential clinical complications is challenging. The

availability of genetic diagnosis and novel imaging methods in this group of disorders is likely to further expand their clinical spectrum. Guidelines for assessment and management will need to be modified based on new available data

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Psychiatr Genet. 2019 Jun;29:63-78.

GENETIC RISK FACTORS AND GENE-ENVIRONMENT INTERACTIONS IN ADULT AND CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Palladino VS, McNeill R, Reif A, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder. In recent years, genetic studies have revealed several risk gene variants associated with ADHD; however, these variants could only be partly replicated and are responsible for only a fraction of the whole heritability of ADHD estimated from family and twin studies. One factor that could potentially explain the 'missing heritability' of ADHD is that childhood and adult or persistent ADHD could be genetically distinct subtypes, which therefore need to be analyzed separately. Another approach to identify this missing heritability could be combining the investigation of both common and rare gene risk variants as well as polygenic risk scores. Finally, environmental factors are also thought to play an important role in the etiology of ADHD, acting either independently of the genetic background or more likely in gene-environment interactions. Environmental factors might additionally convey their influence by epigenetic mechanisms, which are relatively underexplored in ADHD. The aforementioned mechanisms might also influence the response of patients with ADHD to stimulant and other ADHD medication. We conducted a selective review with a focus on risk genes of childhood and adult ADHD, gene-environment interactions, and pharmacogenetics studies on medication response in childhood and adult ADHD

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Psychiatr Serv. 2019;70:874-80.

EVIDENCE OF LOW ADHERENCE TO STIMULANT MEDICATION AMONG CHILDREN AND YOUTHS WITH ADHD: AN ELECTRONIC HEALTH RECORDS STUDY.

Biederman J, Fried R, DiSalvo M, et al.

Objective: The objective of this study was to evaluate rates and correlates of stimulant medication adherence in a sample of pediatric patients using data derived from electronic medical records (EMRs) from a large health care organization in a large metropolitan area. The study relied on a novel definition of medication adherence as a timely renewal of an index prescription determined using the electronically recorded issuance of a stimulant prescription in the EMR (refill).

Methods: Prescription and sociodemographic data were extracted from the Partners HealthCare Research Patient Data Registry to calculate adherence to stimulant medication treatment.

Results: In the EMR, 2,206 patients with prescriptions for central nervous system stimulant medication were identified. Results showed that 46% of the index prescriptions were refilled within the timeframe necessary for the patient to be considered consistently medicated. A multivariable logistic regression model predicting medication adherence from patient demographic and treatment characteristics yielded an area-under-the-curve statistic of 0.57, indicating that these characteristics predicted adherence only modestly better than chance.

Conclusions: EMR data from a large health care organization showed that 46% of pediatric patients were adherent to treatment with stimulants. Rates of medication adherence were worse among patients receiving care from a primary care provider than among those receiving care from a psychiatrist, in older patients, and in female patients and did not appear to be influenced by racial-ethnic group, economic class, stimulant type, or medication formulation (short or long acting). These findings, which show low rates of medication adherence among children and adolescents with ADHD, suggest the need for efforts to improve these rates

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Psychiatry Research: Neuroimaging. 2019 Oct;292:54-61.

BRAIN RESPONSE TO FACIAL EXPRESSIONS IN ADULTS WITH ADOLESCENT ADHD.

Lindholm P, Lieslehto J, Nikkinen J, et al.

The symptoms of ADHD tend to have continuity to adulthood even though the diagnostic criteria were no longer fulfilled. The aim of our study was to find out possible differences in BOLD signal in the face-processing network between adults with previous ADHD (pADHD, n = 23) and controls (n = 29) from the same birth cohort when viewing dynamic facial expressions. The brain imaging was performed using a General Electric Signa 1.5 Tesla HDX. Dynamic facial expression stimuli included happy and fearful expressions. The pADHD group demonstrated elevated activity in the left parietal area during fearful facial expression. The Network Based Statistics including multiple areas demonstrated higher functional connectivity in attention related network during visual exposure to happy faces in the pADHD group. Conclusions: We found differences in brain responses to facial emotional expressions in individuals with previous ADHD compared to control group in a number of brain regions including areas linked to processing of facial emotional expressions and attention. This might indicate that although these individuals no longer fulfill the ADHD diagnosis, they exhibit overactive network properties affecting facial processing

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Psychoneuroendocrinology. 2019;110.

LOW HAIR CORTISOL CONCENTRATION PREDICTS THE DEVELOPMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Pauli-Pott U, Schlo+ſS, Skoluda N, et al.

Objective: Low activity of the hypothalamic-pituitary-adrenal axis (HPAA) resulting from genetic and early environmental factors has been thought to indicate risk for the development of attention deficit hyperactivity disorder (ADHD) and externalizing disorders. However, longitudinal research on this issue is scarce. We analyzed whether hair cortisol concentration (HCC), i.e. accumulated long-term HPAA activity, predicts the development of ADHD between preschool and school age.

Methods: A community-based sample of 126 children was assessed at the ages of 4, 5 and 8 years. ADHD and symptoms of oppositional defiant and conduct disorder (ODD/CD), callous unemotional (CU) traits, and internalizing symptoms were measured by clinical parent interviews and parent and teacher questionnaires. HCC was analyzed in the most proximal 3-cm scalp hair segment using luminescence immunoassay.

Results: Low HCC at preschool age predicted an increase in ADHD symptoms between preschool and school age while adjusting for gender of child, maternal education level, and internalizing symptoms ($F(1,119) = 6.5$; $p = .012$). The prediction held after additionally adjusting for ODD/CD symptoms and CU traits ($F(1,116) = 4.1$; $p = .045$). The same was true for the prediction of the ADHD diagnosis at the age of 8 years ($Chi2(1) = 7.3$; $p = .007$). The prediction of ADHD was mainly based on the presentation of inattention symptoms ($F(1,119) = 7.4$, $p = .008$).

Conclusion: Low HCC in preschool children indicates an increased risk of developing ADHD at school age. In future research, it would be of theoretical and clinical importance to further circumscribe this HCC-related developmental pathway and track its further course of development

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Revista de Psicopatología y Psicología Clínica. 2019 Aug;24:117-29.

ADAPTIVE DEVELOPMENT AND EXECUTIVE FUNCTIONING IN CHILDREN DIAGNOSED WITH CONDUCT DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER HYPERACTIVE-IMPULSIVE TYPE.

Bonilla-Santos J, Bonilla-Santos G, Hernández AG, et al.

Adaptive development allows the subject emotional control, disposition towards new challenges and the expected socio-cognitive adjustment contextually, facilitating learning and executive and social functioning. The objective of the study was to determine executive-adaptive development in children with diagnostic criteria for conduct disorder (CD) or attention deficit hyperactive-impulsive type disorder (ADHD-I). With clinical instruments to identify diagnostic criteria for each nosology, 80 children were classified in control group (30), CD (34) or ADHD-I (16). Based on multinomial logistic regression, Kruskal Wallis, and ?² tests,

we found that an appropriate sleep, persistence in tasks, and academic achievement seem to act as protective factors for the clinical samples. Difficulties were observed in sequential planning, where the CD group presented better metacognitive control than ADHD-I. It was concluded that school environment provides factors to improve clinical symptomatology

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Schizophr Bull. 2019;45:S201.

COMPARATIVE RISK OF PSYCHOSIS WITH AMPHETAMINE VERSUS METHYLPHENIDATE IN ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Moran L, Ongur D, Hsu J, et al.

Background: Prescription stimulant use (amphetamine and methylphenidate) for the treatment of attention deficit hyperactivity disorder (ADHD) is increasing. In 2007, the US Food and Drug Administration mandated changes to stimulant prescribing labels based on findings of new-onset psychosis in patients without pre-existing disease. Although these changes were mandated over 10 years ago, there has been no systematic study of the comparative risk of psychosis between amphetamine and methylphenidate. Studies of dopaminergic function in patients with psychotic disorders have demonstrated increased presynaptic dopaminergic capacity and greater amphetamine-induced release of dopamine compared to controls. In contrast, a meta-analysis has shown no differences in dopamine transporter availability between patients with schizophrenia and controls. The dopaminergic effects of amphetamine are more consistent with abnormalities observed in psychosis than methylphenidate. We sought to compare the risk of psychosis in adolescents and young adults with ADHD who are new users of amphetamine versus methylphenidate.

Methods: This is a cohort study of patients 13 - 25 years old with an outpatient diagnosis of ADHD from two commercial insurance claims databases who started taking amphetamine or methylphenidate between January 1, 2004 and September 30, 2015. The outcome was a diagnosis of psychosis requiring treatment with an antipsychotic medication within 60 days. Two studies were conducted to validate this outcome definition with positive predictive values of 93.1% and 91.3%. We used 1:1 propensity score (PS) matching to match patients on a set of 50 covariates measuring ADHD severity, psychiatric comorbidity, psychotropic medication use, substance use and healthcare utilization. We estimated hazard ratios (HR) in PS-matched patients. Results from the two databases were pooled using fixed effects meta-analysis.

Results: A total of 221,846 participants in the propensity score matched subsets with 143,286 person-years of follow-up experienced 343 psychotic events (2.4 per 1,000 person-years). Use of amphetamine increased substantially over the study period with preferential prescribing of amphetamine to older patients. The majority of patients were prescribed stimulants by family/internal medicine physicians, who had the highest prescribing rates of amphetamine (72.5%) compared to pediatricians (51.6%) and psychiatrists (63.7%). Use of amphetamine was associated with an increased risk of psychosis with a combined HR of 1.65 (95% CI 1.31 to 2.09) based on 237 psychotic events in amphetamine users and 106 psychotic events in methylphenidate users. Findings from the primary analysis were supported by a range of sensitivity analyses using increasingly stringent definitions of psychosis and study design modifications. In addition, negative control analyses using various substance use disorders, including cannabis, as outcomes demonstrated no significant differences between the two exposure groups.

Discussion: Amphetamine use is associated with an increased risk of treatment- emergent psychosis compared to methylphenidate among adolescents and young adults with ADHD

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Thyroid. 2019;29:1316-26.

MATERNAL THYROID FUNCTION IN EARLY PREGNANCY AND CHILD ATTENTION-DEFICIT HYPERACTIVITY DISORDER: AN INDIVIDUAL-PARTICIPANT META-ANALYSIS.

Levie D, Korevaar TIM, Mulder TA, et al.

Background: Thyroid hormone is essential for optimal fetal brain development. Evidence suggests that both low and high maternal thyroid hormone availability may have adverse effects on child neurodevelopmental outcomes, but the effect on behavioral problems remains unclear. We studied the association of maternal

thyrotropin (TSH) and free thyroxine (fT4) concentrations during the first 18 weeks of pregnancy with child attention-deficit hyperactivity disorder (ADHD).
Methods: A total of 7669 mother-child pairs with data on maternal thyroid function and child ADHD were selected from three prospective population-based birth cohorts: INfancia y Medio Ambiente (INMA; N = 1073, Spain), Generation R (N = 3812, The Netherlands), and Avon Longitudinal Study of Parents and Children (ALSPAC; N = 2784, United Kingdom). Exclusion criteria were multiple pregnancy, fertility treatment, usage of medication affecting the thyroid, and pre-existing thyroid disease. We used logistic regression models to study the association of maternal thyroid function with the primary outcome, ADHD, assessed via the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria by parents and/or teachers at a median child age of 4.5 to 7.6 years, and with the secondary outcome, an ADHD symptom score above the 90th percentile. Effect modification by gestational age and sex was tested with interaction terms and stratified analyses.
Results: Overall, 233 (3%) children met the criteria for ADHD. When analyzed continuously, neither fT4 nor TSH was associated with a higher risk of ADHD (odds ratio [OR] 1.1, 95% confidence interval [CI 1.0-1.3], p = 0.060 and OR 0.9 [CI 0.9-1.1], p = 0.385, respectively) or with high symptom scores. When investigating effect modification by gestational age, a higher fT4 was associated with symptoms above the 90th percentile but only in the first trimester (for fT4 per 1 SD: OR 1.2 [CI 1.0-1.4], p = 0.027). However, these differential effects by gestational age were not consistent. No significant effect modification by sex was observed.
Conclusions: We found no clear evidence of an association between maternal thyroid function and child ADHD

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Trends in Psychiatry and Psychotherapy. 2019;41:262-67.

RESILIENCE LEVELS AMONG ADOLESCENTS WITH ADHD USING QUANTITATIVE MEASURES IN A FAMILY-DESIGN STUDY.

Regalla MAR, Segenreich D, Guilherme PR, et al.

Objectives: To investigate resilience levels in adolescents with attention-deficit hyperactivity disorder (ADHD) using quantitative measures when compared to their non-affected siblings and controls. We also aimed to investigate the correlation between resilience and depression, anxiety, intelligence quotient (IQ) and socioeconomic status, which may affect resilience levels and be potential confounders.
Methods: Adolescents (n=45) diagnosed with ADHD referred to an outpatient ADHD clinic, and their siblings without ADHD (n=27), with ages ranging from 12 to 17 years, were interviewed along with their parents using a semi-structured interview (Children's Interview for Psychiatric Syndromes-Parent Version). Intelligence was measured with the Block Design and Vocabulary subtests from the Wechsler Battery. Anxiety and depression were investigated using the Children State-Trait Anxiety Inventory (CSTAI) and the Child Depression Inventory (CDI), respectively. Resilience was investigated using the Resilience Scale. A control group (typically developing adolescents [TDA] and their siblings; n=39) was recruited in another outpatient facility and at two schools using the same methodology.
Results: Socioeconomic status and intelligence levels, which may affect resilience, were similar in all groups. Adolescents with ADHD showed lower resilience levels compared to siblings and TDA even when controlled for anxiety and depression levels, which were higher in ADHD. Resilience levels were higher in siblings than in adolescents with ADHD, and lower than in TDA ΓÇô this last result without statistical significance.
Conclusion: In our sample, ADHD in adolescents was associated with lower resilience, even when controlled for confounders often seen in association with the disorder

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Twin Res Hum Genet. 2019.

POLYGENIC RISK SCORES FOR PSYCHIATRIC DISORDERS REVEAL NOVEL CLUES ABOUT THE GENETICS OF DISORDERED GAMBLING.

Piasecki TM, Gizer IR, Slutske WS.

Disordered gambling (DG) is a rare but serious condition that results in considerable financial and interpersonal harms. Twin studies indicate that DG is heritable but are silent with respect to specific genes or pathways involved. Existing genomewide association studies (GWAS) of DG have been substantially underpowered. Larger GWAS of other psychiatric disorders now permit calculation of polygenic risk scores (PRSs) that reflect the aggregated effects of common genetic variants contributing risk for the target condition. The current study investigated whether gambling and DG are associated with PRSs for four psychiatric conditions found to be comorbid with DG in epidemiologic surveys: major depressive disorder (MDD), attention-deficit hyperactivity disorder (ADHD), bipolar disorder (BD) and schizophrenia (SCZ). Genotype data and survey responses were analyzed from the Wave IV assessment (conducted in 2008) of the National Longitudinal Study of Adolescent to Adult Health, a representative sample of adolescents recruited in 1994-1995 and followed into adulthood. Among participants classified as having European ancestry based on genetic analysis (N = 5215), 78.4% reported ever having gambled, and 1.3% reported lifetime DG. Polygenic risk for BD was associated with decreased odds of lifetime gambling, OR = 0.93 [0.87, 0.99], p =.045, pseudo-R 2(%) =.12. The SCZ PRS was associated with increased odds of DG, OR = 1.54 [1.07, 2.21], p =.02, pseudo-R 2(%) =.85. Polygenic risk scores for MDD and ADHD were not related to either gambling outcome. Investigating features common to both SCZ and DG might generate valuable clues about the genetically influenced liabilities to DG

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World J Pediatr. 2019 Oct;15:516-19.

COMPLEMENTARY AND ALTERNATIVE MEDICINE IN ADHD TREATMENT: MORE SOUNDLY DESIGNED CLINICAL TRIALS NEEDED.

Yang RW, Li R.

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World J Biol Psychiatry. 2019;20:486-95.

DRD4 EXON 3 GENOTYPE AND ADHD: RANDOMISED PHARMACODYNAMIC INVESTIGATION OF TREATMENT RESPONSE TO METHYLPHENIDATE.

Naumova D, Grizenko N, Sengupta SM, et al.

Objectives: Dopamine plays an important role in modulating attention and motor behaviours, dimensions altered in attention deficit/hyperactivity disorder (ADHD). Numerous association studies have linked dopamine receptor 4 (DRD4) to increased risk of ADHD. This study investigated the effect of DRD4 exon 3 polymorphism on child behaviours in response to treatment with methylphenidate.

Methods: A total of 374 children diagnosed with ADHD (ages 6-12 years) were evaluated under three experimental conditions: baseline, placebo and MPH (0.5 mg/kg/day). This was a 2-week prospective within-subject, placebo-controlled, crossover trial. The Conners Global Index for parents and for teachers was used to evaluate the behaviours of the children. One-way repeated measures analysis of variance was used to test the effect of the interaction between DRD4 genotype and experimental conditions.

Results: A significant interaction between DRD4 genotype and treatment was detected when the child's behaviour was evaluated by the parents (P = 0.035, effect size of 0.014), driven by a better treatment response in children homozygous for long 7-repeat allele.

Conclusions: According to the parent assessment, children homozygous for the long 7-repeat allele were more responsive to experimental condition. This is the largest pharmacogenetic investigation of the effect of DRD4 exon 3 polymorphism in childhood ADHD.
Trial Registration: clinicaltrials.gov, identifier NCT00483106

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World J Biol Psychiatry. 2019;20:476-85.

GENETIC ANALYSIS FOR COGNITIVE FLEXIBILITY IN THE TRAIL-MAKING TEST IN ATTENTION DEFICIT HYPERACTIVITY DISORDER PATIENTS FROM SINGLE NUCLEOTIDE POLYMORPHISM, GENE TO PATHWAY LEVEL.

Zhang K, Fan Z, Wang Y, et al.

Objectives: Investigation of the genetic basis of endophenotype and analysis the pathways with multiple genes of small effects might increase the understanding of the genetic basis of attention deficit hyperactivity disorder (ADHD). Here we aimed to explore the genetic basis of cognitive flexibility in ADHD at the single nucleotide polymorphism (SNP), gene and pathway levels.
Methods: The trail-making test was used to test the cognitive flexibility of 788 ADHD patients. A genome-wide association analysis of cognitive flexibility was conducted for 644,166 SNPs.
Results: The top SNP rs2049161 (P = 5.08e-7) involved gene DLGAP1 and the top gene CADPS2 in the gene-based analysis resulted in much literature evidence of associations with psychiatric disorders. Gene expression and network analysis showed their contribution to cognition function. The interval-enrichment analysis highlighted a potential contribution of adenylate cyclase activity and ADCY2 to cognitive flexibility. Candidate pathway-based analysis for all SNPs found that glutamate system-, neurite outgrowth- and noradrenergic system-related pathways were significantly associated with cognitive flexibility (FDR <0.05), among which the neurite outgrowth pathway was also associated with ADHD symptoms.
Conclusions: This study provides evidence for the genes and pathways associated with cognitive flexibility and facilitate the uncovering of the genetic basis of ADHD

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Z Kinder- Jugendpsychiatr Psychother. 2019;47:228-38.

ON THE POSITIVE ASSOCIATION BETWEEN CANDY AND FRUIT GUM CONSUMPTION AND HYPERACTIVITY IN CHILDREN AND ADOLESCENTS WITH ADHD.

Reimelt C, Ehrlich S, H+Âlling H, et al.

Objective: The purpose of the present study was the analysis of the association between consumption of candy and fruit gums, diagnosis of attention deficit hyperactivity disorder (ADHD), and behavioural problems.
Methods: In total, 1,187 children and adolescents of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) were analyzed.
Results: It was observed that children and adolescents with ADHD as compared to healthy controls (HC) reported to consume more frequently and higher amounts of candy and fruit gums and that hyperactivity was associated with frequent candy and fruit gum consumption.
Conclusions: Because with the present design no conclusions on causality or directionality of the found associations could be drawn, results are discussed quite broadly in the light of several previously published interpretations, also to serve as a generator for further research. One more innovative speculation is that children and adolescents with ADHD may consume more frequently candy and fruit gums in order i) to compensate for their higher needs of energy resulting from hyperactive behaviour and/or ii) to compensate for the ADHD-typical deficits in the ΓÇ£reward cascadeΓÇØ

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Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119:44-50.

TENSION TYPE HEADACHES IN CHILDREN AND ADOLESCENTS: CO-MORBIDITY WITH EMOTIONAL AND BEHAVIORAL DISORDERS.

Shipilova EM, Zavadenko NN, Nesterovskiy YE.

AIM: To assess the incidence of emotional and behavioral disorders in children and adolescents with frequent episodic or chronic tension type headaches (TTH).

MATERIAL AND METHODS: One hundred and fifty patients with TTH (75 boys and 75 girls), aged 8-16 years, were included in the study. The severity of emotional and behavioral problems was analyzed in comparison with their healthy peers by means of parents' interviewing with the 'Strengths and Difficulties Questionnaire' (SDQ).

RESULTS: Total difficulties scores measured by SDQ were significantly higher in boys (16.2+/-0.7) and girls (14.3+/-0.7) with TTH compared with their peers (7.9+/-0.4 and 7.7+/-0.4, respectively, $p<0.001$). Patients with TTH had significantly more prominent manifestations than their peers ($p<0.001$) on the four SDQ scales, including Hyperactivity and Inattention, Conduct problems, Emotional symptoms, Peer problems. Clinical examination revealed in many pediatric patients with TTH the following disorders: attention deficit hyperactivity disorder (45.3% boys and 13.3% girls), oppositional defiant disorder (26.7% boys, 18.7% girls), with co-occurrence of both disorders in some patients (17.3% boys, 10.7% girls). Moreover, most patients with TTH had anxiety disorders (68.0% boys, 77.3% girls).

CONCLUSION: Clinical features and duration of TTH may be dependent on the severity of co-morbid emotional and behavioral disorders. This should be taken into account for individualized indication of drug therapy and non-pharmacological treatment approaches in pediatric TTH

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Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119:103-11.

HETEROGENEITY OF CLINICAL CHARACTERISTICS OF FMR1-RELATED DISORDERS.

Pereverzeva DS, Tyushkevich SA, Gorbachevskaya NL, et al.

The objective of this study is to provide a detailed description of clinical characteristics of disorders associated with FMR1 gene, which is located on the long arm of chromosome X. The most frequent FMR1 mutations are related to CGG-repeat expansion in the promoter region: premutation (from 55 to 199), full mutation (more than 200 repeats). The first section of the article is devoted to the fragile X mental retardation syndrome (FX syndrome) caused by FMR1 full mutation. The clinical characteristics of FX syndrome are presented. The second section provides information about specific phenotypes associated with FMR1 premutation that can be observed in maternal relatives (grandmother, mother's siblings, grandfather) of the child. The most frequent symptoms that observed in permutation carriers are mild cognitive impairment, ASD, ADHD in children, fragile X-associated tremor/ataxia syndrome (FXTAS) in older carries, fragile X-associated primary ovarian insufficiency (FXPOI) in women. The last section provides information about screening diagnostic instruments that help to identify the risk of fragile X syndrome. It also presents the key questions to be asked to family members in order to identify the risk of the permutation

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INTERDISCIPLINARY UPDATE

The effect of added sugars on children's health outcomes: Obesity, Obstructive Sleep Apnea Syndrome (OSAS), Attention–Deficit/Hyperactivity Disorder (ADHD) and Chronic Diseases

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ABSTRACT

Increasing attention has been paid to how dietary sugars affect not only tooth decay, but also obesity, Type 2 diabetes mellitus, and cardiometabolic and kidney diseases. Therefore, possible connections of these diseases with oral health and diet are analysed. Healthy approaches to beverage and dietary consumption should be recommended and hopefully established in infancy, with the aim of preventing negative effects on general health in later childhood and adulthood.

KEYWORDS *Added Sugars, Attention-Deficit/Hyperactivity Disorder, Chronic Diseases, Early Childhood Caries, NonAlcoholic Fatty Liver Disease, Obesity, Obstructive Sleep Apnoea Syndrome*

Introduction

Balanced nutrition is very important during childhood, which is a period of increased activity, body growth and development of cognitive ability.

In the last few years dietary sugar has been considered a central risk factor in the development of some important diseases, together with alcohol and tobacco.

Sugars added to foods during processing, preparation or at table, sweeten food and beverage taste, improve their palatability and are used to preserve foods and to confer property such as viscosity, texture and color. They provide sensory enhancement to foods and promote enjoyment but, although they may be required in some clinical situations, they are not a necessary component of the diet in healthy children. In addition to its role in carious disease, for which there is moderate evidence of a direct correlation, increasing attention has been paid to how dietary sugars affect obesity, Type 2 diabetes mellitus, and cardiometabolic and kidney diseases [Fattore et al., 2017].

Carious disease

Dental caries was first described in Miller's chemoparasitic theory in 1890. The caries process can be described as a loss of minerals (demineralisation) of the teeth when the pH of the plaque drops below the critical value of 5.5; reapposition of minerals (remineralisation) occurs when the pH rises. Whether or not a lesion develops, is the outcome of the balance between demineralisation and remineralisation, in which the latter process is significantly slower than the former.

Diet and nutrition may interfere with this mechanism. Sugars and other fermentable carbohydrates, after being hydrolysed by salivary amylase, provide substrate for the actions of oral acidogenic and aciduric bacteria (Streptococci mutans and Lactobacilli especially), which decrease salivary and plaque pH. Otherwise, a diet lower in sugars and fermentable carbohydrates and high in calcium-rich cheese may favour remineralisation.

Studies have confirmed the direct correlation between intake of dietary sugars and carious disease throughout the course of life. The type of food (solid or beverage), exposure time, and frequency of eating also play an important role in the development of carious disease.

Since the first studies, additional factors, besides the diet, have been recognised in the aetiopathogenesis of carious disease that include salivary flow (quality and quantity), the immune system, age, socioeconomic status, level of education, lifestyle behaviours, oral hygiene and use of fluorides [Cianetti et al., 2016].

Early Childhood Caries and added sugar intake

Over the past decades, the American Academy of Pediatric Dentistry introduced the definition of Early Childhood Caries (ECC),

consisting in the presence of one or more cavities, missing or fillings in any primary tooth, in a child under 6 years of age (Fig. 1, 2).

This disease has a widespread diffusion and it has been widely demonstrated that children developing ECC have a diet characterised by high free sugars intake, especially in the form of beverages (fruit juices, soft drinks, etc.). Also the causal role of candies and pacifier dipped in sugar or honey is not negligible [Paglia et al., 2016].

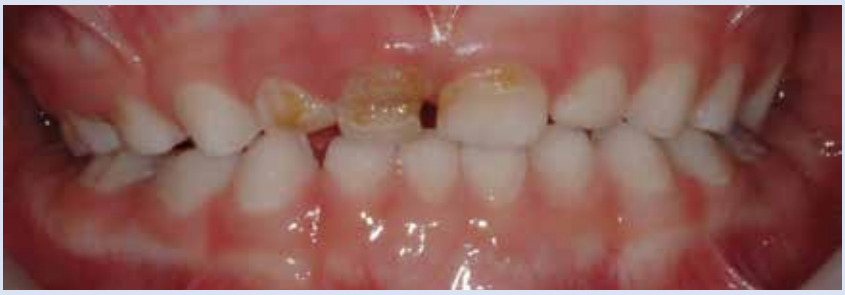
A high incidence of ECC is well documented in Europe [Davies et al., 2001] and Italy [Nobile et al., 2014]. The OMS Collaboration Centre for Epidemiology and Community Dentistry (Milan, Italy) conducted a research in 2004–2005 showing 21.6% decay prevalence in Italian 4-year-old children [Campus et al., 2009].

Generally, children with ECC consume free sugars daily. In particular, sucrose is needed as substratum in the production of extracellular polysaccharides, which in turn facilitate bacterial adhesion to the dental surface and increase the porosity of plaque in close contact with the tooth, with a consequent production of acid on the enamel surface. This condition represents an aggravating factor in carious disease development in primary teeth, due to the thinner and uniform enamel and to the softer dentin in primary teeth than in permanent ones, since dentin tubules have a non-homogenous distribution.

The more frequently free sugars are consumed, the more frequently the pH drops below the threshold value, with consequent difficulty in buffering the general acidity.

The consequences of ECC on a child's health and life quality are numerous and severe: increased risk of malocclusion and development of new decays, in mixed and permanent dentition; increased instances of pain and dental emergencies; risk of bacteremia; possible alteration of a child's development and growth; difficulties in learning with a reduced scholastic performance.

Therefore, it is necessary to apply preventive measures as soon as possible, in children, also considering the possibility of bacteria transmission from mother to child directly through the saliva.



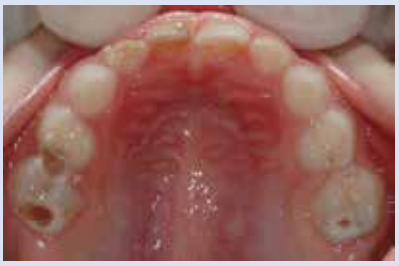


FIG. 1A, 1B Type 2 (moderate to severe) ECC in a 4-years-old girl, frontal and occlusal view: cervical and interproximal areas of yellowish decalcification in maxillary incisors with molars involvement (Photographs courtesy of Dr. Matteo Beretta).

FIG. 2A, 2B Type 2 (moderate to severe) ECC in a 4-years-old boy, frontal and occlusal view: compared to the previous case, carious lesions affect almost all teeth, with crown destruction and consequent permanence of brown black root stumps. Note the presence of fistulas
(Photographs courtesy of Dr. Matteo Beretta).

Does breastfeeding increase risk of ECC?

According to the WHO, "breastfeeding is the normal way of providing young infants with the nutrients they need for healthy growth and development. Exclusive breastfeeding is recommended up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to 2 years of age or beyond". However, several studies have reported prolonged and unrestricted breastfeeding as a potential risk factor for ECC. On-demand breastfeeding, especially during the night, would seem to cause ECC because milk remains in the baby's mouth for long periods of time. There is lack of evidence that human milk is cariogenic; other factors, such as oral hygiene, may be more influential in caries development than on-demand breastfeeding. Moreover, the biomechanics of breastfeeding differs from those of bottle feeding and milk is expressed into the soft palate and swallowed without remaining on teeth. Indeed we cannot forget that the main factor influencing caries development in infants is the presence of bacteria, Streptococcus mutans, that thrive in a combination of sugars, small amounts of saliva and a low pH [Paglia, 2015]. Further studies with more elaborate methods of assessment are needed to determine the cariogenic nature of breastfeeding. In the meantime, given

the many benefits of breastfeeding, the practice should continue to be strongly encouraged. Dental professionals should encourage parents to start proper oral hygiene with their children as soon as the first tooth erupts, and to limit the consumption of sugary beverages to a minimum.

Chronic diseases and sugar-sweetened beverages

Most chronic diseases are associated with preventable risk factors, such as high blood pressure, high blood glucose or glucose intolerance, high lipid levels, sedentary life and physical inactivity, excessive weight and obesity. The occurrence of intermediate outcomes during childhood increases the risk of disease in adulthood.

Sugar-Sweetened Beverages (SSBs) are known to be significant sources of additional caloric intake, and given recent attention to their contribution in the development of chronic diseases. The consumption of SSBs in children is associated with adverse health outcomes [Fidler Mis et al., 2017].

Children have a strong preference for a sweet taste and early introduction of added sugars in the diet of infants and toddlers may further promote a sweet taste preference. Introduction of SSBs before 12 months of age is associated with an increased likelihood of consuming SSBs ≥1 time/day at 6 years of age. Recent research demonstrating the use of sucrose and glucose, sweeter than lactose (the sugar present in breast milk) in infant formulas, emphasising the importance of new researches on this topic due to the importance of this early period on growth and future obesity and metabolic risk [Tan et al., 2016].

Scientific evidences suggest that during childhood, a crucial phase for the formation of individuals, some eating habits tend to consolidate until adolescence and adulthood.

Added sugar, obesity and cardiovascular disease

Consumption of drinks containing added sugars, fructose in particular, continues to increase and can play an important role in the onset of obesity and cardiovascular disease (CVD). There is, in fact, evidence that a reduction in the consumption of soft drinks is related to a decrease of being overweight and an improvement of sugar metabolism.

A systematic review on the effects of free sugars intake on adiposity development enables to conclude that the decrease or increase of free sugars in diet influences weight in children and young adults [Te Morenga et al., 2012].

In 2015 the World Health Organization (WHO) recommended to further limit free sugars intake to less than 10% of the total energy intake for adults and children, observing that a further reduction of 5% would provide additional health benefits [WHO, 2015]. It is reasonable to recommend that children consume ≤ 25 g (100 cal or 6 teaspoon) of added sugars per day and to avoid added sugars for children < 2 years of age [Vos et al., 2017].

Again in 2015, the American Heart Association (AHA), in collaboration with the American Academy of Pediatrics (AAP), affirmed that "sweetened beverages and naturally sweet beverages, such as fruit juices, should be limited to 4 to 6 ounces per day for children 7 to 18 years old" [Gidding et al., 2005].

Fructose and glucose have similar effect but have significant different metabolic destiny in the human body. After assumption, digestion and absorption, both fructose and glucose are absorbed into the portal circulation and taken up into the liver. The liver has a major role in controlling the amount of glucose that reaches peripheral tissues after a meal. Increased glucose in the portal blood stimulates insulin secretion, leading to increased uptake of glucose into muscles and adipose tissues, increased synthesis of glycogen, increased fatty acid synthesis in the fat, increased amino-acid uptake and induction of lipoprotein lipase into muscles and fat. Fructose does not stimulate insulin secretion to the same measure and is absorbed primarily into the liver where it stimulates de novo lipid synthesis. It is therefore considered responsible for the pathologic conditions previously mentioned [Houston and Minich, 2015; Malik and Hu, 2015].

The form in which added sugars are consumed also may influence the metabolic effects. SSBs provide a lot of calories and are composed almost exclusively of just 2 ingredients: added sugar and water. This makes them a good mean for testing the effect of added sugars with minimal risk of confounding by other nutrients. Several short-term studies have shown that carbohydrates consumed as solids satisfy hunger more than those consumed as liquids and subsequent calorie balance appears to be compensated for by the additional calories, resulting in less body weight gain. In a 6-year longitudinal study of 8–10-year-old children, Olsen et al. [2012] demonstrated a stronger association between liquid sucrose consumption and fat storage in terms of Body Mass Index (BMI) and waist circumference compared with solid sucrose consumption. Moreover, randomised and controlled trials in which children and adolescents switched from SSBs to noncaloric beverages show reductions in their weight. This supports the concept that the association between added sugars and weight gain is mediated by total energy intake, but also it suggests that liquid sugars may uniquely affect body fat distribution. In view of the above, the reduction of all added sugars, SSBs in particular, is recommended as a way to improve long-term cardiovascular health.

Importantly, the associations between added sugars intake and adverse outcomes, in longitudinal and cross-sectional studies, may also be driven by others factors such as: the home environment, a more unhealthy diet and level of activity.

Evidence in both aepidemiological and clinical trials suggests that excessive fructose intake results in increased blood pressure in children and young adults. This effect would seem to be mitigated by urate-lowering therapy based on the hypothesis that the hypertensive effect of dietary sugars is mediated by the induction of hyperuricemia [Nguyen et al., 2009]. Current evidence suggests that added sugars are a source of excess fructose whereas the reduction of fructose (from added sugars) is likely to decrease uric acid, possibly improving blood pressure in children [Vos et al., 2016]. However, further researches are needed to test whether or not a reduction in added sugars results in improved blood pressure in children.

The preponderance of evidence

from the available cross-sectional and longitudinal studiesshows improved triglycerides and HDL values in children with low consumption of added sugars. Although traditionally triglycerides and HDL have not been a primary focus for decreasing CVD risk, newer data demonstrate that a high ratio of triglycerides to HDL predicts smaller dense low-density lipoprotein, an important cardiovascular risk factor [Burns, 2012]. However, even in this case more studies are needed.

Obesity and Obstructive Sleep Apnoea Syndrome

Obesity is a significant risk factor in the pathogenesis of Obstructive Sleep Apnea Syndrome (OSAS), since it alters the anatomy and the collapsibility of the airways as well as it alters the respiratory control. The association between obesity and OSAS has led to increasing attention to the role of weight loss as a potential treatment for OSAS.

Obese children have a greater risk of developing Sleep Disorders Breathing (SDB). Numerous evidences in literature show a correlation between OSAS and obesity, with a prevalence ranging from 13% to 50% of obese children and adolescents with OSAS and a prevalence of 25% polysomnographic alterations in obese children. Redline et al. examined the risk factors for SDB in a group of children between 2 and 18 years of age and found that there is a 4-5 times greater risk of developing RSD in obese children. In particular, for every 1 Kg/m^2 increase in BMI, compared to the mean BMI value for age and sex, the risk of OSAS increases by 12%.

In obese children with OSAS, the reduction of upper air way space is due not only to adenotonsillar hypertrophy, but also to the infiltration of adipose tissue between the neck and the lymphatic structures. In addition, subcutaneous fat in the anterior region of the neck and in the submental region, makes the upper airways more susceptible to collapse when the subject is in a supine position.

The subject with obesity is typically affected by a restrictive respiratory disorder in which visceral fat mechanically reduces lung volumes. Moreover, the increased abdominal adipose tissue, as well as in the thorax, increases the overall respiratory load and reduces the diaphragmatic excursion and the intrathoracic volume, especially in the supine position.

The mechanical role assumed by adipose tissue is not the only feature at the basis of aetiopathogenesis of SDB in obese children. Recent studies show that the abdominal adipose tissue induces a state of chronic inflammation, with increased levels of both C-Reactive Protein (CRP) and cytokines. The adipose tissue is able to produce and release various proinflammatory factors such as leptin and resistin, cytokines (IL-1, TNF-α, IL-6, IL-8, IL-10, VEGF, EGF, MCP-1) and chemokines (adiponectin) that contribute to the development of insulin resistance and predispose to cardiovascular damage.

Type-2 diabetes mellitus, NonAlcoholic Fatty Liver Disease and diet

In a balanced diet, the consumption of fructose naturally contained in foods (fruit, vegetables, flour used for bread, pasta and pizza) has no negative effect. The enemy of children is the added fructose present in syrups and sweetners widely used by industry in various preparations (jam or fruit preserve, drinks, snacks, fruit juices, sweets). A jar of jam has a fructose concentration 8 times greater than the daily requirement; a snack contains on average 45% more of it, while a small bottle of fruit juice contains just over half of the daily requirement.

Fructose is metabolised mainly in the liver. This synthesis process produces energy for the body, but also other derivatives such as uric acid. If the amount of fructose ingested systematically is excessive, its metabolism is altered and too much uric acid is produced. When the body cannot dispose of high concentrations of uric acid in circulation, dangerous mechanisms for health are triggered: oxidative stress increases and insulin resistance and inflammatory processes of the liver cells are activated. These mechanisms are precursors to the onset of diabetes and fatty liver.

Nonalcoholic Fatty Liver Disease (NAFLD) is a disease of lipid metabolism in which an excess of triglycerides accumulates in hepatocytes, thus increasing adiposity, hypertriglyceridemia, and increasing free fatty acid flux to the liver caused by insulin resistance.

NAFLD has increased in the world population to a worrying rate, becoming the most prevalent paediatric chronic liver disease [Berardis and Sokal, 2014]. This disease includes a spectrum of hepatic histological alterations. Diagnosis is made when at least 5% of hepatocytes is characterised by fatty infiltration with no evidence of infection, metabolic or autoimmune disorder, or steatogenic drug or alcohol consumption [Vos et al., 2017].

A relationship between fructose consumption in children and hepatic fat has been suggested [Jensen et al., 2018].

NAFLD in childhood has been demonstrated to have different characteristics from adults, primarily concerning histological findings with a predominant periportal inflammation in the pediatric age. Fructose consumption with consequent hyperuricemia has been shown to induce greater damage in the periportal zone than the perivenous zone [Abdullah et al., 2018].

In children with a liver already compromised, that relationship accelerates the progression of the disease to more severe stages (non-alcoholic steatohepatitis, liver fibrosis, and cirrhosis). Scientific confirmation comes from a study by researches of the area of hepato-metabolic disease of the Bambino Gesù Pediatric Hospital, in Italy, the results of which were published on the Journal of Hepatology. This study including 271 obese adolescents with biopsy-proven NAFLD showed that fructose consumption was significantly higher in patients with NASH (Non-Alcoholic Steatohepatitis) compared with NAFLD, and patients from the first group had significantly higher uric acid levels [Mosca et al., 2017]. However, more studies are needed because NAFLD doesn't occur in isolation and is almost always accompanied by visceral obesity, hypertriglyceridemia, low HDL, high non-HDL cholesterol, and/or insulin resistance [Jin et al., 2012].

SSBs contribute to high dietary glycemic load which leads to

inflammation, insulin resistance and impaired β-cell function. Studies suggest that greater SSBs consumption in childhood or adolescence predict weight gain into adulthood [Nissien et al., 2009; Viner and Cole, 2006]. Obese children are more likely to become obese adults, besides increasing their risk for higher rates of Type 2 diabetes mellitus (T2DM), heart disease and some cancer later in life [Cantley, 2014; Batrina and Rodrigo, 2013].

T2DM is a long-term multifactorial disease that is characterised by high blood sugar, insulin resistance and relative lack of insulin. In adolescents and young adults, T2DM seems to be a more aggressive disease than in middle age subjects, demonstrated by a less response to conventional treatment and a high mortality rate [Constantino et al., 2013].

A recent large cohort study found that a child with obesity has a 4-fold greater risk of being diagnosed with T2DM by age 25 than a counterpart who has normal weight [Abbasi et al., 2017]. Another well powered meta-analysis also found that individuals in the highest quartile of SSBs intake (most often 1-2 servings/day) have a 26% greater risk of developing T2DM than those in the lowest quartile (none/< 1 serving/month). This suggests the independent effect of SSBs intake on T2DM in addition to weight gain. Several high quality-systematic reviews and meta-analysis have assessed the correlation of SSBs with the T2DM incidence. Moreover, it remains unclear whether the association between SSBs and T2DM can be explained by the fructose that these beverages contain. Furthermore, added sugars appear to have a relationship with insulin resistance in overweight children but this findings is not demonstrated in normal-weight children.

Attention-Deficit/Hyperactivity Disorder and sugar intake

Children hyperactivity is a neurodevelopmental condition that is usually diagnosed in childhood and can last into adulthood. Symptoms include excessive motor activity and impulsivity, which lead to distraction and to significant attention deficit.

Diagnosis is made when these symptoms are more severe and persistent than is expected for the child's age and developmental level. Attention-Deficit/Hyperactivity Disorder (ADHD) is 6 to 9 times more common in boys than girls [Yujeong and Hyeja, 2011].

Some correlations between the consumption of sugar and the onset of ADHD have been highlighted, but these must be reconfirmed [Johnson et al., 2011; Del-Ponte et al., 2019]. However, from a physiological point of view, sugar should influence hyperactivity in children because it can quickly enter the bloodstream, making rapid changes in glucose levels and starting adrenaline production. Adrenaline is a hormone produced under stress, capable of providing a short-term energy boost to cope with critical situations. A recent study by paediatric researchers of Yale University confirmed the connection between sugar and adrenaline. The study showed that in a few hours healthy children who took high doses of sugar, on an empty stomach, produced high levels of adrenaline. The variation in the levels of this hormone caused tremor, anxiety, excitement and concentration problems. These reactions were observed only in children and a specialised examination revealed significant changes in their ability to pay attention.

Despite this, no direct association was established between ADHD and sugar consumption, since the study involved ingesting large quantities of sugar on an empty stomach. Thus, it can only be concluded that sugar can cause hyperactivity in children only when taken in large quantities.

We can conclude that it is still controversial whether or not there is an association between ADHD and sugar consumption.

Conclusions

Healthy approaches to beverage and dietary consumption should be established in infancy, with the aim of preventing negative health effects in later childhood and adulthood. Sugar should preferably be consumed as part of a main meal and in a natural form (human milk, cow or sheep milk, unsweetened dairy products, fresh fruits) rather than as SSBs, smoothies, fruit juices and sweetened milk products. Free sugars in liquid form should be replaced by water or unsweetened drink. The choice of fresh vegetables, whole foods, nuts and seeds and proteins with a low content of saturated fatty acids should be promoted. The consumption of added sugars, sugary snacks and drinks, salt and processed meats should be drastically reduced.

The consequences of poor nutrition in children can be permanent. Healthy and varied nutrition during childhood leads to a healthy and long life.

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Neurodevelopmental Disorders and Adaptive Functions: A Study of Children With Autism Spectrum Disorders (ASD) and/or Attention Deficit and Hyperactivity Disorder (ADHD)

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Introduction: Autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD) are the two most common neurodevelopmental disorders observed in childhood. The DSM-5 accepts a combined diagnosis of ADHD and ASD, while the DSM-IV did not. The aim of this study was to identify and evaluate the adaptive profile of children and adolescents with a diagnosis of comorbid ADHD and ASD, in comparison with adaptive functioning in subjects with a diagnosis of only ASD or ADHD.

Materials and Methods: Ninety-one children (77 boys, 14 girls), aging from 3.1 to 13.4 years (mean age: 8.3 ± 7.2), who met the criteria for a diagnosis of ASD and/or ADHD were enrolled. A neuropsychological evaluation involving cognitive and adaptive assessment was conducted using the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2), the Conners' Parent Rating Scale – Revised: Long Version (CPRS-R), the Wechsler Intelligence Scale – Fourth Edition or the Griffiths Mental Developmental Scales – Extended Revised, the Vineland Adaptive Behaviour Scale – Second Edition (VABS-II).

Conclusion: As to the adaptive skills in the three groups evaluated, a worse general profile was ascertained in the ASD and in ASD plus ADHD groups in comparison with respect to the ADHD-only group. With VABS-II evaluation, we found significant differences among the three groups across all domains and combined scores: Communication ($F = 18.960$; $p < 0.001$), Socialization ($F = 25.410$; $p < 0.001$), Daily Living Skills ($F = 19.760$; $p < 0.001$), Motor ($F = 9.615$; $p < 0.001$), and Adaptive behavior composite [ABC] ($F = 29.370$; $p < 0.001$). Implications of neurodevelopmental double diagnosis such as ASD plus ADHD are discussed.

Keywords: autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), adaptive function, children, comorbidity

INTRODUCTION

Autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD) are the two most common neurodevelopmental disorders observed in childhood (1, 2). According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (1), ASD is a disorder characterized by deficits in social communication as well as restricted, repetitive patterns of behaviors. In the child population, ASD prevalence has been estimated to be about 1%, but a recently published US study put it at 1.68% (3). Approximately 30% of children with ASD undergo a regression of development with variable course that maybe associated with epileptic abnormalities in an undetermined percentage (4, 5).

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental disorders affecting children. Symptoms of ADHD include inattention, hyperactivity, and impulsivity. Current estimated prevalence is 5% of children and 2.5% in adults. ADHD is often first identified in school-aged children when it leads to disruption in the classroom and/or difficulties with school duties. It is more common among boys than girls (DSM-5) (1).

Impairment of social competences in neurodevelopmental disorders is common and needs to be thoroughly addressed. In recent years, there has been increasing interest in the diagnostic overlap and similarities between ADHD and ASD (6–11). Evidence indicated that both disorders co-occur with a high frequency, in 20–50% of children with ADHD meeting criteria for ASD and in 30–80% of ASD children meeting criteria for ADHD. (12). The co-occurrence of ASD and ADHD was found to increases with age, appearing in school age children more clearly, with severity of ASD and ADHD symptoms and with lower IQ (8, 13). Moreover, the increase in inattention and impulsivity concomitant with increases in ASD severity may be able to predict the severity of challenging behaviors and social skills deficits in toddlers and should be carefully evaluated in this population (14–16). In addition individuals with ASD frequently experience additional psychiatric comorbiditties (17).

As to adaptive functions, some studies found that children with ASD+ADHD showed a more severe impairment in adaptive functioning and a poorer quality of life than children with ASD alone (18) while other studies found varying profiles depending on cognitive level and age (19, 20).

A specific social-communication core deficit, associated with restricted and repetitive behaviors (RRBs) is the hallmark of ASD. In contrast to the DSM-IV (APA 1994), the DSM-5 (1) allows a combined diagnosis of ADHD and ASD. Both ASD and ADHD develop from interactions among multiple genetic and environmental factors, which have an effect on complex neurobiological systems already during prenatal life. These interactions are likely to be involved in the distinct developmental trajectories, clinical characteristics, and outcomes of the two disorders (21).

Children with ADHD frequently display peculiar social difficulties. Social competences in ADHD are thought to be related to self-regulation difficulties, low social skills adaptive level, and attentional issues, which can impact the overall ability to process social information. Children diagnosed with predominantly inattentive ADHD (PI) are more passive, less aggressive, less assertive, and less knowledgeable of appropriate social behavior than those diagnosed with combined ADHD (CB). Children with PI are more likely than typical children to be socially neglected, whereas children with CB are more likely to be socially rejected (6). Children with ADHD may have low social impact; their isolation and/or intrusive approaches to other children can be mistaken for unawareness of social rules, as in ASD (22). At the neuropsychological level, both ADHD and ASD present difficulties in executive function (EF), even if EF deficits might differ between the two disorders. Inhibitory dysfunction is characteristic of ADHD, while in ASD central coherence and theory of mind deficits play a major role (23–25). Studies investigating the potential influence of ADHD on ASD have reported contrasting results regarding its influence on autistic symptoms severity (26, 27). Furthermore, several studies have noted that children suffering from both disorders generally present a more severe psychiatric burden. It was observed that children with both ASD and ADHD were more likely to have conduct problems or anxiety or depression symptoms than children with ASD only (28–30). Neurophysiological investigation using event-related potentials (ERPs) on these conditions detected a dissociation between disorders on the basis of distinct stages of emotion processing (31, 32). Further investigations demonstrated that children with ASD and ASD + ADHD showed reduced theta and alpha power on quantitative electroencephalographic studies compared to children without ASD e.g. controls and ADHD (33).

In research on interventions, children with ASD+ADHD undergoing social skills training failed to improve, as opposed to children with ASD only and children with ASD and anxiety disorder (34).

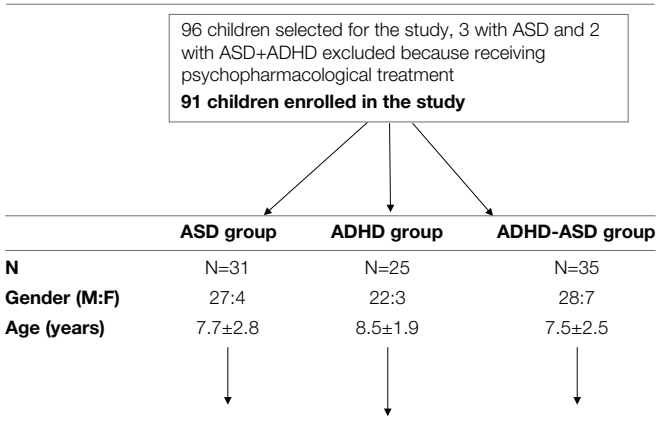
The main aim of this study was to identify and evaluate the adaptive functions of children and adolescents with a diagnosis of ASD+ADHD, in comparison with adaptive functioning in subjects with a diagnosis of ASD or ADHD.

PARTICIPANTS

This cross-sectional study included 91 children (77 boys, 14 girls), ranging from 3.1 to 13.4 years (mean age: 8.3 ± 7.2), who met the criteria for a diagnosis of ASD and/or ADHD (**Table 1**). The children were consecutively recruited between January 2016 and December 2017 among those referred to our outpatient clinic for assessment and diagnosis of developmental difficulties, and were enrolled in the study according to the clinical features that were ascertained during evaluation and that pointed to the mentioned diagnostic domains.

All children underwent a full clinical evaluation, including medical history, clinical observations, and assessment. Diagnosis of ASD was based on DSM-5 criteria. Impairments in intentional communication, eye contact engagement, shared attention behavior, use of gestures, and restrictive and repetitive behaviors were assessed and detailed. Diagnoses were also confirmed by using the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2) (35).

TABLE 1 | Flow chart of the protocol of the study.



ADOS-2 for ASD diagnosis in n= 31+35; CPRS-R to quantify ADHD n= 25+35; WISC-IV for subjects > 6 years or the Griffiths Mental Developmental Scales – Extended Revised for subjects < 6 years; the Vineland Adaptive Behaviour Scale – Second Edition (VABS-II) to rate adaptive functioning

Diagnosis of ADHD was based on DSM-5 criteria. Overall, clinical criteria evaluation contributed to defining the diagnostic classification. In addition to the ADHD features of hyperactivity, impulsivity, and/or inattentive problems, relevant social deficits – if present – were also thoroughly described. We also used the Conners' Parent Rating Scale – Revised: Long Version to confirm the ADHD diagnoses n = 25 (CPRS-R) (Conners 2001).

Exclusion criteria included (1) genetic and neurodevelopmental disorders of known etiology (such as tuberous Sclerosis, fragile X syndrome, and chromosomal abnormalities), (2) serious chronic diseases, (3) significant sensory or motor impairment, (4) presence of seizures, and (5) use of psychoactive drugs as possibly interfering with the clinical profileAccording to the diagnostic criteria, 31 children have been identified as ASD only (ASD group), 25 as ADHD only (ADHD group), and 35 as ADHD and ASD (ASD+ADHD group). Characteristics of the groups are described in **Table 2**.

After complete description of the study to parents and/or guardians, written informed consent for data acquisition and clinical examination was obtained according to procedures approved by the local ethics committee. The research was conducted according to the rules of the Helsinki Declaration regarding good clinical practice and ethics.

The study was approved by our local ethics committee.

MEASURES

All children were examined by our research team. The neuropsychological evaluation involving cognitive and adaptive assessment was conducted by means of a diagnostic protocol in order to identify the main clinical and developmental features and to depict a comprehensive profile of the children enrolled in the study. The protocol included the administration of (1) the ADOS-2 for measuring the severity of autistic symptoms (35) to children with ASD symptoms n = 31 + 35; (2) the CPRS-R to quantify the severity of ADHD symptoms (Conners 2001); (3) the Wechsler Intelligence Scale – Fourth Edition (WISC-IV) (36) for subjects >6 years or the Griffiths Mental Developmental Scales – Extended Revised (GMDS-ER; Griffiths) for subjects < 6 years to evaluate intellectual functioning; (4) the Vineland Adaptive Behaviour Scale – Second Edition (VABS-II) (37) to rate adaptive functioning.

TABLE 2 | Demographic and clinical characteristics of the study groups.

	ASD group	ADHD group	ADHD-ASD group	p
N	31	25	35	
Gender (M:F)	27:4	22:3	28:7	0.625
Age (years)	7.7 ± 2.8	8.5 ± 1.9	7.5 ± 2.5	0.300
IQ	81.4 ± 18.7	103.3 ± 17.0	76.5 ± 20.6	<0.001
VABS-II				
Socialization	71.5 ± 11.2	88.4 ± 7.5	68.6 ± 13.0	<0.001
Communicativon	75.3 ± 11.8	87.3 ± 8.7	71.0 ± 10.0	<0.001
Daily living skills	73.6 ± 8.4	89.4 ± 12.8	70.9 ± 13.6	<0.001
Motor skills	84.5 ± 11.7	95.3 ± 12.1	80.7 ± 14.4	<0.001
ABC	71.9 ± 8.2	86.8 ± 8.0	69.4 ± 10.6	<0.001
CPRS-R (ADHD Index)				
PI		74.3 ± 10.5	78.4 ± 10.7	0.163
PH		68.7 ± 13.2	68.2 ± 12.0	0.893
CB		73.9 ± 12.0	75.6 ± 9.6	0.631
PI : CB		5:20	11:24	0.324
ADOS-2				
ADOS value	16.5 ± 4.9		15.2 ± 4.5	0.244
CSS (comparison severity scores)	7.8 ± 1.7		7.6 ± 1.6	0.622

Quantitative variables presented as mean ± standard deviation. VABS-II, Vineland Adaptive Behaviour Scale, second edition; CPRS-R: Conners' Parent Rating Scale-Revised: Long Version; ADOS-2: Autism Diagnostic Observation Schedule- Second Edition. ABC, Adaptive Behaviour Composite; PI, Prevalent inattentive clinical presentation; PH, Predominantly Hyperactivity/Impulsivity clinical presentation; CB, Combined clinical presentation; CSS, Calibrated Severity Score. Quantitative variables presented as mean ± standard deviation.

The ADOS-2 was administered by experienced and board certified examiners to determine the severity of ASD symptoms. It is a semi-structured, standardized assessment instrument designed to obtain information about social-communication development and repetitive and restricted interests in children. This tool is considered the gold standard for ASD evaluation and is widely used in clinical practice. The ADOS-2 diagnostic algorithm yields classifications of ASD versus non-ASD children and a calibrated severity score (CSS) for the algorithm total that provides further information, including the severity of the disorder.

The CPRS-R is a tool for obtaining parental reports of childhood behavior problems that contains summary scales supporting ADHD diagnosis and quantifying ADH severity. This scale has a seven-factor model composed of the following factors: Cognitive Problems, Oppositional, Hyperactivity–Impulsivity, Anxious–Shy, Perfectionism, Social Problems, and Psychosomatic. It has good internal reliability, high test–retest reliability, and effective discriminatory power. In addition, the CPRS-R includes a corresponding factor structure with the Conners Teacher Rating Scale – Revised and comprehensive symptom coverage for ADHD and related disorders. Three types of ADHD are now recognized: predominantly inattentive (PI), predominantly hyperactive–impulsive (PH) and combined (CB).

To evaluate intellectual functioning and determine the IQ, we administered – according to the age of the child – the WISC-IV or the GMDS-ER. Both scales provide a value that represents the subject's general intellectual ability. These measures are standardized by chronological age, with a mean of 100 ± 15. In this study, we considered IQ indicators to be the Full Scale Intellectual Quotient (FSIQ) for the WISC-IV and the developmental quotient (DQ) for the Griffiths Scales.

The VABS-II is a semi-structured parent interview used to obtain parent ratings of children's adaptive functioning across three domains: Communication, Socialization, and Daily Living skills. Standard scores were obtained for each domain and combined to provide an Adaptive behaviour composite (ABC) standard score. VABS-II scores have a mean of 100 ± 15, with lower scores indicating more severe impairment.

STATISTICAL ANALYSIS

Comparisons between groups were examined, as appropriate, by means of one-way analysis of variance (ANOVA) followed by post-hoc Welch two-sample t-test and Tukey contrasts for multiple comparisons of means, as well as by means of Pearson's chi-squared test, Kruskal-Wallis rank sum test, and Wilcoxon rank sum test with continuity correction. Linear regression model with ABC as outcome variable was used to model several covariates. Variables were entered according to a procedure of forward selection. The first variable entered into the equation was the one with the largest correlation with ABC. The next variables were added according to the largest change in the R 2 statistic, until no more change occurred. The chosen model was the one with the largest R2. Goodness-of-fit statistics are shown: Multiple R 2, Adjusted R 2,

F-statistics, standard error of the estimate, and p-value. An alpha level of 0.05 was used for all statistical analyses. Results, if not otherwise specified, are given as means ± SDs. All statistical analyses were performed using the *R* Language and Environment for Statistical Computing program (http://www.R-project.org; accessed October 2018).

RESULTS

As shown in **Table 2**, mean age and gender ratio did not differ between the three groups ($F = 1.221$; $p = 0.300$ and $\chi^2 = 0.939$; $p = 0.625$). IQ was different among groups ($F = 15.140$; $p < 0.001$). The post-hoc analysis showed that IQ was significantly higher in the ADHD group, compared to the ASD ($t = 4.232$; $p < 0.001$) or to the ASD+ADHD group ($t = 5.317$; $p < 0.001$), while there was no significant difference between the ASD and the ASD+ADHD group ($t = 1.048$; $p = 548$).

In terms of parent ratings of children's adaptive functioning, measured by means of the VABS-II, we found significant differences among the three groups across all domains and combined scores: Communication ($F = 18.960$; $p < 0.001$), Socialization ($F = 25.410$; $p < 0.001$), Daily Living Skills ($F = 19.760$; $p < 0.001$), Motor ($F = 9.615$; $p < 0.001$), and ABC ($F = 29.370$; $p < 0.001$) (**Table 3**). Subsequent post-hoc analyses showed that higher mean scores always depended on ADHD either alone or combined, while there were no statistically significant differences between the groups that presented with ASD.

Considering clinical presentations in the two groups presenting ADHD features, in the ADHD-only group we observed 20 CB and 5 PI presentations; in the ASD+ADHD group, 24 CB and 11 PI presentations. The difference between the two groups was not statistically significant ($\chi^2 = 0.974$; $p = 0.324$).

In terms of ADHD symptom severity, the mean score of the Conners Index was 76.7 ± 7.2 in the ADHD group and 79.6 ± 10.9 in the ASD+ADHD group. The difference was not statistically significant ($W = 376$; $p = 0.360$). Overall, none of Conners indexes showed relevant differences between the ASD+ADHD and the ADHD-only group (**Table 2**).

ADOS-2 total scores were similar in the two groups with ASD features (ASD group: 16.5 ± 4.9; ASD+ADHD group: 15.1 ± 4.5) with no statistically significant differences between the two groups ($t = 1.177$; $p = 0.244$).

TABLE 3 | *Post-hoc* analyses for VABS-II values.

Domains	ASD vs. ADHD		ASD+ADHD vs. ADHD		ASD+ADHD vs. ASD	
	t	p	t	P	t	p
Socialization	5.663	<0.001	6.782	<0.001	1.028	=0.561
Communication	4.344	<0.001	6.061	<0.001	1.700	=0.211
Daily living skills	4.969	<0.001	5.992	<0.001	0.946	=0.612
Motor skills	3.067	<0.01	4.314	<0.001	1.165	=0.477
ABC	6.086	<0.001	7.291	<0.001	1.108	=0.512

VABS-II, Vineland Adaptive Behaviour Scale, second edition; ABC, Adaptive Behaviour Composite.

In a linear regression model, higher VABS-II ABC scores were negatively associated with age and ASD diagnosis, and positively associated with IQ. There was no significant association with gender (**Table 4**).

DISCUSSION

Research focusing on co-occurring ADHD and ASD has been directed primarily on origins and clinical characteristics and with minor effort on interventions. Children with ADHD and ASD experience more difficulty in daily situations as compared to those with only one disorder. Co-occurrence of ADHD and ASD is associated with a lower quality of life and poorer adaptive functioning as compared to children with ASD only (38). In addition, co-occurring ADHD and ASD may be less responsive to standard treatments for either disorder than individuals with only one form of the disorders. At present there are few reports regarding developmental trajectories when ADHD and ASD co-occur and it may be important to examine whether early ASD treatment can influence the stability of ADHD symptoms and vice versa (22).

As to the adaptive skills, in the current study a worse general profile was ascertained in ASD and in ASD+ADHD groups with respect to the ADHD-only group in all VABS-II domains (Communication, Daily Living Skills, and Socialization) and ABC. Slightly lower scores not statistically significant were found in the combined group with ASD+ADHD in comparison to ASD group detected with respect to all the VABS-II domains: Communication, Daily Living Skills, and Socialization (37).

Other studies compared adaptive profiles in the three groups of children with ASD, ADHD, and ASD+ADHD and demonstrated the following findings (19, 20). In the study of Ashwood et al. (19), all children had a normal intellectual level representing a selected population and the combined group ASD+ADHD had the worst performance in adaptive evaluation with lowest scores among the three groups enrolled in this research. Further, it raised the question of whether intellectual abilities and social cognition are partly independent and act in different skill domains in ASD profiles. All the children with ASD+ADHD had a cognitive level in the normal range nonetheless demonstrated relevant adaptive difficulties supporting the hypothesis of distinct domains of neurodevelopment within the single child.

Also in the study by Turygin et al. (20), adaptive scores were lowest in the combined group, ASD+ADHD, and children with ASD resulted to be the more impaired among the three groups of study. However, this difference was not found to be significant between the combined and ASD group similar to the findings of the current study. Toddlers with co-occurring ASD+ADHD may represent a group that demonstrates greater early deficits in functioning compared to those with ASD that deserve further studies and follow-up monitoring. As to the cognitive level in the current study a higher range of intellectual abilities was found for the ADHD-only group, the other two groups presented IQ scores between the mean and borderline range of value (ASD: IQ about 81 and ASD+ADHD: IQ about 76). The wider range of IQ level in this sample represents more reliably the ASD population, in which differences in IQ scores are usually observed. Importantly it has been reported that children with ASD+ADHD with lower cognitive level have more severe social impairment, and greater delays in adaptive functioning than children with ASD only (39). In conclusion children with ASD+ADHD demonstrated a more severe adaptive impairment in comparison to children with ASD only even if not reaching statistic significance.

As an additional remark and a future direction in the evaluation of adaptive skills in ASD it is important to note that minimal clinically important differences (MCIDs) on VABS-II scores have not been rigorously established in ASD. To fill that gap a large multisite study has been carried out and lower VABS-II standardized score MCID estimates were observed for younger and more cognitively impaired children. This should be taken in account when evaluating adaptive functions in ASD concomitant to intellectual disability alone or combined with ADHD (40–42,).

There are some limitations in the current study that should be mentioned. Adaptive functions have been detailed in three different clinical groups, but the lack of a typically developing control group is the first limitation to be noted. A second limitation pertains to the relatively small sample size that may have influenced the between-group differences reported as to adaptive and cognitive ability and to the effect of IQ on adaptive function that may be underestimated. A higher number of participants would likely reflect more accurately these differences between the groups. Lastly this is a cross sectional evaluation of the three clinical groups and longitudinal studies of adaptive functioning in ASD+ADHD are strongly needed in order to increase the understanding of the development, change, and stability of symptoms over time and to identify protective and worsening factors of these conditions.

Children with ASD+ADHD had a greater treatment need which could imply additional treatments for both school and community services (26, 43, 44).

When symptoms are not managed, they may lead to more severe psychiatric comorbidity as well as poorer school, family, and cognitive outcomes among this population

TABLE 4 | Linear Regression Model. Outcome variable: Adaptive Behaviour Composite (ABC) of the VABS-II.

	Beta	SE	t	p
(Intercept)	77.567	5.952	13.032	<0.001
Age	–0.871	0.373	–2.336	<0.05
ASD diagnosis	–12.387	2.533	–4.890	<0.001
ASD+ADHD diagnosis	–14.218	2.592	–5.484	<0.001
IQ	0.164	0.048	3.453	<0.001
Gender	0.487	2.723	0.179	=0.858

Overall model: p < 0.001, Multiple R2: 0.505; Adjusted R2: 0.482. F-statistics: 21.7; Residual standard error: 8.46 on 85 degrees of freedom (1 observation missing). SE, Standard Error; VABS-II, Vineland Adaptive Behaviour Scale, second edition.

and so specific attention is warranted to readily provide appropriate intervention.

ETHICS STATEMENT

The study is carried out in accordance with the recommendations of Good Clinical Practice (GCP) guidelines, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki and its later supplements and local legal requirements. The IRB is the Institutional Review Board, at the University Hospital of Siena approved the study procedure and all study documents.

AUTHOR CONTRIBUTIONS

VS contributed to the design of the study, recruit and made multiple assessments of the children. FB, MS and AP contributed to the evaluation and recruitment of the children. LG participated in the design and the statistical analysis of the study. RC contributed in writing of the article and revised the methods of recruitment and selections of the study groups.

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Review

Advances in Understanding the Relationship between Sleep and Attention Deficit-Hyperactivity Disorder (ADHD)

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Abstract: Starting from the consolidated relationship between sleep and cognition, we reviewed the available literature on the association between Attention Deficit-Hyperactivity Disorder (ADHD) and sleep. This review analyzes the macrostructural and microstructural sleep features, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA). We included the polysomnographic studies published in the last 15 years. The results of macrostructural parameters are mixed. Almost half of the 18 selected investigations did not find differences between sleep architecture of children with ADHD and controls. Five studies observed that children with ADHD show a longer Rapid Eye Movement (REM) sleep duration than controls. Eight studies included microstructural measures. Remarkable alterations in sleep microstructure of ADHD are related to slow wave activity (SWA) and theta oscillations, respectively, during Non-REM (NREM) and REM sleep. Specifically, some studies found higher SWA in the ADHD group than controls. Similarly, higher theta activity appears to be detrimental for memory performance and inhibitory control in ADHD. These patterns could be interpreted as a maturational delay in ADHD. Also, the increased amount of these activities would be consistent with the hypothesis that the poor sleep could imply a chronic sleep deprivation in children with ADHD, which in turn could affect their cognitive functioning.

Keywords: ADHD; sleep; PSG; macrostructure; microstructure; theta; slow wave activity; EEG; memory; cognition

1. Introduction

Attention Deficit-Hyperactivity disorder (ADHD) is one of the most common early childhood disorders, classified into three subtypes: predominantly inattentive, hyperactive-impulsive, and a combination of these two subtypes [1]. The prevalence of ADHD ranges from 5 to 7% and is more frequent in males [2].

Children with ADHD show heterogeneous symptoms, e.g., aggressiveness, inappropriate social conduct, and impaired academic functioning, due to a compromised inhibitory control [3,4]. It is well known that the neurobiological mechanisms underlying ADHD pathophysiology include some neurochemical agents, especially dopamine and noradrenaline [5].

A high percentage of subjects with ADHD (59–87%) reports psychiatric comorbidities, such as learning disabilities (15–25%), language disorders (30–35%), mood and emotional disorders (15–25%), motor coordination deficits (60%), and conduct disorders (20%) [5,6].

Sleep alterations are also significantly observed in 25–55% of children with ADHD compared to 7% among healthy individuals [7]. Subjective parent reports referred to sleep initiation problems

or sleep fragmentation, with several night awakenings of their children [7]. Objective measures also revealed that Sleep-Disordered Breathing (SDB), Periodic Leg Movements during Sleep (PLMS) and Restless Leg Syndrome are strongly related to ADHD [8]. Excessive daytime sleepiness in children with ADHD represents a direct consequence of these sleep disturbances [9]. Besides, subjects with ADHD frequently suffer from the circadian-rhythm disorder and idiopathic sleep-onset insomnia [10]. These disturbances may be due to a delayed endogenous circadian pacemaker, as demonstrated by the alterations observed in the nocturnal pattern of melatonin secretion [10]. Difficulties in sleep offset are also reported in children with ADHD [11].

Starting from these observations, it can be hypothesized that sleep architecture (i.e., macrostructure) of children with ADHD shows significant changes compared to healthy individuals, especially concerning sleep onset latency, rate of awakenings, wakefulness after sleep onset, and other measures of sleep fragmentation. However, it is still unclear whether the alterations in sleep architecture in ADHD are only related to full-blown comorbid sleep disorders or whether the abnormalities in polysomnographic (PSG) measures are actually markers/symptoms of ADHD.

Interestingly, an overlap has been observed between neurocognitive deficits characterizing children with ADHD and those affecting healthy people with a poor sleep quality [12]. Indeed, sleep problems in healthy individuals impact on inhibitory control and enhance their impulsivity [13]. On the one hand, sleep alterations may induce ADHD-like manifestations, and, on the other hand, altered sleep architecture could exacerbate ADHD symptoms [7].

In the last decades, several findings underlined that sleep features are associated with cognitive functioning [14]. In this view, early studies showed that poor sleep quality associated with SDB is related to low performance on the Verbal intelligence quotient (IQ) in subjects with ADHD [15]. Also, a reduced amount of Rapid Eye Movement (REM) sleep has been linked with impaired language, visuo-spatial, attention/executive functioning, and memory processes in children with ADHD [16], while an increased REM percentage is negatively correlated with IQ [17].

Beyond this, it is worth noting that some electroencephalographic (EEG) oscillations during sleep (e.g., sleep spindles, slow waves, and theta activity) seem to play a crucial role in neural plasticity and learning processes [18,19]. Specifically, several findings revealed that both slow wave activity (SWA) and theta oscillations show quantitative and topographical changes during development, which parallel the brain maturation [14]. Considering that some neuroanatomical studies highlighted a delay in cortical maturation of children with ADHD [20], we suggest that a better understanding of the relationship between sleep alterations and this neurodevelopmental disorder could be helpful to design protocols aimed to enhance sleep quality and to manipulate sleep EEG oscillations to ameliorate ADHD symptoms.

In light of the above, we reviewed the available literature of the last 15 years on the association between ADHD and sleep, focusing on the macrostructural and microstructural features of sleep. We aim to provide a comprehensive background that underlines the strengths and limitations of the current knowledge, to track future researches and perspectives.

2. Materials and Methods

2.1. Search Strategy

This systematic review was performed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [21]. A search was conducted on two electronic databases: PubMed and Scopus, entering the following search terms in English: "ADHD" OR "attention deficit" OR "hyperactivity" AND "sleep" AND "polysomnography". Also, the following search string was considered: "ADHD" OR "attention deficit" OR "hyperactivity" AND "sleep" AND "EEG". Search fields were title, abstract and keywords. Only quantitative research/original articles published in the last 15 years were further analyzed. Eligible articles were selected through a multi-step procedure (title reading, abstract and full-text assessment) by 2 independent expert researchers. Then, the literature

search was completed with a manual search, reviewing the references included in the selected articles and the citations that they had received.

2.2. Selection Criteria

Articles available from 2004 until May 2019 were selected if they met the following criteria: (1) Inclusion of children with ADHD, according to the criteria of the Diagnostic and Statistical Manual of mental disorders (DSM) or any other diagnostic manual; (2) absence of intellectual disabilities (IQ < 70); (3) comparative studies in which the control group was composed of children without ADHD; (4) focus on PSG recordings of a night of sleep with macrostructural (and/or microstructural) measures were reported, assessing differences in sleep between children with and without ADHD; (5) peer-reviewed articles (not just abstracts or conference papers). Reviews, meta-analyses and papers in non-English languages were excluded.

A first selection was performed by filtering duplicates and, subsequently, a title and abstract screening was conducted. All potentially relevant articles were then independently reviewed and assessed for their eligibility. Studies which included ADHD samples, but whose primary focus was on other disturbances, were also excluded. We considered only studies that fulfilled the inclusion criteria previously described and addressed the question on the relation between PSG/EEG measures and ADHD and/or reported microstructural sleep measures. Any disagreement between the reviewers was resolved through a consensus session with a third reviewer. Figure 1 shows the flowchart of the article selection.

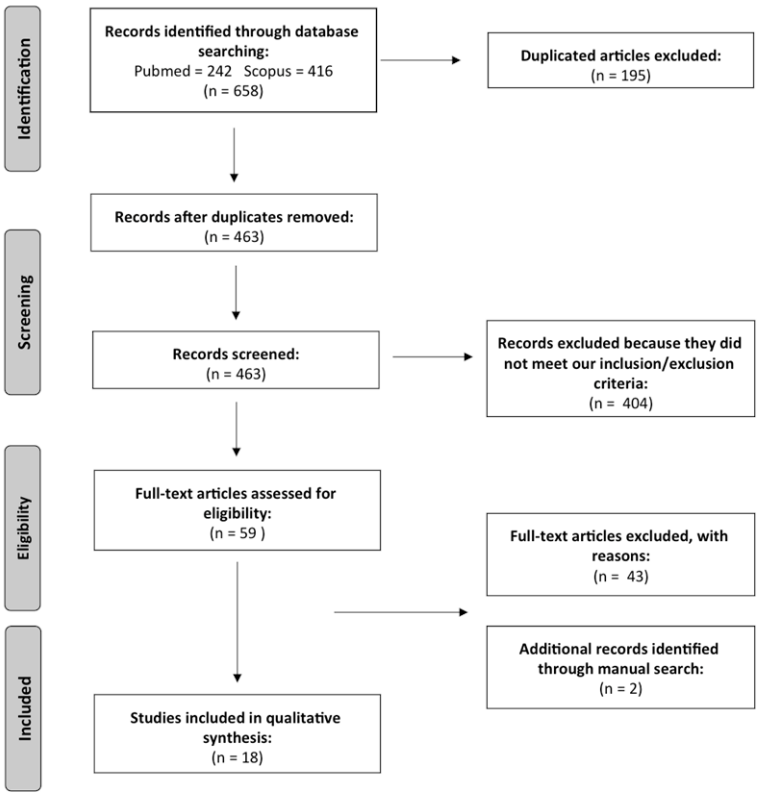

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) workflow. Eighteen studies were considered for this systematic review.

3. Results

At the end of the multi-step process, 18 articles [22–39] were included in the systematic-review. The results were grouped in the following section, on the basis of the sleep measures obtained in each study:

(a) Macrostructural pattern (18 articles) [22–39];
(b) Microstructural pattern (8 articles) [23,26,30,31,33,34,36,37].

Table 1 summarizes the characteristics and main results of the reviewed studies. Table S1 (Supplementary Materials) reports the list of abbreviations and their definitions.

Only data on PSG recordings during nighttime were considered (e.g., excluded Multiple Sleep Latency Test, MSLT or daytime naps). In the case of longitudinal protocols, only the first PSG assessment was taken into account.

Table 1. Summary of characteristics of included studies.

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Kirov et al. [22]	17 ADHD (all M; 11.2 ± 2.0) vs. 17 HC (all M; 11.2 ± 2.3)	All combined	Full-scale IQ ≥ 80 ADHD: 12 with dyslexia; 3 with conduct disorder; 1 with panic disorder; 1 with nocturnal enuresis	11 ADHD stopped medications at least 3 days previous the experimental session	Laboratory recording with adaptation night; 1 EEG channel (C3)	Macrostructure	Children with ADHD had higher TBT, longer SPT, longer REM sleep duration and more sleep cycles than HC.
Miano et al. [23]	20 ADHD (18 M; 9.3 range: 6–13) vs. 20 HC (18 M; 9.3 range: 6–13)	2 inattentive 18 combined	Full-scale IQ ≥ 70 ADHD: 10 with learning disabilities; 4 with mild neurological signs; 2 with language disorder; 4 with psychiatric comorbidities	None	Laboratory recording with adaptation night; EEG channels not specified (at least 8 electrodes)	Macrostructure CAP parameters	Children with ADHD had lower TST, SPT, TBT and higher rate of SS than HC. Children with ADHD had lower total CAP rates and lower CAP rates during stage 2 than HC. Children with ADHD had lower CAP sequences and a reduced total A1 index in stages 1 and 2.
Gruber et al. [24]	15 ADHD (10 M; 8.45 ± 1.39) vs. 23 HC (13 M; 8.58 ± 1.27)	1 hyperactive 2 inattentive 12 combined	Full-scale IQ ≥ 80 ADHD: 2 with PLMD HC: 2 with PLMD	ADHD stopped medications at least 7 days previous the experimental session	Home recording; 8 EEG channels (F3, F4, C3, C4, P3, P4, O1, O2)	Macrostructure	Children with ADHD had lower TST, lower percentage of REM sleep than HC.
Prihodova et al. [25]	31 ADHD (26 M; 9.3 ± 1.7) vs. 26 HC (22 M; 9.2 ± 1.5)	4 inattentive 27 combined	Full-scale IQ ≥ 80 None	None	Laboratory recording with adaptation night; 4 EEG channels (F4–C4, C4–P4, F3–C3, C3–P3, C4–A1, C3–A2)	Macrostructure	No significant differences were found on sleep parameters between groups.

Table 1. *Cont.*

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Prehn-Kristensen et al. [26]	16 ADHD (not provided, 10.6 ± 0.88) vs. 16 HC (not provided, 11.00 ± 0.99)	8 inattentive 8 combined	full-scale IQ ≥ 85 ADHD: 4 with ODD.	12 ADHD stopped medications 2 days previous the experimental session	Laboratory recording with adaptation night; 2 EEG channels (C3, C4)	Macrostructure	No significant differences were found on sleep parameters between groups. A sleep-associated gain in reaction times of procedural memory task was positively correlated with the amount of stage 4 and REM sleep density in ADHD group.
Prehn-Kristensen et al. [27]	12 ADHD (all M; 12.22 ± 0.52) vs. 2 HC (all M; 12.64 ± 0.24)	Not provided	full-scale IQ ≥ 85 ADHD: 3 with ODD	5 ADHD stopped medications 2 days previous the experimental session	Laboratory recording with adaptation night; 2 EEG channels (C3, C4)	Macrostructure EEG power analysis at C3 (SWA; delta; theta; alpha; sigma, during REM and NREM sleep) Visual spindle detection in Stage 2	Children with ADHD had longer REM sleep duration and SOL than HC Children with. ADHD had shorter SWS latency and lower SE than HC. No significant differences on EEG power and spindle density were found between groups. Children with ADHD showed reduced sleep-associated consolidation of declarative memory. HC showed a correlation between sleep-associated recognition enhancement in declarative memory task (IAPS) and <1 Hz power during the first sleep cycle. NREM sleep duration in HC was positively correlated to sleep-related memory consolidation.
Gruber et al. [28]	26 ADHD (17 M; 8.61 ± 1.27) vs. 49 HC (30 M; 8.61 ± 1.27)	1 hyperactive 8 inattentive 17 combined	full-scale IQ ≥ 80 ADHD: 8 with ODD; 2 with conduct disorder	ADHD stopped medications 2 days previous the experimental session	Home recordings; 8 EEG channels (F3, F4, C3, C4, P3, P4, O1, O2)	Macrostructure	No significant differences were found on sleep parameters between groups.

Table 1. *Cont.*

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Kirov et al. [29]	20 ADHD (19 M; 11.24 ± 2.31) vs. 19 HC (17 M; 11.26 ± 2.49)	All combined	full-scale IQ ≥ 80 None	11 ADHD stopped medications at least 7 days previous the experimental session	Laboratory recordings with adaptation night; 2 EEG channels (C3, C4)	Macrostructure	Children with ADHD had higher TBT, TST, shorter REM sleep latency and longer REM sleep duration than HC.
Prihodova et al. [30]	14 ADHD (12 M; 9.6 ± 1.6) vs. 12 HC (8 M; 9.0 ± 1.6)	2 inattentive 12 combined	IQ not specified, exclusion of mental retardation None	None	Laboratory recording with adaptation night; 4 bipolar EEG channels (F4-C4, C4-P4, F3-C3, C3-P3, C4-A1, C3-A2)	Macrostructure CAP analysis	No significant differences were found on sleep parameters between groups.
Prehn-Kristensen et al. [31]	16 ADHD (all M; 10.6 ± 0.95) vs. 16 HC (all M; 11.1 ± 0.95) vs. 20 HC adults (all M; 24.7 ± 2.8)	8 inattentive 8 combined	full-scale IQ ≥ 85 ADHD: 4 with ODD.	12 ADHD stopped medications 2 days previous the experimental session.	Laboratory recordings with adaptation night; 4 EEG channels (F3, F4, C3, C4)	Macrostructure EEG power analysis at F4. (SWA, delta and sigma during stage 2; theta during REM sleep)	No significant differences were found on sleep parameters between children groups. After merged all healthy subjects (children and adults), a correlation between emotional memory (investigated by IAPS) and slow/delta during SWS was found. ADHD showed negative correlation between performance and <1 Hz power during SWS. The same correlation was found with theta activity during REM sleep.

Table 1. *Cont.*

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Wiebe et al. [32]	20 ADHD (13 M; 9.2 ± 1.6) vs. 46 HC (28 M; 8.8 ± 1.1)	3 hyperactive 13 inattentive 4 combined	mean IQ ADHD =100.4 mean IQ HC = 104.0 None	ADHD stopped medications at least 2 days previous the experimental session.	Home recordings; 8 EEG channels (F3, F4, C3, C4, P3, P4, O1, O2)	Macrostructure	No significant differences were found on sleep parameters between groups.
Ringli et al. [33]	9 ADHD (8 M; 11.9 range: 9.7–13.4) vs. 9 HC (8 M; 11.6 range: 9.6–14.2)	All combined	mean IQ 120±15 None	2 ADHD were treated at the day of experimental session. The second dose of medications was not given at the day of measurement.	Laboratory recording; High-density EEG (128 channels)	Macrostructure EEG power analysis in all cortical channels. (SWA during NREM sleep)	Children with ADHD had lower duration of stage 1 than HC. Children with ADHD showed higher SWA power over central than HC.
Akinci et al. [34]	28 ADHD (20 M; 10 range: 8–12) vs. 15 HC (9 M; 10 range: 9–13)	7 inattentive 21 hyperactive or combined	full-scale IQ > 70. None	None	Laboratory recordings with adaptation nigh; 10 EEG channels	Macrostructure CAP analysis	Children with ADHD had higher REM sleep duration than HC. Children with ADHD had lower total CAP rates than HC. Children with ADHD had a reduced total A1 index in stage 2.
Virring et al. [35]	76 ADHD (74% M; 9.6 ± 1.8) vs. 25 HC (68% M; 9.4 ± 1.5).	5 hyperactive 14 inattentive 57 combined	full-scale IQ > 70 ADHD: 6 with autism, 9 with internalizing comorbidity, 20 with externalizing comorbidity; 7 with tic disorder	None	Home recording; 6 EEG channels (F4, C4, O2, F3, C3, O1)	Macrostructure	Children with ADHD had higher numbers of sleep cycles, lower TST, lower stage 1 and 3 and longer REM sleep duration than HC. When children with comorbidity were excluded from the analyses, ADHD group showed only longer SOL than HC.

Table 1. *Cont.*

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Saletin et al. [36]	7 ADHD (5 M; 11.9 ± 0.9) vs. 14 HC (10 M; 11.7 ± 0.9)	Not provided	mean IQ 110.3 ± 14.1. None	ADHD stopped medications 2 days previous the experimental session.	Laboratory recordings with adaptation night; 4 EEG channels (C3, C4, O1, O2)	Macrostructure EEG power analysis at C3, C4 (slow and fast sigma; SWA during Stage 2)	Children with ADHD had lower TBT than HC. Children with ADHD showed reduced sigma power (spindle-related) than HC. Children with ADHD showed lower MST before sleep than HC, but no overnight gain was observed. MST precision was positively associated with slow spindle activity for the children with ADHD.
Cremone et al. [37]	18 ADHD (13 M; 6.70 ± 1.07) vs. 15 HC (11 M; 6.73 ± 0.71)	All hyperactive	IQ not specified, exclusion of mental retardation None	ADHD stopped medications 2 days previous the experimental session	Laboratory recordings; 24 EEG channels	Macrostructure EEG power analysis in all cortical channels. (delta during stage 2 and SWS; theta, during REM and NREM sleep)	No significant differences were found on sleep parameters between groups. HC showed greater accuracy at go/noGo task in the morning vs. baseline after sleep. The performance was significantly associated with REM theta activity at F4. Children with ADHD showed greater theta activity in REM sleep than controls, however they revealed no changes in their performance after sleep.

Table 1. *Cont.*

Authors.	Sample Size (Sex; Mean Age)	ADHD Subtypes	IQ and Comorbidities	Medications	PSG Recording (Setting; EEG Channels)	Sleep Measures	Main Results
Wiesener et al. [38]	17 ADHD (All M; 11.3 ± 0.4) vs. 17 HC (all M; 11.1 ± 0.2)	2 hyperactive 15 combined	full-scale IQ ≥ 85 ADHD: 14 with ODD, 3 with conduct disorder; 6 with learning disabilities.	13 ADHD stopped medications 2 days previous the experimental session	Laboratory recording with adaptation night; 2 EEG channels (C3, C4)	Macrostructure	No significant differences were found on sleep parameters between groups. Children with ADHD did not show sleep-dependent consolidation of rewarded behavior. Their consolidation of rewarded behavior did not correlate with sleep. Instead, HC consolidated rewarded behavior better during a night of sleep than during a day awake.
Chin et al. [39]	71 ADHD (54 M, 8.83 ± 1.86) vs. 30 HC (15 M, 8.48 ± 2.36)	35 inattentive 36 hyperactive or combined	full-scale IQ > 70 None	ADHD had no medications in the 6 months previous the experimental session.	Laboratory recordings; 32 EEG channels	Macrostructure	Children with ADHD had lower percentage of SWS and higher apnea-hypopnea index than HC.

ADHD, attention-deficit/hyperactivity disorder; IQ, intellectual quotient; PSG, polysomnographic; EEG, electroencephalographic; M, males; HC, healthy children; TBT, total bed time; SPT, sleep period time; REM, rapid eye movement; ODD, oppositional defiant disorder; CAP, cycling alternating pattern; TST, total sleep time; SS, stage shift; SWS, slow wave sleep; SE, sleep efficiency; PLMD, periodic limb movement disorder; SWA, slow wave activity; NREM, non-rapid eye movement; SOL, sleep onset latency; IAPS, international affective picture system; MST, motor sequence task.

3.1. Macrostructural Pattern

All of the 18 selected studies [22–39] reported at least the following sleep measures: sleep onset latency (SOL); stages duration (stage 1,2,3,4 or SWS, REM sleep); total bedtime (TBT); total sleep time (TST); sleep efficiency (SE); wakefulness after sleep onset (WASO). Some investigations also reported the sleep latency of other sleep stages (REM; SWS); sleep period time (SPT) [22,23]; stage shift (SS) [23] and the number of cycles [22,35].

Eight out of 18 studies did not report any difference in sleep macrostructural measures between children with ADHD and healthy controls (HC) [25,26,29–32,37,38].

Concerning TST and TBT, mixed results were observed. On the one hand, TBT seems to be longer in children with ADHD, as compared to HC [22,29]. On the other hand, shorter TBT was described in the ADHD group [23,36].

Multiple recordings revealed that TST is lower in the ADHD than the HC group [23,24,35], while only one study reported the opposite finding [29]. Instead, a study reported longer SPT [22] and another lower SPT in the ADHD compared with the HC group [23].

Reduced SE was reported in the ADHD compared with the HC group [27] and, consistently, several measures of sleep fragmentation were observed: a higher rate of SS [23] and a higher number of sleep cycles in the ADHD groups [22,35].

Concerning REM sleep, only a study reported a lower REM sleep percentage in the ADHD group [24], while others observed a higher REM sleep duration [22,27,29,34,35], as compared to the control group. Also, a shorter REM sleep latency was found in the ADHD group [29].

Some results revealed alterations of NREM sleep in ADHD, pointing to a reduction of SWS in children with ADHD [35,39]. A lower duration of stage 1 was also detected in the ADHD than in the control group [33,35].

Nine studies included an ADHD sample without comorbidities [25,29,30,32–34,36,37,39]. Virring et al. [32] reported analyses also on ADHD without comorbidities, showing only longer SOL, compared with controls. Consistently, longer SOL in children with ADHD than HC was found by Prehn.-Kristensen et al. [27].

Eleven studies were carried out with an adaptation night in a laboratory setting [22,23,25–27,29–31,34,36,38], while 4 studies used home recordings [24,28,32,35].

Interestingly, PSG parameters were studied in relation with cognitive performance in 6 studies [26,27,31,36–38]. In this respect, sleep-related gains in reaction times to procedural memory tasks were positively correlated with the percentage of stage 4 and with REM sleep density in the ADHD group [26]. The same study also found a positive correlation between the amount of NREM sleep and the sleep-associated declarative memory consolidation in HC, while no relation between macrostructural measures and performance was found in children with ADHD [27]. Wiesner et al. [38] revealed no significant correlation between the consolidation of rewarded behavior and sleep measures. The other studies administering cognitive tasks have not reported correlational analyses between the children's performance and macrostructural measures: the authors provided correlational analyses exclusively considering microstructural measures (see next paragraph) [31,36,37].

3.2. Microstructural Pattern

Eight out of 18 studies reported microstructural sleep measures [23,27,30,31,33,34,36,37].

3.2.1. NREM Sleep

Microstructural features of sleep in children with ADHD were firstly investigated by Miano et al. [23] through CAP analysis. The main result of their study was a reduction of CAP A1 phase (i.e., synchronized EEG sleep pattern with sequences of K complexes and delta bursts) during light sleep (i.e., stage 1 and stage 2 NREM), but no differences were detected in other CAP subtypes. These results were recently confirmed [34], while another investigation did not replicate them [30].

Moreover, the quantitative EEG analysis of sleep revealed some differences between children with ADHD and HC, providing information on the topographic distribution of sleep EEG activity (e.g., [33,37]) and its relation with neurobehavioral and/or cognitive domains [27,31,36,37].

Ringli et al. [33], using high-density EEG (128 channels), observed a higher SWA during stage 2 and stage 3 over the central area in the ADHD group, with a maximum placed posteriorly as compared with HC. The differences between the two groups were maintained across the entire night. Moreover, they did not find the typical decrease of SWA across consecutive sleep cycles, when analyzing the homeostatic decay in the motor area [33]. The waking EEG activity of children with ADHD and the percentage of SWA were not correlated, contrary to the expectation of the authors based on the "local sleep hypothesis" (i.e., local use-dependent view, [40]).

Other studies investigated EEG power during NREM sleep without confirming the higher amount of SWA in the ADHD group [27,31,36,37]. However, some studies assessed SWA in relation to memory processes [27,31]. Children with ADHD, as compared to HC, showed a lower overnight improvement of recognition accuracy at the picture recognition task (i.e., participants were asked to rate their emotional state while fixing a set of emotional and neutral picture; then memory were assessed by an immediate and delayed recognition session) [27]. Specifically, while this gain was positively correlated to the amount of SWA in the first sleep cycle, no correlation was observed for children with ADHD. Partly in line with these results, an investigation from the same research group found that the overnight gain at a memory task (i.e., picture recognition) was positively correlated with slow oscillations of sleep EEG (i.e., <1 Hz activity) in the healthy group including children and adults [31]. This study also showed that the compromised memory performance in the ADHD group was negatively correlated to the slow oscillations during SWS [31].

The EEG theta activity during NREM sleep was not investigated in the absence of any neurocognitive task. Prehn-Kristensen et al. [27] did not find any significant difference between children with ADHD and HC in this frequency band, and no correlation with memory performance was significant [27]. More recently, Cremone et al. [37] observed that the theta activity in NREM sleep did not differ between the ADHD and the control group. In both samples, the inhibitory control was tested and no correlation was observed between theta activity and the overnight gain at the Go/noGo task [37].

Both sigma and theta activity during NREM sleep were examined in relation to motor learning with the Motor Sequence Task (MST) [36] The theta power in stage 2 was mildly higher in children with ADHD than HC, but no correlation was found with the motor task. Concerning the sigma spindle-related activity, precision at the motor task was positively correlated with slow-frequency sigma power in the ADHD group, but no correlation with the sleep-related gain was observed. It is worth noting that performance of the ADHD group did not differ from that of HC. However, the slow and fast sigma activity during stage 2 was reduced in children with ADHD compared to controls [36].

When sigma power [31] and spindle density [27] were assessed in children engaged in the episodic/emotional memory task, no differences were found between the ADHD and control group. In addition, the sigma/spindle activity and overnight gain were not correlated [27,31].

Concerning alpha EEG activity, no difference was found between children with ADHD and HC when examined in association with declarative/emotional memory [27].

3.2.2. REM Sleep

As mentioned for NREM sleep, theta activity was assessed only in protocols involving specific learning/memory tasks [27,31,37]. On the one hand, the theta activity did not show correlation with the gain at the Picture Recognition Task in children with ADHD and HC [27], and no differences were found in the theta power between children with ADHD and children with typical development [27,31]. On the other hand, the memory performance in the ADHD group was negatively correlated to the theta activity, similarly to what has been observed for the amount of SWA [31]. Healthy subjects including

children and adults, differently from children with ADHD, revealed a positive correlation between the overnight gain on a memory task and theta activity [27].

Finally, theta power was examined in relation to inhibitory control as measured by a Go/noGo task, tested before and after sleep [37]. This study reported that children with ADHD had a higher theta power during REM sleep than HC. Moreover, HC showed a greater accuracy at the inhibitory control task after sleep (vs. performance before sleep), and this improvement was related to theta power. Conversely, children with ADHD did not report any sleep-related gain [37].

No remarkable finding on the alpha activity was reported [27].

4. Discussion

We reviewed for the first time the studies concerning the relation between macrostructural and/or microstructural features of sleep and ADHD, considering the investigations of the last 15 years.

4.1. Macrostructural Pattern

The results concerning the macrostructural parameters are quite conflicting, and drawing a coherent framework is challenging. Almost half of the selected studies did not find differences in the sleep architecture of children with ADHD, compared to those with typical development [25,26,28,30–32,37,38].

The investigations revealing significant differences between the ADHD and HC groups demonstrated that the clinical samplea are characterized by poorer sleep than controls. Indeed, the longer SOL [27,35], the shorter TST [23,24,35], along with the reduced SE [27] and the indices of faster transition of stages/cycles (e.g., a higher rate of SS and a greater number of sleep cycles) [22,23,35] reflect -to some extent- the sleep dysregulation in ADHD. On the one hand, the assumption that children with ADHD have an altered sleep architecture is consistent with the subjective parent reports, mentioning a delayed sleep onset or a sleep fragmentation with several night awakenings [7]. On the other hand, the sleep difficulties reported by parents appear to be significantly higher as compared to objective measures [8,39]. The gap between subjective and objective measures may be ascribed to other factors that cannot be revealed by the PSG recordings. The subjective reports of increased SOL—confirmed only by some investigations using objective measures (e.g., [27,35])—may be explained by "behavioral" sleep problems occurring *before* bedtime [7]. In this regard, the bedtime resistance could depend on multiple factors: (a) inadequate parenting; (b) Inadequate pre-sleep bed routines and/or sleep environment; (c) pharmacotherapy side-effects. This disturbance in ADHD children is often interpreted as oppositional behavior, a significant source of distress for parents [41]. In light of the above, it is fair to assume that subjective reports could overestimate sleep problems in ADHD, reflecting parental concerns.

NREM sleep architecture did not show specific and consistent differences between children with ADHD and HC [22–26,28–30,32,34,36–38]. We have to underline that a lower SWS has been found in an ADHD sample characterized by a higher rate of comorbidities [35] or when a higher apnea-hypopnea index was detected [39]. In this respect, a strong relationship between SDB and ADHD behavior was found (e.g., [42]), likely inducing the disruption of sleep homeostasis and less deep sleep [43]. Moreover, as previously mentioned, the exclusion of subjects with externalizing and internalizing problems from the analysis abolished all differences in NREM sleep [35].

Although no other differences in SWS were found, it should be underlined that both stage 4 amount and REM sleep density were correlated with the improvement in motor skills performance after sleep in children with ADHD, as assessed by Prehn-Kristensen et al. [26]. This study suggested a possible beneficial role of sleep on tasks measuring procedural memory in ADHD, that –instead- showed compromised performance during the waking state [26].

REM sleep abnormalities seem to be widespread among children with ADHD, consistently with previous meta-analysis [44]. REM sleep alterations could be related to the dysfunctional reward learning, one of the core deficits of ADHD, due to the dopamine hypofunction [45].

Specifically, several findings highlighted that REM sleep duration is longer in children with ADHD compared to controls [22,27,29,34,35], and only Gruber et al. [24] found a reduced amount of REM sleep in ADHD. It is worth noting that this latter study included patients with PLMS that may induce REM sleep instability, contributing to its shorter duration [46].

Interestingly, the higher REM sleep percentage in the ADHD group was found along with a higher number of sleep cycles in two studies [22,35]. As already suggested, the increased number of sleep cycles may result in a faster transition to REM sleep, contributing to the increased REM sleep amount [22]. Once again, the presence of comorbidities could have affected these results.

4.2. Microstructural Pattern

Concerning the eight studies reporting sleep microstructural features in the ADHD group, the results are not homogenous [23,27,30,31,33,34,36,37].

Findings on spindle activity are still scarce [27,31,36] and very difficult to interpret. In particular, some methodological differences in the spindle analysis should be taken into account: (a) Saletin et al. [36] did not provide a specific spindle detection, analyzing the whole sigma band; (b) some protocols [27,31,36] did not include parietal derivations, where the spindles typically show their maximum [47].

The most relevant alterations in sleep microstructure of ADHD are related to SWA and theta activity during NREM and REM sleep, respectively.

Firstly, starting from the perspective that SWA has an age-dependent shift along the postero-anterior axis from 2 years of age to adolescence [48,49], some findings point to an alteration of SWA in children with ADHD [33]. Also, during a typical development the distribution of SWA mirrors the cortical maturation changes, characterized by an increment in the first years of life with a peak in puberty and a decrease during adolescence [48,49]. In this vein, the higher SWA over the central region in ADHD—observed by Ringli et al. [33]—may represent a sign of developmental delay. The existence of a maturational delay in ADHD has also been proposed on the basis of the improvement of ADHD symptoms during growth (e.g., [20,50]). Consistently, neuroimaging studies showed that the onset of grey matter maturation in ADHD is delayed by around 3 years compared to HC, and the remission of ADHD symptoms appears associated with cortical normalization [50]. However, other investigations did not confirm this finding [27,31,36,37], likely because of the different age brackets of the included sample [34] and the lower number of EEG channels considered [27,31]. Moreover, it should be emphasized that the EEG measures in most of the studies have been recorded in combination with specific cognitive tasks [27,31,36,37], that may have induced changes in sleep EEG oscillations [14]. When the memory domain was assessed, the expected relation between SWA and performance was not observed in the ADHD group. It could be hypothesized that impairment in the sleep-dependent memory processes is due to compromised functioning over the frontal region, where the slow oscillations originate [51].

Since CAP A1 subtypes are involved in the buildup of NREM deep sleep, the finding of a reduced A1 rate during light sleep in children with ADHD [22,31] is partially not coherent with the higher SWA revealed by Ringli et al. [33]. It should be mentioned that the higher slow/delta activity in the ADHD group could represent a microstructural index of chronic partial sleep deprivation due to an arousal dysregulation in this neurodevelopmental disorder [23,34]. However, we point to that the CAP analysis does not provide direct information about the specific CAP components (e.g., delta bursts and K-complexes for A1). Hence, CAP A1 should be interpreted only cautiously in terms of high EEG synchronization, which is conventionally measured by the quantitative EEG analysis.

Concerning REM sleep microstructural features, we highlighted that studies were focused only on the theta activity [27,31,37]. Along with SWA, the theta oscillations also mirror changes in cortical plasticity and brain maturation [14,49]. Specifically, the theta activity in HC declines earlier during development than SWA, and it appears to be independent from the sleep stage [3,27]. In this view, the findings by Cremone et al. [37] on the higher theta activity in an ADHD sample, characterized by a

lower mean age (6.7 vs. 11.9), could represent a sign of maturational delay, as already suggested for SWA [33].

Moreover, the abnormal theta functioning in children with ADHD is related to a bad cognitive performance [31,37]. A higher theta activity is associated with an impaired inhibitory control in ADHD [37]. Similarly, concerning the memory consolidation at the picture recognition task, the greater theta activity in the ADHD group, along with the amount of SWA, is linked to a weaker performance [31]. It should be considered that the picture recognition task included emotional stimuli from the International Affective Picture System, providing –to some extent- a measure of emotional memory [31].

Several EEG waking studies showed that the theta activity has a pivotal role in ADHD functioning [52]. In particular, children with ADHD show an increased absolute theta power, often associated with a decreased beta power. This leads to an increased theta/beta ratio, recognized as a neurophysiological marker for helping to diagnose ADHD [52]. These findings could be conceptualized in terms of "cortical hypoarousal" and of unstable vigilance regulation [53]. Moreover, waking theta EEG activity is related to inhibitory control in healthy children [54].

In light of these considerations, we can speculate that the altered theta functioning could represent a biomarker of ADHD during sleep as well as during waking state. Considering that theta oscillations in healthy individuals are usually associated to some cognitive functions when they occur during REM sleep [31,55–57], it could be hypothesized that theta activity has a cut-off level which, if exceeded, leads to a compromised performance [31,37].

4.3. Limitations

The reviewed studies assessing macrostructural and microstructural sleep features are affected by several confounding variables, and some methodological considerations are needed: (a) the occurrence of sleep disorders [22] or psychiatric disturbances [22,23,35] could strongly affect the sleep structure of children [58]. Indeed, a high percentage of ADHD samples included subjects with oppositional defiant/conduct disorders [22,26–28,31,35,38], learning disabilities [22,23,38] or internalizing comorbidities [22,23,35], without tracking any linear relation among these disorders and sleep patterns; (b) the age range of the considered sample can explain some discrepancies on sleep measures (e.g., [33] vs. [36]), since the sleep microstructure significantly changes during development co-varying with brain maturation [48,49]; (c) the different subtype of ADHD could impact on sleep pattern [59]. In particular, the prevalence of the combined subtype in most of the reviewed studies [22–25,28–30,33–35,37–39] did not allow to draw any conclusion on the differences between subtypes; (d) the children's medications should be also assessed, considering the interaction between stimulants and sleep [60]. All considered studies reported that subjects stopped the medications during the experimental session. However the long-term stimulant effects could be significant. Moreover, some moderating factors could impact on the effects of medications (e.g., Body Mass Index/weight, length and time on stimulants, gender [60]), and these factors should be taken under control; (e) the presence/absence of an adaptation night and the experimental setting (laboratory or home recordings) may impact on sleep fragmentation [29]; (f) the inclusion of borderline cognitive participants (e.g., [22,35,39]) should be controlled, considering that some studies revealed that borderline intellectual functioning could impact on sleep features [61]; (g) the absence—in certain studies—of baseline sleep recordings without a task administration during the evening represents a substantial limitation. Indeed, the differences between ADHD groups and controls were found only when the correlational analyses on performance were considered and not when microstructural features were directly compared between the clinical and control groups [27,31,36,37].

Besides, concerning microstructural measures, specific methodological limitations should be underlined. Firstly, the studies -with some exceptions [33,37]—included a small number of EEG channels and analyses on CAP parameters are not effective in providing information on the regional/topographical distribution of the observed phenomena. Moreover, although the relationship between the frontal

theta rhythm and cognitive functioning is well-established in wakefulness (for review, see [62]) and sleep [55,56], we underline that the conventional quantitative EEG analysis (i.e., by using Fast Fourier Transform routines) used in the reviewed studied [27,31,33,36,37] is mainly designed for stationary signals [63] and could fail in the detection of oscillatory activity. We point to that the rhythmic/oscillatory theta activity should be distinguished from the non-rhythmic theta waves identified in relation to hypoarousal and sleepiness during the waking state (i.e., local sleep; [40,64]). In this regard, it has been recently demonstrated, by using a technique for detecting bursts of theta activity, that the theta activity associated with prolonged wakefulness is expressed by "isolated" waves and not by rhythmic oscillations [64]. In this vein, recent studies introduced a new method (i.e., Better OSCillation [65]) to successfully discriminate theta oscillations from background signals [63], revealing that rhythmic theta is related to mental/cognitive sleep activity [66,67]. Taken into account these considerations, a protocol including this specific analysis/detection may shed light on the nature of the abnormal theta activity in ADHD, providing differentiation between theta oscillations (related to cognitive encoding) and non-rhythmic activity (related to the hypoarousability).

5. Conclusions

To sum up, consistently with a recent meta-analysis [57], we emphasized that the sleep architecture of children with ADHD reported only slight differences compared to HC. The results are mixed, and the available findings did not provide a clear and comprehensive framework on the issue. Conversely, some microstructural EEG signatures, albeit heterogeneous, account for the specific link between sleep pattern and the domains of cognitive or neurobehavioral functioning. Specifically, the microstructural features showed that both SWA and theta oscillations are altered in children with ADHD, while evidence on other activities is still scarce.

The dysfunctional modulation of these—predominantly fronto-central—activities may represent the expression of a general deficit in the interplay of the fronto-limbic circuits in ADHD. Consistently, neuroimaging data revealed dysfunctions over the frontal region, the striatum and the cerebellum and, not surprisingly, neuropsychological deficits may arise from reduced brain functions [50].

Another perspective suggested that greater SWA and theta activity could be a sign of higher sleep pressure in children with ADHD [68]. The increased amount of these activities would be consistent with the hypothesis that the poor sleep could imply a sort of chronic sleep deprivation in children with ADHD [23], which in turn could affect their cognitive functioning. This appears to be in line also with the fact that sleep deprivation can impact on the prefrontal cortex, involved in several cognitive processes [12].

Although the empirical evidence is still preliminary, we propose that the detection of sleep EEG anomalies in children with ADHD could represent a starting point to provide a target to develop future interventions. In this respect, recent studies revealed that the slow oscillating (0.75 Hz) transcranial direct current stimulation [69] during NREM sleep increased the slow frontal oscillations in children with ADHD, positively contributing to declarative memory performance [50] as well as behavioral inhibition [70]. Based on these promising results [69,70], it would be interesting to design protocols aimed to ameliorate sleep and cognitive/ behavioral functioning in children with ADHD using tools that can modulate the altered sleep signatures. However, further investigations are necessary to provide useful insights at this issue.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/10/1737/s1, Table S1: List of abbreviations. The abbreviations including in the text are reported alphabetically.

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6.45 EFFICACY STUDY OF AN OMEGA-3/6 COMBINATION FOR MILD- TO MODERATE-INATTENTIVE ADHD: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN ITALIAN CHILDREN

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Objectives: ADHD treatment is based on a multimodal approach that combines behavioral and pharmacological treatment. Recently, there has been a growing interest in dietary supplementation of polyunsaturated fatty acids (PUFAs), such as omega-3 and omega-6 that showed that they are possibly effective in the control of inattentive symptoms. A specific omega-3/6 combination dietary supplement therefore was administered to a sample group of Italian children with ADHD-Inattentive (ADHD-I) presentation to evaluate its clinical efficacy and effects on essential fatty acid (EFA) plasma levels.

Methods: A randomized, double-blind, multicenter, placebo-controlled efficacy trial was conducted; the trial studied omega-3/6 combination in children aged 6 to 12 years who were diagnosed with mild/moderate ADHD-I. The study included a phase 1 evaluation of omega-3/6 supplement versus placebo (6 months) and a further 6-month phase 2 open-label treatment with omega-3/6 in all patients. Clinical effects and EFA plasma profiles (omega-3, omega-6, and omega-3/6 ratio) were assessed at 5 time points: baseline, 1 month, 3 months, 6 months, and 12 months.

Results: A total of 160 patients (118 boys and 42 girls) were enrolled from 4 Italian sites. A significant change in the total and inattention score was found from baseline to the end of the study within each group with no significant differences between omega-3/6 and placebo groups. At baseline, EFA levels did not show a statistically significant correlation with clinical severity. After 12 months, a slight (not statistically significant) reduction in omega-6/3 ratio was measured in the group taking active treatment only during phase 2. Dietary supplementation was well-tolerated, and no subjects reported severe adverse effects.

Conclusions: In our sample group, the plasma omega-6/3 ratio was not related to ADHD clinical severity or to clinical improvement. To evaluate the real effectiveness of omega supplementation in reducing the core symptoms

of ADHD, it would be essential to establish the target characteristics of potential "responder" subjects in terms of the basal level of the fatty acid and possible individual variables (clinical symptoms, diet, optimal age and duration of PUFA treatment, and ethnicity).

ADHD, RCT, TREAT

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Article

Association Between Fatty Acids Profile and Cerebral Blood Flow: An Exploratory fNIRS Study on Children with and without ADHD

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Abstract: Polyunsaturated fatty acids (PUFAs) biostatus has been proposed as possible attention deficit hyperactivity disorder (ADHD) diagnosis biomarker. The present exploratory study aimed to investigate the association between PUFAs biostatus and cerebral cortex metabolism measured by functional Near Infrared Spectroscopy (fNIRS) in a sample of children with and without ADHD. 24 children with ADHD and 22 typically developing (TD) peers, aged 8–14, were recruited. Linoleic, arachidonic, docosahexaenoic and eicosapentaenoic acids levels were evaluated in whole blood. All children underwent fNIRS while performing an n-back working memory task. Between groups comparisons revealed lower levels of arachidonic acid in children with ADHD and stronger NIRS signal in TD participants, especially when completing more difficult tasks. Correlations conducted between fNIRS activation and PUFA biostatus revealed several associations between hemodynamic changes in the frontoparietal regions and fatty acids profile across participants. This result was also confirmed by the multiple hierarchical regression analyses that remarked an inverse effect of eicosapentaenoic acid levels on oxyhemoglobin values in right frontoparietal region. Such preliminary findings, if confirmed, would suggest that PUFAs could play a role in atypical neurodevelopment.

Keywords: polyunsaturated fatty acids; NIRS; cerebral blood flow; ADHD; biomarker; attention; rehabilitation

1. Introduction

Attention deficit hyperactivity disorder (ADHD), which affects approximately 7.2% of children worldwide, is the most common childhood neurodevelopmental disorder [1]. ADHD is a complex and multifactorial condition. Its core symptoms reflect a lack of self-regulating behavior, cognition

and emotional responses, as well as difficulties in paying attention, excessive motor activity and high impulsivity levels [2].

ADHD manifestations are heterogeneous and impact cognition and behavior through a multifaceted aetiopathogenesis that involves biological, psychosocial, and environmental aspects.

Given this complexity, an objective diagnosis biomarker has not been established. Conventionally, the ADHD diagnostic process relies on subjective criteria, such as clinical interviews, observations, and rating scales. Insight into the biological markers associated with typical and atypical development could offer clinicians more reliable tools for ADHD assessment and the opportunity to implement targeted treatment plans [3].

Taking these premises into account, there has been growing interest in recent years in the role of nutrition in the development, treatment, and prevention of neurodevelopmental disorders. In particular, attention has been focused on the role of polyunsaturated fatty acids (PUFAs) as possible biological markers in ADHD (see, for example, [4–6]), suggested also by the relevant role for these biological components in normal brain functionality [7].

PUFAs represent an indispensable component of lipids that cover a relevant role in human diet and biological functions such as provision of energy, functionality of cell membranes and tissue metabolism [8]. The simplest lipids are fatty acids, which contain a hydrophilic carboxyl group, a hydrocarbon chain and a methyl group. Fatty acids carbon chain can be saturated (with no presence of double bonds) or unsaturated (with one or more double bonds). PUFAs fall into the unsaturated group, and they can be divided into two classes: omega-3 (n-3) and omega-6 (n-6) fatty acids (FAs), which are distinguished by the location of their double bonds in the carbon chain [9].

Cis-linoleic acid (LA 18:2, n-6) and α-linoleic acid (ALA 18:3, n-3) are considered "essential" fatty acids because mammals cannot biosynthesize them. They are primarily plant-derived and exclusively available from diet. Mammals metabolize LA and ALA in long-chain PUFAs: n-6 PUFAs (e.g., arachidonic acid - AA 20:4, n-6) derived from LA and n-3 PUFAs (e.g., docosahexaenoic acid-DHA 22:6 n-3-and its precursor eicosapentaenoic acid-EPA 20:5 n-3) derived from ALA [10,11]. PUFAs are relevant components of cellular membranes, phospholipids, and precursors of eicosanoids, which influence neuronal development and functioning [12]. DHA and AA are the brain's major lipid constituents and, in different roles, are involved in cell growth, neural signaling, and gene expression [7,8]. Long-chain FAs have pro- and anti-inflammatory properties. Generally, AA and DHA have opposite effects on synaptic transduction and inflammation [7]. AA and its derived eicosanoids tend to exhibit pro-inflammatory activity in various cell types and disorders [10–12]. Nevertheless, AA also plays an important role in brain cell division and signaling [13,14].

EPA, DHA and their derived eicosanoids, on the other hand, are powerful regulators of biological process, with anti-inflammatory properties [10,12]. The main natural dietary source for EPA and DHA is fish oil.

DHA represents the 10–20% of the fatty acids in mammalian grey matter. It is important for neuronal cell membrane integrity and for the signaling system because it influences various neurotransmitter pathways, including the cholinergic system, which is known to play a key role in memory and learning [7,15]. Therefore, DHA plays a crucial role in the cellular structure of the cerebral cortex, especially within the frontal lobe [16]. The physiology of this brain region, which is involved in executive functions and behavioral and emotional regulation, has been often reported as altered in individuals diagnosed with ADHD [17].

On the other hand, EPA-derived eicosanoids regulate the immune and endocrine systems and cardiovascular functions [7].

N-3 deficiency and high n-6/n-3 ratios are indicators of inflammation and have been linked with various mental disorders, including ADHD [10,16]. In addition, evidence from preclinical studies indicates that n-3 deficiency may be associated with impaired attention and learning ability [18,19].

Within the last decade, an increasing number of studies has evaluated the association between PUFA intake or biostatus and human brain structure and function using various neuroimaging

methods. To date, studies involving healthy subjects indicate that increased dietary fish intake and higher blood levels of DHA and EPA are usually associated with increased grey matter volume and greater activity-dependent cerebral blood flow [7]. The relationship between n-3 and cognitive performance might be partly mediated by grey matter volume [7].

Near infrared spectroscopy (NIRS) is a viable approach with which to obtain information about cerebral cortex metabolism in a non-invasive manner and at relatively low cost. NIRS is an optical technique that uses light at specific wavelengths to detect changes in oxygenated and deoxygenated hemoglobin (HbO and HbR, respectively) concentrations over time [20]. NIRS has been successfully used to detect activations of the frontal, parietal, and temporal cortices during neuropsychological tasks [21–23]. It is therefore an optimal choice when studying children with neurodevelopmental disorders [24,25].

Hamazaki-Fujita and colleagues [26] used NIRS with healthy adults and found that increased EPA and DHA levels were associated with increased tissue oxygenation indices in the prefrontal cortex while completing an arithmetic task. A similar association was not found in another cross-sectional study on healthy male adults performing a working memory task [27]. However, the participants' fish consumption was associated with a greater increase in HbO in the left dorsolateral prefrontal cortex during the task.

A clinical trial conducted on healthy adult volunteers evaluated the effect of DHA and EPA supplementation on cortical hemodynamics measured using functional NIRS (fNIRS) during a cognitive task that elicited prefrontal cortex activation [28]. The study revealed a significant effect of DHA, but not EPA, in increasing cerebral HbO in prefrontal cortex when compared to the placebo condition. In a second double-blind, placebo-controlled trial [29], the authors evaluated the effect of DHA-rich fish oil at a dose of 1 or 2 g on cerebral blood flow measured using NIRS. In total, 65 healthy adult participants performed nine computerized cognitive tasks. Both doses of DHA, when compared with the placebo, were associated with an increased concentration of HbO and total Hb, as well as a dose-response effect on total Hb concentrations, during cognitive tasks, but no effect on behavioral performances.

Although PUFA supplementation is one of the most popular non-pharmacological treatments for ADHD [30], few studies have evaluated the association between FAs, cerebral activation, and cognition in children with ADHD.

To our knowledge, only Bos and colleagues [30] have investigated the effect of n-3 PUFAs on ADHD in a randomized placebo-controlled trial of young boys with and without ADHD diagnoses using functional magnetic resonance imaging during a go-no go paradigm. n-3 supplementation improved inattention symptoms in both groups; however, no effect was found on brain activity or task performance after supplementation.

Based on previous considerations, the goal of the present study was to investigate the association between cerebral hemodynamic activation measured using fNIRS and blood PUFA levels in children with ADHD and typically developing (TD) peers. To elicit the cortical hemodynamic responses, we used an n-back working memory task with blocks of increasing difficulty [31]. The same task was used by Crippa, Salvatore and colleagues [32] to successfully differentiate patients with ADHD from TD children by means of their cortical hemodynamic responses measured with fNIRS. To the best of our knowledge, no studies have examined the association between PUFA biostatus and task-dependent cortical activity in children with and without ADHD.

2. Materials and Methods

The present study is a cross-sectional, observational study of children with and without ADHD that investigates the association between PUFA biostatus and brain hemodynamic responses to a cognitive task with differing workloads as measured with fNIRS. Our research is part of a placebo-controlled double-blind intervention trial (June 2012–October 2014) that explored the efficacy of DHA supplementation in children with ADHD ("The Effects of DHA on Attention Deficit and Hyperactivity Disorder - DADA Study"). The trial was registered at ClinicalTrials.gov as NCT01796262

and was approved by our institute's ethics committee in accordance with the Declaration of Helsinki (1967) and its later amendments. Written informed consent and assent were obtained from all caregivers and participants.

2.1. Participants

2.1.1. Children with ADHD

As a part of a larger project [12], 24 children with ADHD aged 8 to 14 were recruited from our institute's child psychopathology unit over a 22-month period. All children had been previously diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders criteria (4th ed., text rev.; DSM-IV-TR; APA, 2000) by a child neuropsychiatrist with expertise in ADHD. Moreover, a child psychologist experienced in the diagnosis of ADHD (AC) independently confirmed the diagnosis through direct clinical observation and the administration of the semi-structured interview Development and Well-Being Assessment (DAWBA) [33]. According to the clinical assessment, 16.7% of the children met the criteria for the ADHD inattentive subtype, 33.3% fulfilled criteria for the hyperactive–impulsive subtype, and 50% had the combined subtype.

2.1.2. Typically Developing Children

Twenty-one TD children living in the same areas as the children with ADHD were recruited as a control group. The research team excluded possible neuropsychiatric diagnoses in control subjects, using the DAWBA parent diagnostic interview. The genders and ages of TD children were matched to those of the clinical sample. Children in the control group completed the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children-III (WISC-III) [34] to estimate their Full-Scale Intelligence Quotient (FSIQ). This measure was used to match the clinical and control groups [35].

Regarding the whole research sample, only participants with FSIQ scores or estimated FSIQ scores higher than 80 were included. Moreover, all children were drug-naïve and did not consume omega-3 or omega-6 supplements during the 3 months prior to recruitment. Exclusion criteria included a history of seizures, other psychiatric or neurological disorders, and diagnosed genetic disorders. All participants were Caucasian and had normal or corrected-to-normal vision.

2.2. Measures

Participants were assessed at our institute's child psychopathology unit. Each child's weight and the blood pressure were measured. Familial socioeconomic status was coded according to the Hollingshead scale for parental employment [36].

2.2.1. Cognitive and Clinical-Behavioral Profile

Four subtests from the Amsterdam Neuropsychological Tasks (ANT) [37] were administered to evaluate executive function domains: baseline speed, focused attention 4 letters, shifting attentional set–visual, and sustained attention. Furthermore, participants' parents completed the Conners' Parent Rating Scale (CPRS-R) [38] and ADHD rating scale IV - Parent Version-Investigator (ADHD-RS) [39] to assess ADHD behavior severity. More detailed information regarding cognitive and behavioral domain measures is available in [40].

2.2.2. Fatty Acids Profile

After a minimum 1-hour fast, biological samples were obtained from all children by collecting drops of blood using an automatic lancing device that punctured the participant's fingertip; a strip of paper was used to collect each sample. FAs profile was evaluated in whole blood, which is more easily obtainable than other blood components, such as red blood cells and plasma. Thus, we measured the status of long- and short-chain circulating FAs in relation to dietary habits [41]. All blood samples were preserved at 4 °C until they were analyzed through transmethylation for gas chromatography

analysis using a well-validated protocol [42]. We detected FAs from 14 to 24 carbons, and their values were expressed as a percentage of total FAs. In the present work, we report single-FA data for the main n-3 and n-6 FAs: LA, AA, EPA, and DHA.

2.2.3. Stimulation Protocol

During fNIRS recording, each participant completed a computerized protocol (approximately 15 min long) developed with the Presentation®software (Neurobehavioral Systems Inc., Denver, CO, USA. The stimulation protocol was a variant of the visuospatial n-back working memory task (n-back VSWM) developed by Cui and colleagues [31,32]. The paradigm consisted of a rest condition and three tasks with increasing difficulty [0-back, 1-back, and 2-back] (see Figure 1). During rest conditions, children passively viewed a white cross on a black screen. In the three task conditions, a clown's face was displayed on a location of a 3 × 3 matrix. In the 0-back task, children were instructed to respond only when the clown's face was presented in the center of the screen. In the 1-back task, children were required to respond if the stimulus remained in the same position as in the previous trial. In the 2-back task, participants had to respond if the stimulus recurred in the same location, as in the two previous trials. Each experimental epoch included 32 stimuli that lasted 0.5 seconds each, with a 1.5-second inter-stimulus interval.

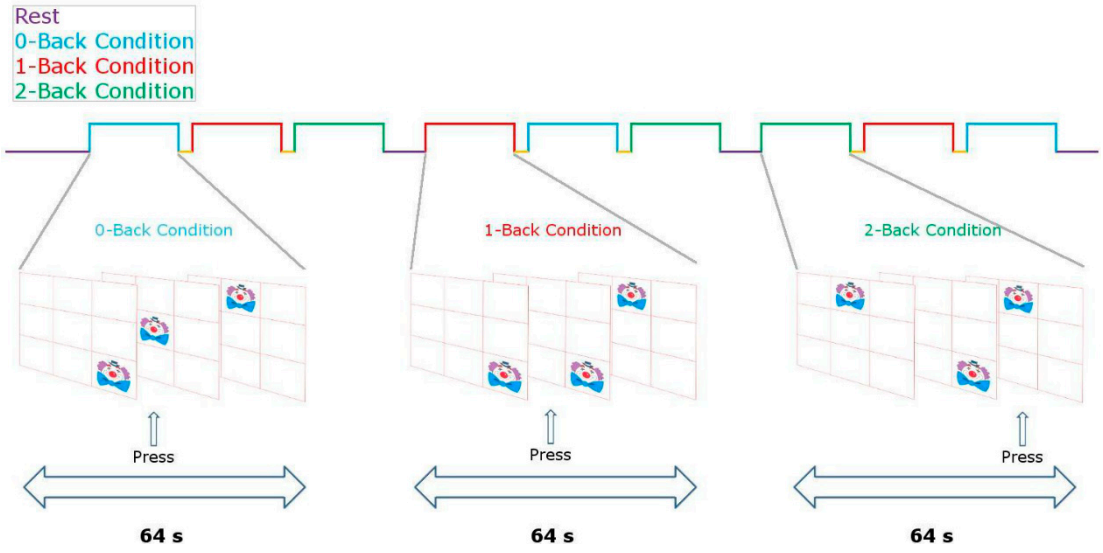

Figure 1. Task design.

fNIRS data acquisition, optode localization and data preprocessing. We acquired fNIRS data with a commercial continuous-wave NIRS device (DYNOT Compact 9-32, NIRx, Berlin, Germany). An elastic cap of the proper head size with 32 channels was used. Specifically, 8 light sources and 24 light detectors were placed on the bilateral frontotemporal areas centered at F3 and F4, according to the International 10–20 system [43]. The source–detector distance was 2.7 cm (Figure 2). Recordings were performed at two wavelengths, 760 nm and 830 nm, to measure both HbO and HbR concentration changes after data conversion using the modified Beer-Lambert Law [44]. NIRS data preprocessing was performed using the Homer2 v2.3 software [45,46].

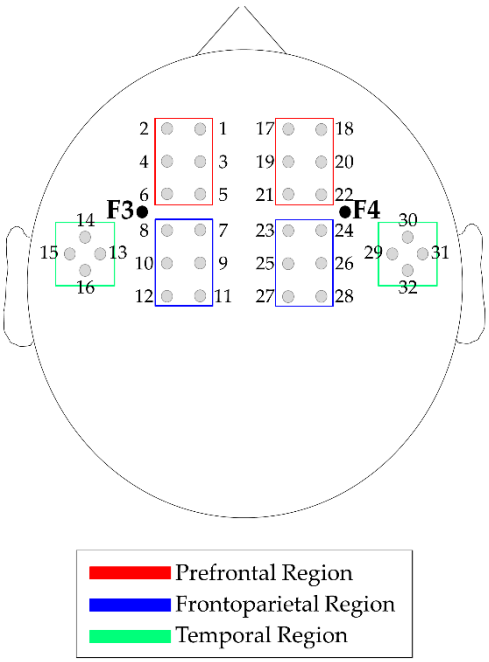

Figure 2. fNIRS channels and region of interest (ROI) map. Note: Sources and detectors are localized on a 10–20 system. Left-prefrontal ROI: Channels 1–6. Left-frontoparietal ROI: Channels 7–12. Right-prefrontal ROI: Channels 17–22. Right-frontoparietal ROI: Channels 23-28. Temporal areas were not considered in the analyses.

2.2.4. Neurophysiological Profile

The preprocessed fNIRS time series and prior to fNIRS analysis, were standardized applying at each data point (p0) of the nine task blocks the following formula:

$$p1 = (p0 - m_{3s})/s_{3s}$$

where m_{3s} and s_{3s} are the mean and the standard deviation of the 3 seconds before the block's beginning [32,47]. Then, time point concentration data were averaged accordingly to the different task conditions. Specifically, four task conditions were identified: 0-back (0B), 1-back (1B), 2-back (2B) and overall task ("Task"), i.e., the three-condition considered together. To evaluate the channels more involved in the task execution, the possible activations of each channels in respect to the baseline were identified by performing channel-wise Wilcoxon tests on the control group, between the "Task" and a time window of the baseline "Rest" (from 25 seconds to 5 seconds before the first task section) for HbO and HbR. Based on the Wilcoxon test results, bilateral temporal ROIs (channels 13–16 and channels 29–32) were excluded from further analysis because fewer than half of the channels were able to detect significant Hb changes. Finally, HbO and HbR data were averaged in four ROIs to increase signal-to-noise ratio; each was composed of six contingent channels: left-prefrontal (l-PF: channels 1–6), left-frontoparietal (l-FP: channels 7–12), right-prefrontal (r-PF: channels 17–22) and right-frontoparietal (r-FP: channels 23–28) (see Figure 2).

Statistical analyses were conducted using the SPSS statistical software package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Data were visually and statistically inspected to check whether the variables were normally distributed and to address assumptions of linearity, independence of observations and homogeneity of error variance. Fisher's exact test, Mann-Whitney, and independent-samples *t* test analyses (according to variables distribution) were conducted to examine between-group differences for demographic, clinical, cognitive, behavioral (n-back task performance) measures, and blood FAs levels.

2.2.5. Neurophysiological Profile

Mann-Whitney or two-tailed independent-samples *t* test analyses (depending on the distributional nature of the data) were computed to examine the between-groups difference of activation in each task condition for HbO and HbR in the four ROIs.

2.2.6. ADHD Severity-Neurophysiological Profile Association

To investigate possible associations between cortical hemodynamics and ADHD severity in the clinical sample, Spearman correlations were conducted between fNIRS activation significantly different between-groups and clinical scales for ADHD severity (ADHD index from CPRS-S and "*Total*" measure from ADHD-RS). Since this study was exploratory, no correction was applied for family-wise error rate. However, confidence intervals (CIs) of 95% were calculated for Spearman's Rho using the bootstrapping method (1000 bootstrap resamples) to indicate the likely size of the effect [48].

2.2.7. Fatty Acids-Neurophysiological Profile Association

Relationships between fatty acid composition (LA, AA, EPA, and DHA) and HbO and HbR activation in each task condition in the four ROIs were analyzed using Spearman correlations. After verifying the assumptions and controlling for the effects of age, socioeconomic status, and total IQ, we conducted multiple hierarchical regression analyses to estimate HbO or HbR changes to varying blood FAs biostatuses, with FA level as an independent variable and brain hemodynamic activation as a dependent variable [49].

3. Results

Sample demographic characteristics and FAs biostatus are reported in Tables 1 and 2, respectively.

Table 1. Sample demographic characteristics.

	ADHD	TD	Value	*p*
N	24	21	-	-
F:M	0:24	1:20	1.169 [a]	0.467
Age	11.5 ± 1.5	11.3 ± 1.8	−0.485 [b]	0.630
IQ	101.8 ± 11.1	110 ± 20	1.683 [b]	0.103
SES	54 ± 20.2	56 ± 18.7	0.344 [b]	0.734

Note. ADHD = Children with ADHD; Controls = Typically developing children; F = Females; M = Males; IQ = Intelligence quotient; SES = Socioeconomic status. [a] Fisher's Exact Test; [b] Student's *t* test.

Table 2. Blood fatty acids analysis data.

	ADHD	TD	Value [a]	*p*
LA	22.80 ± 2.34	22.63 ± 2.47	−0.242	0.810
AA	9.34 ± 1.19	10.07 ± 0.94	2.264	0.029
EPA	0.98 ± 0.56	1.13 ± 0.46	0.963	0.341
DHA	1.75 ± 0.49	1.92 ± 0.54	1.107	0.274

Note. ADHD = Children with ADHD; TD = Typically developing children; LA = linoleic acid; AA = arachidonic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid. Contrast in bold is significant at alpha = 0.05. [a] Student's *t* test value.

Demographic characteristics were balanced between groups (all $p > 0.05$).

With respect to participants' blood FA profiles, children with ADHD showed lower levels of AA compared to typically developing peers. No additional significant difference was found regarding the FA profile.

The groups' cognitive and clinical characteristics are illustrated in the Supplementary Materials (Table S1). Task performances during fNIRS are depicted in Table S2.

Several significant between-group differences were found in cognitive variables (ANT, Table S1). Children with ADHD committed more inhibition errors (visual set-shifting) and showed more difficulties with sustained attention, as highlighted by an increased variability in reaction times (sustained attention).

Moreover, as expected, participants with ADHD manifested significantly higher values in all clinical measures of ADHD (ADHD rating scale and Conners' parents rating scales, Table S1).

Lastly, a statistical assessment of data revealed two outliers in the ADHD group in terms of number of errors during n-back task (2 standard deviations from the next highest score). Thus, the two participants' data were excluded from all further analysis. We found similar performances across participants for the n-back task, except for slower responses to stimuli in the 0B condition in children with ADHD. No other significant differences were found in any task condition.

3.1. Neurophysiological Profile

The results of between-groups differences for mean HbO and HbR activation in each ROI and task condition are summarized in Table S3a and S3b in the Supplementary Materials. Absolute values of HbO and HbR data showed weaker activation in subjects with ADHD compared to TD children in each area and task condition. These findings reached statistical significance level in several ROIs and workloads, as depicted in Figure 3.

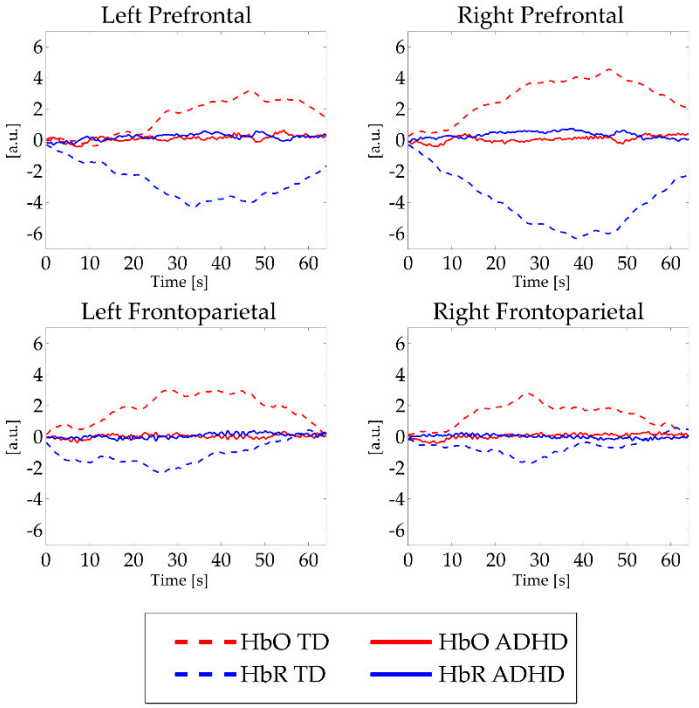

Figure 3. Mean fNIRS activations in all task conditions. Note: a.u. = Arbitrary units; s = seconds. Red lines indicate HbO signal, blue lines depict HbR signal. Hatch pattern represents activations from typically developing children, continuous lines illustrate activations in children with ADHD. For significant between-group differences, see Table S3a, S3b.

3.2. ADHD Severity-Neurophysiological Profile Association.

With respect to the association between hemodynamic activations that differentiate the clinical group from the TD group (see Table S3a, S3b) and ADHD severity scores, our results showed a marginally significant positive correlation (Spearman's rho = 0.501, $p < 0.05$) between HbO values in

right frontoparietal ROI in the 2-back condition and Conners' ADHD index. No additional significant correlation was found between HbO or HbR signals and ADHD clinical scores.

3.3. Fatty Acids-Neurophysiological Profile Association

Table S4a, S4b in the Supplementary Materials section show the Spearman correlation results. With respect to HbO values, the Spearman coefficients revealed a significant negative correlation between left frontoparietal values in the 0-back condition, all task conditions and EPA blood levels. In the right frontoparietal ROI, significant negative correlations were found between HbO values in the 0-back condition and both AA and EPA.

Regarding HbR levels, significant correlation coefficients were found in the right frontoparietal ROI: positive associations were found between HbR in the 0-back condition and EPA biostatus and HbR in the 2-back condition and AA levels; a negative correlation was found between HbR in the 1-back condition and DHA value. Lastly, a significant negative correlation coefficient was found for left prefrontal HbR in the 1-back condition and DHA.

Table 3 shows multiple hierarchical regression results.

Table 3. Multiple hierarchical regression results with arachidonic acid (AA) and eicosapentaenoic acid (EPA) as independent variables, age, socioeconomic status (SES) and intelligence quotient (IQ) as covariates, and HbO in right frontoparietal ROI in 0B condition as dependent variable.

AA and EPA → rFP HbO, 0B	**Regression Coefficients**		
	***β* [Bootstrap c.i.]**	*t*	*p*
Age	−0.323 [−0.936; 0.051]	−1.976	0.055
IQ	0.042 [−0.050; 0.057]	0.259	0.810
SES	0.216 [−0.006; 0.061]	1.351	0.094
AA	−0.030 [−0.860; 0.562]	−0.208	0.840
EPA	**−0.494 [−4.678; −0.813]**	**−3.280**	**0.015**
	Model summary		
	Adjusted R^2	F	*p*
Age, IQ, SES	0.070	1.955	0.139
AA and EPA	**0.268**	**3.786**	**0.008**

Note. → = AA and EPA are the independent variables of the multiple hierarchical regression; 0B = 0 Back task condition; AA = Arachidonic acid; *β* = Regression beta coefficient; c.i. = confidence intervals; EPA = Eicosapentaenoic acid; F = F value; HbO = Oxyhemoglobin; IQ = Intelligence quotient; rFP = Right frontoparietal area; ROI = Region of interest; SES = Socioeconomic status; *t* = *t* value; *p* = probability value; R^2 = R-squared (coefficient of determination). Values in bold are significant according to *p* value and bootstrap confidence intervals. Lower and upper limits of 95% confidence intervals from bootstrapping methodology with 1000 resamples iteration are reported in square brackets.

Our regression model with AA and EPA fatty acids as independent variables and HbO concentration in right frontoparietal ROI, in 0-back condition, as dependent variable (controlling for age, socioeconomic status and total IQ), was statistically significant. Our model explained 26.8% of variance (adjusted R^2 = 0.268, F = 3.786, p = 0.008). Specifically, EPA blood levels had a significant negative effect on HbO concentration (β = –0.494, t = –3.280, p = 0.015), and, as such, explained approximately 24.6% variance of HbO concentration in right frontoparietal ROI, in 0-back condition.

4. Discussion

In the last decades, an increasing body of research has drawn considerable interest to the possible impact of dietetic factors on ADHD symptomatology as playing a potential role in the

pathophysiology of the condition and, therefore, as a possible coadjutant non-pharmacological intervention to pharmacological and psychological treatment [11].

Given these premises, our study was aimed at evaluating the association between blood PUFA biostatus and cerebral hemodynamics as measured by fNIRS in a sample of Italian children with and without ADHD. To the best of our knowledge, no studies have examined the association between PUFA biostatus and fNIRS data in a sample with the above-mentioned characteristics.

To this end, we recruited two groups of school-aged children, one composed of children with a clinical diagnosis of ADHD and one composed of TD children; all were of average IQ.

As a preliminary step, we compared individual PUFA biostatus and task-related cortical activations between the two groups of children, observing lower levels of AA in children with ADHD than in TD children. As expected, this result is consistent with our preliminary findings in children with ADHD in an Italian setting [40]. The importance of AA in humans and other mammals is indicated by the variety of functions that this FA performs in a range of metabolic events in spite of relatively constant levels in body pools [13,14]. Blood AA deficiencies in children with ADHD and other learning disorders have been reported previously [50,51]. However, the reason for the specific neurocognitive effect of lower blood AA levels in children with atypical development, especially with ADHD, remains unclear.

In regard to the changes in the oxygenated and deoxygenated hemoglobin concentrations measured by fNIRS during performance of n-back working memory tasks, we found different activation patterns in children with ADHD than in their TD peers (see Figure 3). The results indicated a stronger increase in HbO and HbR concentrations in healthy participants compared to the ADHD group. The present results suggest that ADHD children, in light of n-back task performances comparable to healthy controls, show weaker cortical activation when completing more difficult tasks, especially when the tasks require more complex stimuli retention (1-and 2-back conditions). We found no differences in HbO or HbR concentrations between ADHD and TD participants in the 0B condition, which is traditionally ascribed to indexes of selective attention rather than working memory [51]. These findings are consistent with a previous fNIRS study by Ehlis and colleagues that used similar cognitive tasks in patients with ADHD [52]. Again, in a functional magnetic resonance imaging study, Kobel and colleagues [51] also found significantly higher activation in bilateral frontal and parietal areas related to the increasing difficulty of n-back tasks in children with typical development compared to peers with ADHD. Dorso-lateral areas cover a relevant role in manipulation of information (in our case, 1B and 2B conditions) [52]. Conversely, ventral areas activity has been consistently found in association with detection of transient stimuli (0B condition, in our task) [52]. Thus, the lack of between-group differences in lower executive functions load could be possibly reconducted to our NIRS probe configuration that enables the identification of dorso-lateral areas hemodynamic activity rather than ventral cortices metabolism. However, these peculiarities in cerebral blood dynamics seem to be limited to the physiological level and not significantly correlated to ADHD severity, as evaluated by parents through CPRS and ADHD rating scales. This observation extends our previous findings [31] suggesting that the characterization of ADHD functioning could be enriched by broader biological measures, including PUFA biostatus and cortical hemodynamic data. In the actual clinical practice, ADHD is diagnosed on the basis of symptoms as judged by clinicians and by means of qualitative measures. We believe that the integration of information from different sources and levels of analysis (biological, behavioral, cognitive, and neurophysiological) could lead to a more comprehensive description of children with ADHD, supporting the clinical practice of diagnosing ADHD.

With respect to the main goal of this study—to investigate the association between blood PUFA biostatus and cortical hemodynamics—we found, regardless of diagnosis, a few puzzling findings when exploring PUFA percentages and changes in the concentration of oxygenated and deoxygenated hemoglobin (see Table 3). Most correlations between FAs and fNIRS signals were found for hemodynamic changes in the frontoparietal regions. Moreover, these associations seem more evident for HbO and HbR values recorded in the 0-back condition. This weakly significant trend was confirmed by the regression model results. When controlling for participants' sociodemographic

characteristics, such as age, intellectual functioning and socioeconomic status, we found an inverse effect of EPA blood levels on HbO values measured over the right frontoparietal region only in the 0-back condition. This baseline task condition requires concentration and selective attention from the participants rather than more complex and demanding cognitive processes, such as working memory. Paradoxically, Hamazaki-Fujita and colleagues [26] also found a significant association, though in the opposite direction, between EPA and change in tissue oxygenation index estimated by fNIRS in healthy adults performing a simple arithmetic task that did not require complex mental manipulation of the information. A supplementation study [28] reported no effect of EPA-rich fish oil on cerebral blood flow measured using fNIRS in adults. Nevertheless, this significant degree of heterogeneity in findings could be explained by the 250–300-fold lower EPA concentrations in brain compared to the DHA concentration, raising concerns on its consistency [53].

In light of this consideration, we were surprised to find no significant association between DHA, which derives from EPA and cortical hemodynamic changes after having controlled for the participants' demographics. As also described in the Introduction, DHA is the brain's major lipid constituent and plays a critical role in maintaining membrane integrity and fluidity and influencing inter-cell communications. Even though several previous studies that used various imaging techniques suggested a direct effect of DHA on cortical blood flow with regard to the effect of DHA supplementation [28,29,54] or as simple association with DHA status [53,55], results in literature are controversial [9]. The causes of this discrepancy could be various, as the present work differed from the previous studies in several important methodological aspects, such as the participants' ages, the nature of the cognitive task and the fNIRS parameters used to evaluate changes in hemoglobin concentrations. In addition, it is possible that the association between DHA (as well as AA) and cortical hemodynamics would be better explained by additional latent variables not included in our regression model (i.e., genetics of enzymatic steps, grey matter volume, and dietary intakes of PUFAs). These variables should be taken into account in future extensions of the present study. We highlight that associations between DHA levels and brain functionality might depend on manifold factors [56,57], that could have intervened also in the conflicting statistical effects found in our work. For instance, we did not control for dietary sources of PUFAs, aspect that could have contribute to the discrepancy between EPA and DHA results.

The present study has relevant limitations. The novelty of our approach did not allow us to contextualize the results in a broader research area; in fact, to the best of our knowledge, there is no previous study addressing PUFA and brain cortex metabolism in a developmental-aged sample of children with and without ADHD. Previous fNIRS studies conducted with healthy adults gave inconsistent results [25,27], which are hardly comparable with ours. Therefore, this work was limited by its small sample size mainly due to its exploratory nature, and the statistical testing was not adjusted for multiple comparisons (many of the experimental measures were intercorrelated). Indeed, even though some correlations between PUFA and fNIRS data were found, the rho values were generally low. Greater sample size is needed to generalize these preliminary results. In addition, there was also a disproportionate gender distribution across participants. Future studies addressing gender differences could be fruitful. Finally, it is biologically plausible that the inverse relation found between brain metabolism and PUFA biostatus could be influenced by a number of latent confounding factors not considered in this work, such as children's genetic characterization of PUFA metabolism, total brain volumes and dietary intakes of PUFAs, as underlined also elsewhere.

5. Conclusions

For the first time in the literature, the present exploratory study suggests a possible association between blood FA composition and cerebral hemodynamics in a sample of children with ADHD and TD peers. Such preliminary findings should be now considered as a relevant area of research and addressed in samples with sufficient size to disentangle possible mediating effects of genetics, brain structure or volume, nutrition and ADHD subtypes, and allowing for family-wise error rate

correction as appropriately required. If confirmed, these results would suggest that dietary components, such as FAs, could play a role in atypical neurobehavioral development.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/11/10/2414/s1, Table S1: Cognitive and clinical measures (means ± standard deviations) in participants groups.; Table S2: N-back task performance (means ± standard deviations).; Table S3a: HbO (a.u.) mean activations in each ROI and task condition in both groups. Table S3b: HbR (a.u.) mean activations in each ROI and task condition in both groups; Table S4a: Spearman's rho values for correlations between HbO and blood fatty acid measures in the whole sample; Table S4b: Spearman coefficients values for correlations between HbR and blood fatty acid measures in the whole sample.

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Capitolo VI
SALUTE, DISABILITÀ E SERVIZI DI BASE

…

3. SALUTE MENTALE

29. Continuando a rilevare l'assenza di un sistema completo di monitoraggio dello stato di salute mentale dei minorenni, l'accesso limitato a un'adeguata assistenza sociosanitaria per i minorenni con disturbi neuropsichiatrici, il rilevante incremento delle richieste di diagnosi e intervento per disturbi neuropsichici dell'età evolutiva, la disomogeneità delle risposte diagnostico-terapeutiche e in considerazione dell'Obiettivo di Sviluppo Sostenibile 3.4, il Comitato raccomanda allo Stato italiano di:

(a) garantire un sistema uniforme e integrato di servizi di neuropsichiatria infantile e dell'adolescenza (NPIA) omogeneo su tutto il territorio nazionale, dotato di sufficienti risorse umane, tecniche e finanziarie;

(b) istituire un efficace sistema di monitoraggio della salute mentale dei bambini e degli adolescenti e condurre una sistematica e continua valutazione della qualità e appropriatezza delle cure erogate;

(c) garantire che i minorenni e i loro genitori siano adeguatamente informati sull'efficacia attesa e i possibili effetti avversi delle terapie proposte, sia farmacologiche che non farmacologiche;

(d) garantire che i minorenni e i loro genitori siano adeguatamente informati sui possibili effetti collaterali derivanti dalla prescrizione di farmaci e riguardo la medicina alternativa.

CRC/C/ITA/CO/5-6, punto 29

L'intesa raggiunta tra il Governo, le Regioni, le Province Autonome e gli Enti locali sulle "**Linee di indirizzo sui disturbi neuropsichiatrici e neuropsichici dell'infanzia e della adolescenza**"[1] a luglio 2019 rappresenta una significativa novità in un sistema che dimentica troppo spesso e con perseveranza i bisogni ed i diritti dei bambini e delle famiglie. È un documento di intenti, sarà quindi il passaggio del recepimento a livello locale delle indicazioni espresse, saranno le iniziative intraprese per il miglioramento dei servizi di cura e saranno la valutazione e il continuo monitoraggio dell'efficacia degli interventi che ne determineranno il vero valore. Il documento approvato non fa riferimento ad alcuno standard, neppure minimo, o ad indicatori di qualità o a possibili benchmark per i servizi locali e questo rappresenta un grosso limite alla garanzia dell'"essenzialità" e dell'appropriatezza delle cure in una realtà nazionale cronicizzata sulle disuguaglianze inter e intra-regionali sia delle domande, ma ancor più delle risposte in termini di qualità e appropriatezza. La **disomogeneità delle risposte da parte dei servizi di NPIA** è in parte imputabile all'insufficiente disponibilità di risorse (umane, economiche, tecnologiche) a fronte del continuo aumento delle domande, ma anche alla maggior ottimizzazione delle risorse in termini organizzativi e culturali. Finalità di

[1] Conferenza Permanente per i rapporti tra lo Stato, le Regioni e le Province Autonome di Trento e Bolzano. Repertorio atto n. 70/CU del 25 luglio 2019. "Linee di indirizzo sui disturbi neuropsichiatrici e neuropsichici dell'infanzia e della adolescenza", disponibili su http://www.statoregioni.it/it/conferenza-unificata/sedute-2019/seduta-del-25072019/atti/repertorio-atto-n-70cu/

percorsi che necessitano anche un aggiornamento dell'offerta, condivisa, integrata, omogenea e accessibile su tutto il territorio nazionale.
Sebbene un accurato, preciso e continuo nel tempo quadro epidemiologico nazionale non sia a tutt'oggi disponibile, da quanto emerge dai documenti dei gruppi di lavoro di alcune regioni (per esempio Lombardia, Piemonte, Toscana[2]), **l'accesso ai servizi di NPIA interessa il 6-8% delle persone di età minore residenti**, a fronte di una richiesta stimata, anche in accordo con i dati internazionali, di oltre il doppio[3]. Le stime di incidenza e prevalenza si basano su rilevazioni e analisi di altri contesti nazionali con approssimazioni che necessiterebbero di validazione. Come, per esempio, mancano informazioni sull'incidenza e sull'evoluzione dei disturbi comportamentali ed emotivi nei minorenni con disabilità intellettive o ASD (Disturbi dello Spettro Autistico), benché il rischio di svilupparli sia da tre a quattro volte più elevato rispetto ai coetanei[4] e la loro frequenza sia di oltre l'80% nei soggetti con disabilità intellettiva grave o gravissima. Ma anche per quanto riguarda la struttura, l'organizzazione e le risorse disponibili dei servizi di NPIA in rapporto alle domande di cura di un territorio (ricovero ordinario, accessi in PS, interventi residenziali terapeutici, semiresidenzialità terapeutica), la frazionata e occasionale valutazione fatta in alcune regioni preclude un'efficace organizzazione delle risposte diagnostiche, terapeutiche e riabilitative. In mancanza di tali informazioni, una pianificazione efficace degli interventi, sia a livello nazionale che locale, e una ripartizione equa degli investimenti e delle risorse risultano pressoché impossibili, ancor più nella definizione dei tempi adeguati per gli interventi.
La rete integrata dei servizi di NPIA anche con altri ambiti e servizi rimane a tutt'oggi un'ambiziosa velleità anche in quelle realtà più virtuose. **I modelli organizzativi proposti nel tempo soffrono della mancanza di continuità, aggiornamento, adeguamento e sostegno** (anche economico), e di adeguata valutazione e generalizzazione degli interventi dimostrati efficaci. Un esempio a tutt'oggi unico sia a livello nazionale che internazionale è il Progetto della regione Lombardia iniziato nel 2011 con l'obiettivo di garantire a tutti i bambini e adolescenti che accedono ad uno dei 18 Centri regionali di riferimento per l'ADHD (Disturbo da Deficit di Attenzione e Iperattività) un percorso diagnostico-terapeutico appropriato, condiviso e comune, sottoposto a valutazione continua (audit) sia dell'efficacia che dell'efficienza delle cure erogate[5]. I positivi risultati della creazione della nuova rete di cure, che prevede anche la partecipazione dei servizi territoriali di NPIA, della medicina del territorio e della scuola, supportano una messa a regime di quella che sinora è stata una sperimentazione e una sua possibile generalizzazione anche per altri disturbi in ambito regionale. L'iniziativa può inoltre rappresentare un utile esempio (da adattare e ottimizzare) anche per altre realtà regionali.
La partecipazione attiva e finalizzata dei genitori, degli insegnanti e dei medici e pediatri di famiglia è uno dei fattori che influiscono sugli esiti degli interventi delle diverse professionalità coinvolte nei percorsi di cura di disturbi complessi, ad alta prevalenza e ad elevato rischio di cronica disabilità, quali i disturbi neuropsichiatrici e neuropsichici

[2] *Ibidem.*
[3] Baranne, M.L. & Falissard B. (2018), Global burden of mental disorders among children aged 5–14 years. *Child Adolesc Psychiatry Ment Health*, 12: 19, disponibile su https://doi.org/10.1186/s13034-018-0225-4
[4] Ageranioti-Bélanger, S. et al. (2012), Behaviour disorders in children with an intellectual disability, *Paediatr Child Health*, 17(2): 84–88.
[5] Bonati M et al. (2019), Waiting times for diagnosis of attentiondeficit hyperactivity disorder in children and adolescents referred to Italian ADHD centers must be reduced. *BMC Health Research Services*, 19:673, disponibile su https://doi.org/10.1186/s12913-019-4524-0

dell'infanzia e della adolescenza. Troppo poco ancora si è fatto in proposito sia in ambito informativo che formativo lungo un percorso che prevede un accompagnamento nel tempo (per esempio nel passaggio all'età adulta[6]) e un'interazione e sostituzione di diverse competenze professionali (sociosanitarie).

Pertanto, alla luce delle osservazioni del Comitato ONU, il **Gruppo CRC raccomanda**:

1. **Al Ministero della Salute e alla Conferenza delle Regioni e delle Province Autonome** di istituire un osservatorio epidemiologico nazionale permanente della salute mentale in età evolutiva che possa monitorare in modo sistematico, continuo e appropriato i bisogni evasi e inevasi della popolazione;
2. **Alla Conferenza delle Regioni e delle Province Autonome e ai servizi di NPIA** di implementare le valutazioni di audit dei percorsi diagnostici, terapeutici e riabilitativi;
3. **Al Ministero della Salute, alla Conferenza delle Regioni e delle Province Autonome e ai servizi di NPIA** di attivare percorsi formativi mirati per gli operatori sociosanitari coinvolti nei percorsi di cura e iniziative e strumenti informativi per i pazienti, le famiglie, gli insegnati.

[6] Reale, L. et al. (2018), Transition to adult mental health services for young people with ADHD. *Journal of Attention Disorders*, 22(6) 601–608.

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016, N. 1077 del 02/02/2017 N. 1938 del 15/02/2019) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Percorsi diagnostico-terapeutici per l'ADHD*".

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