



NEWSLETTER



INDICE:

Dalle banche dati bibliografiche

Grazioli S, et al.

LIGHT UP ADHD: II NEUROPHARMACOLOGICAL EFFECTS MEASURED BY NEAR INFRARED SPECTROSCOPY: IS THERE A BIOMARKER?

J Affective Disord. 2019 Feb;244:100-06

pag. 2

Somma A, et al.

CONSTRUCT VALIDITY AND DIAGNOSTIC ACCURACY OF THE ITALIAN TRANSLATION OF THE 18-ITEM WORLD HEALTH ORGANIZATION ADULT ADHD SELF-REPORT SCALE (ASRS-18) ITALIAN TRANSLATION IN A SAMPLE OF COMMUNITY-DWELLING ADOLESCENTS.

Psychiatry Res. 2019 Mar;273:753-58

pag. 56

Segnalazione

Bonati M.

REGISTRI DI MALATTIA: STRUMENTI DINAMICI PER LA QUALITÀ DELLE CURE.

IL REGISTRO ADHD DELLA REGIONE LOMBARDIA

Epidemiol Prev 2019; 43 (1):104-105

pag. 62

BIBLIOGRAFIA ADHD APRILE 2019

Acta Med Port. 2019;32:195-201.

CLINICAL VALIDATION OF THE PORTUGUESE VERSION OF THE CHILDREN SLEEP HABITS QUESTIONNAIRE (CSHQ-PT) IN CHILDREN WITH SLEEP DISORDER AND ADHD.

Parreira AF, Martins A, Ribeiro F, et al.

Introduction: The Portuguese version of the Children's Sleep Habits Questionnaire showed adequate psychometric properties in a community sample but the American cut-off seemed inadequate. This study aimed to validate this questionnaire in clinical populations of children with sleep disorders and with attention deficit/ hyperactivity disorder.

Material and Methods: The study sample included 148 Portuguese children aged 2 to 10 years old that were divided in 3 groups: 1. Clinical group with sleep disorders (behavioral insomnias, parasomnias or sleep-related breathing disorders); 2. Clinical group with attention deficit/ hyperactivity disorder; 3. Control group. The sleep habits and sleep problems were evaluated using the Children's Sleep Habits Questionnaire. Sleep-related disorders were confirmed by polysomnography.

Results: The questionnaire's internal consistency (Cronbach) in the clinical sample (sleep disorders and attention deficit/ hyperactivity disorder) was 0.75 and ranged from 0.55 to 0.85 for the subscales. Children with sleep disorders and attention deficit/ hyperactivity disorder had a higher sleep disturbance index (full scale score) compared to the control group. The subscales presented significant differences between the subgroups with different sleep disorders showing discriminative validity. The receiver operating characteristic analysis of the sleep disturbance index comparing the sleep disorder and control sample determined a cut-off of 48 (sensitivity 0.83; specificity 0.69).

Discussion: Children with sleep disorders and attention deficit/ hyperactivity disorder evidenced higher Sleep Disturbance Index (full scale score) comparing to the control group. The subscales presented significant differences between the subgroups with different sleep disorders showing discriminative validity. **Conclusion:** The Portuguese version of the Children's Sleep Habits Questionnaire showed adequate psychometric properties for children with sleep disorders and/or attention deficit/ hyperactivity disorder. The cut-off value 48 is better adjusted for the Portuguese population

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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;11:107-11.

FAMILY-BASED ASSOCIATION STUDY ON FUNCTIONAL α -SYNUCLEIN POLYMORPHISMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gerlach M, Sharma M, Romanos M, et al.

Studies have strongly suggested a disturbed regulation of dopaminergic neurotransmission in attention-deficit/hyperactivity disorder (ADHD) and Parkinson's disease (PD). A genetic and phenotypic overlap between both disorders is discussed. A well-studied risk gene for PD is the gene coding for α -synuclein (SNCA). α -Synuclein, a protein located primarily in the presynaptic vesicles, has been suggested to play a role in the modulation of dopamine transporter (DAT) function. DAT is the target of psychostimulants for the treatment of ADHD and plays a key role in regulating the dopamine concentrations in the synaptic cleft. In our sample consisting of German families with children affected by ADHD, we tested for association of allelic variants of two functionally relevant polymorphisms of the α -synuclein gene (NACP-Rep1: 156 families, 232 children; rs356219: 195 families, 284 children) with ADHD. Transmission disequilibrium test analysis revealed no over-transmission for NACP-Rep1 (OR 1, pnom=1 padj=1) and rs356219 (OR 1.28; pnom = 0.288) in affected siblings. However, a subanalysis on trios with index children showed a nominal association of rs356219 with ADHD (OR 1.43, pnom=0.020), which survived Bonferroni correction (padj=0.039); again, no association for NACP-Rep1 (OR 0.8, p=0.317, padj=0.634) was found. In conclusion, we found in our pilot study a trend for an association of the rs356219 genotype in SNCA that may affect α -synuclein function and contribute to the aetiology of ADHD. In light of the small sample size of our study, the link between PD and ADHD through dopamine-related neurobiology warrants further investigations. Future studies on SNCA in large ADHD samples should focus on specified symptoms and traits, e.g. attentional capacities or emotional dysregulation

ADHD Atten Deficit Hyperact Disord. 2019;11:21-29.

PARENT-CLINICIAN AGREEMENT IN RATING THE PRESENCE AND SEVERITY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.

Nobel E, Brunnekreef JA, Schachar RJ, et al.

We determined the validity of a parent-report questionnaire as a research tool for rating attention-deficit/hyperactivity disorder (ADHD) symptoms in children. Using Cohen's kappa and Pearson correlation, we examined the agreement between parent reports of ADHD symptoms (using the Swanson, Nolan and Pelham Questionnaire-IV; SNAP-IV) and clinical judgment (using a semi-structured parent interview). Also, we explored factors that may be associated with the level of agreement, using regression analyses. We found moderate levels of agreement for severity of overall ADHD ($r = 0.43$) and for hyperactive-impulsive symptoms ($r = 0.54$), but no significant agreement for inattentive symptoms. On individual symptom level (range kappa = -0.05-0.22) and for the presence/absence of ADHD (kappa = 0.14), agreement was poor. Therefore, we conclude that parent-report questionnaires may be acceptable to rate the overall severity of ADHD symptoms in treatment effect studies, but not to detect the presence of ADHD in epidemiological studies

ADHD Atten Deficit Hyperact Disord. 2019;11:47-58.

REACTION TIME VARIABILITY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IS INCREASED REACTION TIME VARIABILITY SPECIFIC TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? TESTING PREDICTIONS FROM THE DEFAULT-MODE INTERFERENCE HYPOTHESIS.

Salum GA, Sato JR, Manfro AG, et al.

Increased reaction time variability (RTV) is one of the most replicable behavioral correlates of attention-deficit/hyperactivity disorder (ADHD). However, this may not be specific to ADHD but a more general marker of psychopathology. Here we compare RT variability in individuals with ADHD and those with other childhood internalizing and externalizing conditions both in terms of standard (i.e., the standard deviation of reaction time) and alternative indices that capture low-frequency oscillatory patterns in RT variations over time thought to mark periodic lapses of attention in ADHD. A total of 667 participants (6-12-áyears old) were classified

into non-overlapping diagnostic groups consisting of children with fear disorders ($n = 91$), distress disorders ($n = 56$), ADHD ($n = 103$), oppositional defiant or conduct disorder (ODD/CD; $n = 40$) and typically developing controls (TDC; $n = 377$). We used a simple two-choice reaction time task to measure reaction time. The strength of oscillations in RTs across the session was extracted using spectral analyses. Higher RTV was present in ADHD compared to all other disorder groups, effects that were equally strong across all frequency bands. Interestingly, we found that lower RTV to characterize ODD/CD relative to TDC, a finding that was more pronounced at lower frequencies. In general, our data support RTV as a specific marker of ADHD. RT variation across time in ADHD did not show periodicity in a specific frequency band, not supporting that ADHD RTV is the product of spontaneous periodic lapses of attention. Low-frequency oscillations may be particularly useful to differentiate ODD/CD from TDC

Advances in Integrative Medicine. 2019;6:S142-S143.

PATHWAYS TOWARDS AN INTEGRATIVE TREATMENT FOR ADHD AND IRRITABLE MOOD IN CHILDREN: UTILIZING PARTNERSHIPS IN A MULTISITE, RANDOMIZED CONTROLLED TRIAL.

Johnstone J.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is impairing, common, and often leads to poor long-term outcomes, even with standard treatment. Impairment is driven by emotion dysregulation, irritability and aggression, as much as by core ADHD symptoms. Seeking to address symptoms of the hypothesized irritable ADHD subtype, while conducting a rigorous study, the Micronutrients in ADHD Youth, the MADDY study ($n = 135$ at 3 sites) partners clinical outcomes with biological mechanisms to understand whether this intervention works, and for whom.

Methods: Implementation of the first North American, three-site, sixteen-week trial: eight weeks randomized controlled trial (RCT), followed by eight weeks open label (OL), of micronutrients (vitamins and minerals) for children, 6-12 years old, with ADHD and irritable mood will be discussed.

Measures include clinical: Child and Adolescent Symptom Inventory -5 (CASI-5), Patient-Reported Outcomes Measurement Information Systems (PROMIS), and biological samples: blood, hair, urine, stool, saliva.

Results: Comparing the OL data (weeks 8 to 16, following the RCT) on ADHD and irritability symptom counts, using a Wilcoxon-Rank Sum Test, a significant decrease in symptoms was found for inattention ($p < 0.001$), hyperactivity (0.001), oppositionality (0.001), and dysregulated mood (0.001) ($n = 27$). Child anger, reported using the PROMIS by parent and child, improved in 79% and 74% of cases, respectively, during the OL phase.

Conclusion: Supplementation with micronutrients in children with ADHD and irritable mood showed a preliminary trend towards benefit for classic ADHD symptoms, as well as irritability and anger. These trends require confirmation in the RCT phase, following full sample analyses. The study described in my submission has been prospectively registered and has a Federal Drug Administration (FDA) Investigation New Drug (IND) application.

Trial registration: NCT03252522. Registered 26 July 2017

Am J Occup Ther. 2018 Nov;72:7206205020p1-p8.

PERCEPTION OF AVERSIVE AUDITORY STIMULI IS DIFFERENT IN SENSORY MODULATION DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mazor-Karsenty T, Shalev L, Parush S, et al.

This study examined whether sensory modulation disorder-sensory overresponsivity (SMD-SOR) and attention deficit hyperactivity disorder (ADHD) have a significant effect on the perception of aversive auditory stimuli. Participants were 66 young adult women. The diagnosis of SOR was made using the Sensory Responsiveness Questionnaire, and ADHD was diagnosed by a qualified psychiatrist or neurologist using criteria from the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.). Participants were presented with the Battery of Aversiveness to Sounds, short presentations of daily life sounds, and rated

each sound stimulus verbally according to its perceived unpleasantness. Participants with SOR rated low-intensity aversive sounds as significantly more aversive than participants without SOR. High-intensity sounds obtained a marginal significant difference exclusively in participants with ADHD. The perception of aversive auditory stimuli in adults with SOR appears to be unique and different than the profile of adults with ADHD

Am J Epidemiol. 2019;188:768-75.

USE OF NEGATIVE CONTROL EXPOSURE ANALYSIS TO EVALUATE CONFOUNDING: AN EXAMPLE OF ACETAMINOPHEN EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN NURSES' HEALTH STUDY II.
Liew Z, Kioumourtzoglou M-A, Roberts AL, et al.

Frequent maternal use of acetaminophen in pregnancy has been linked to attention-deficit/hyperactivity disorder (ADHD) in children, but concerns regarding uncontrolled confounding remain. In this article, we illustrate use of the negative control exposure (NCE) approach to evaluate uncontrolled confounding bias in observational studies on pregnancy drug safety and explain the causal assumptions behind the method. We conducted an NCE analysis and evaluated the associations between maternal acetaminophen use during different exposure periods and ADHD among 8,856 children born in 1993-2005 to women enrolled in the Nurses' Health Study II cohort. Information on regular maternal acetaminophen use was collected prospectively in biennial questionnaires. A total of 721 children (8.1%) in the cohort had been diagnosed with ADHD as reported by the mothers. Our NCE analysis suggested that only acetaminophen use at the time of pregnancy was associated with childhood ADHD (odds ratio = 1.34, 95% confidence interval: 1.05, 1.72), and the effect estimates for the 2 NCE periods (about 4 years before and 4 years after the pregnancy) were null. Our findings corroborate those of prior reports suggesting that prenatal acetaminophen exposure may influence neurodevelopment. The lack of an association between acetaminophen use in the pre-and postpregnancy exposure periods and ADHD provides assurance that uncontrolled time-invariant factors do not explain this association

Asia-Pacific Psychiatry. 2019.

A STUDY ON THE SCHOOL VIOLENCE EXPERIENCE OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN THE CONTEXT OF BULLYING.

Huh S-Y, Kim S-G, Lee J-S, et al.

Introduction: School violence causes harmful effects to victims. Harmful effects are likely to persist into adulthood. There are many studies about the relationship between attention-deficit hyperactivity disorder (ADHD) and school violence. But, there are few comparative studies dividing groups by the context of bullying and by the school grade. Therefore, this study will identify the differences between general students and patients with ADHD under treatment, creating two groups (one with experience of the perpetration of violence and one with victimization).

Methods: This study was conducted by questionnaires that dealt with experiences of being a bully and being bullied at school in the past year as six items each. A 5-point Likert scale was used. The ADHD group was 49, and the general students group was 245. The data were compared using the chi-squared test. Statistical analysis was performed using SPSS version 24, with statistical significance at $P < .05$.

Results: The ADHD group was significantly high who reported severely beating other people than the general group. Likewise, ADHD group who reported threatening other people was significantly higher than in the general group. However, for the remaining items, there was no significant difference between the ADHD group and the general student group.

Discussion: Previous studies suggested that ADHD symptoms are major causes of both bullying and being the victim of bullying. However, in this study, ADHD patients have more being the victim of bullying experiences than general students. Further, a well-designed study will be needed to accurately evaluate the relationship between school violence and ADHD

Behav Brain Res. 2019;367:117-27.

RESPONSE CONTROL CORRELATES OF ANOMALOUS BASAL GANGLIA MORPHOLOGY IN BOYS, BUT NOT GIRLS, WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Tang X, Seymour KE, Crocetti D, et al.

Anomalous basal ganglia morphology may contribute to deficient motor response control in children with attention-deficit/hyperactivity disorder (ADHD). This study expands upon recent evidence of sex differences in subcortical morphology and motor response control deficits among children with ADHD to examine basal ganglia volume and shape in relation to motor response control. Participants included 81Çô12 year-old children with ADHD (n = 52, 21 girls) and typically developing (TD) controls (n = 45, 19 girls). High resolution T1-weighted 3D MPRAGE images covering the whole brain were acquired for all participants on a 3 T scanner. Participants performed two computer-based go/no-go tasks that differed in the extent to which working memory was necessary to guide response selection. Shape-based morphometric analyses were performed in addition to traditional volumetric comparisons and correlations with measures of motor response control were examined. Boys with ADHD consistently demonstrated increased commission error rate and response variability, regardless of task demands, suggesting broad response control deficits. In contrast, response control deficits among girls with ADHD varied depending on task demands and performance measures. Volumetric reductions and inward deformation (compression) on the dorsal surface of the globus pallidus and within subregions of the putamen receiving projections from limbic, executive and motor cortices were observed in boys, but not girls, with ADHD relative to TD children. Mediation analyses revealed that putamen and globus pallidus volumes mediated the relationship between diagnosis and commission error rate. Furthermore, reduced volumes of these structures and localized inward deformation within executive and motor circuits correlated with poorer response control, particularly under conditions of increased cognitive load. These findings suggest that anomalous basal ganglia morphology is related to impaired motor response control among boys with ADHD

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Biochemical and Biophysical Research Communications. 2019.

POSITIVE EFFECT OF EXOGENOUS BRAIN-DERIVED NEUROTROPHIC FACTOR ON IMPAIRED NEURITE DEVELOPMENT AND MITOCHONDRIAL FUNCTION IN DOPAMINERGIC NEURONS DERIVED FROM DENTAL PULP STEM CELLS FROM CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Nguyen Nguyen HT, Kato H, Sato H, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders and is characterized by impaired attention, hyperactivity, and impulsivity. While multiple etiologies are implicated in ADHD, its underlying mechanism(s) remain unclear. Although previous studies have suggested dysregulation of dopaminergic signals, mitochondria, and brain-derived neurotrophic factor (BDNF) in ADHD, few studies have reported these associations directly. Stem cells from human exfoliated deciduous teeth (SHED) can efficiently differentiate into dopaminergic neurons (DNs) and are thus a useful disease-specific cellular model for the study of neurodevelopmental disorders associated with DN dysfunction. This study aimed to elucidate the relationships between DN, mitochondria, and BDNF in ADHD by analyzing DN differentiated from SHED obtained from three boys with ADHD and comparing them to those from three typically developing boys. In the absence of exogenous BDNF in the cell culture media, DN derived from boys with ADHD (ADHD-DNs) exhibited impaired neurite outgrowth and branching, decreased mitochondrial mass in neurites, and abnormal intracellular ATP levels. In addition, BDNF mRNA was significantly decreased in ADHD-DNs. Supplementation with BDNF, however, significantly improved neurite development and mitochondrial function in ADHD-DNs. These results suggest that ADHD-DNs may have impaired neurite development and mitochondrial function associated with insufficient production of BDNF, which may be improved by exogenous BDNF supplementation. Findings such as these, from patient-derived SHED, may contribute to the future development of treatment strategies for aberrant dopaminergic signaling, mitochondrial functioning, and BDNF levels implicated in ADHD pathogenesis

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Bipolar Disord. 2019;21:118-19.

METACOGNITION-THANATOLOGY AND THE SCIENTIFIC EVIDENCE ON GRIEF CARE-TRAUMA EXPERIENCE TO PREVENT MENTAL ILLNESS.

Hirai T.

Nakayama and Yotsumoto (2012) [1] give the following description of metacognition: Metacognition is a notion that spread in the 1970s, and the term of 'Metacognition' was first used by J. H. Flavell (1976 p. 232) [2]: Metacognition refers to one's knowledge concerning one's own cognitive processes or anything related to them, e.g., the learning-relevant properties of information or data. For example, I am engaging in metacognition if I notice that I am having more trouble learning A than B; if it strikes me that I should double check C before accepting it as fact. Monitoring of one's cognitive activity is the fundamental basis of metacognition, and ranges from basic sensory responses to high-order cognitive function comprising complex combinations of neural procedures until a behavioral goal is achieved. Scrutinizing monitored information consciously or unconsciously also makes it possible to control a variety of cognitive activities. Some examples include making the appropriate judgment about future behavior by comparing ability of the self to task difficulty, selecting the optimal strategies or tools adapted to the situation, or performing monitoring itself efficiently. These adaptive cognitive activities are supported by the abilities to understand and execute the actions that should be taken based on knowledge and determine when they should be taken in order to solve complex problems [3]. Cultural studies have shown that instances of metacognition are found commonly throughout cultures, suggesting that metacognition is a universally effective ability for human survival and social life [4]. The initial descriptions of metacognition go back to Greek philosopher Aristotle's works *De Anima* and *Parva Naturalia*. Metacognitive studies in various fields: Studies have been conducted in the fields of developmental and educational psychology, primarily through the perspective of evaluating task execution abilities of children or for improving learning abilities. Studies on self-regulation led by Piaget are based on the notion that humans actively make adjustments or learn [5]. Vygotsky's notion of metacognition took development from the development of language. According to his theory, children first use words to others (external speech), then as they grow, they demonstrate that they can moderate their thoughts and behaviors through internal speech, and that the transition from external to internal speech is the manifestation of awareness of their thoughts. Since metacognition is the awareness of one's own thoughts, it is used in psychotherapy as well. Cognitive therapy seeks to improve emotional disorder by first recognizing it as a disorder of thought, and correcting it. Many studies in experimental psychology focus on the qualitative differences in metacognition between monitoring (judgment related to one's own memory) and control (linking judgments to actions). In cognitive neuroscience, metacognitive monitoring and control are identified as functions of the prefrontal cortex that receive input and feedback from other cortical areas. Metacognition research is conducted in the fields of artificial intelligence [6] and modeling as well. Neuronal basis: Case studies of trauma patients suggest that the prefrontal cortex is deeply involved in meta-memory or meta-level cognitive processes [7]. These incorporate recording methods of neuronal activity during execution of tasks and related secondary (metacognitive) behaviors, and in animals other than humans, methods to record electrical activity in independent cells is used. However, the objectives of these methods were to distinguish between the neural expressions related to metacognitive processes from those related to actions themselves [8]. In case studies on neuropsychiatric diseases, there are many cases in which the insights on the patient's own pathologies do not match their insight on other areas at all. fMRI studies on patients with schizophrenia have reported that unlike healthy individuals, patients with schizophrenia show no activity in the anterior medial prefrontal cortex during self-examination, noting the relationship between the medial prefrontal cortex and metacognition [9]. Metacognitive regulation: Metacognitive regulation consists of metacognitive monitoring such as awareness, sensations, predictions, inspection and evaluation, and metacognitive control such as goal-setting, planning and revision (Nakayama, Yotsumoto 2012). Nurses routinely become aware and reflect in the clinical setting, and studies on metacognition suggest scientific evidence of metacognitive function in the awareness and reflections of nurses. Nursing care plans are cycles of planning, revising, and evaluation. The communication techniques that nurses use in speaking to the patients include psychiatric therapy using Socratic questioning and Buddha's questions. Self-distancing proposed by Viktor Emil Frankl enabled (Figure Presented) drawing out the patients' anxieties, and mind sequencing allowed the patient himself to visually recognize changes to his cognition by peering at it. This refers to the function of scrutinizing reality here, in the present, or the other self that becomes aware of one's own thoughts, as described by metacognitive function. The following figures are presented to show the

therapeutic effects of the steps of creating mind sequences as given by nurses. Toyomi Hirai is the first to make this link between mind sequences and cognition. Case: Boy A with ADHD, 10 years old The child's suffering is indescribable, because he is living with these serious conflicts. When asked who he spoke to when he became anxious again, the 10-year-old Child A responded that he would Talk about it only to god. Japanese houses traditionally had a shinto shrine and speaking to the deceased and praying was part of daily life. Self-awareness, that is, metacognitive processes were being utilized through communicating with the deceased or the other self. Intentional and therapeutic encouragement of these behaviors by a nurse to promote changes in cognition is what comprises cognitive therapy. Grief (Figure Presented) care is a treatment that actively promotes metacognition, and mind sequences suggested that they can contribute to the treatment of patients with mental disorders, and more generally, of people with psychological pain. As illustrated in Fig. 3, one realizes that positive memories are better preserved than negative memories through cultivating the ability to monitor oneself. fMRI imaging results also revealed that hippocampal activity was involved in the preservation of positive memories [10]. The evidence elucidated by Moriguchi was visualized and validated through mind sequences

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Bipolar Disord. 2019;21:59-60.

DO SYMPTOMS OF ADHD AND HYPOMANIA SHARE GENETIC AND ENVIRONMENTAL INFLUENCES IN YOUNG PEOPLE? A LONGITUDINAL TWIN STUDY.

Hosang GM, Lichtenstein P, Ronald A, et al.

Objectives: Attention Deficit Hyperactivity Disorder [ADHD] and bipolar disorder are highly comorbid and their symptoms significantly correlated. But the shared origins that account for the co-occurrence of these two phenotypes are largely unknown. This study aimed to determine the degree genetic and environmental influences on ADHD across childhood and adolescence accounted for adolescent hypomania in a large longitudinal twin study.

Methods: Over 13,000 twin pairs participated in an ongoing prospective study of Swedish youths at ages 9/12, over 4,000 were followed up at age 15 and over 3,000 at 18. ADHD and hypomanic symptoms were assessed using parent-rated instruments. The association between ADHD symptoms across childhood and adolescence and adolescent hypomania was investigated using generalized estimating equations. A multivariate twin design was used to assess the extent to which genetic and environmental influences on ADHD account for hypomania.

Results: ADHD and hypomanic symptoms were significantly correlated (+) [95% confidence intervals] (hypomania at 15 years: 0.30 [0.26-0.34]; hypomania at 18 years: 0.19 [0.16-0.22]), especially for the hyperactivity-impulsivity ADHD symptom domain (hypomania at 15 years: 0.53 [0.46-0.60]; hypomania at 18 years: 0.36 [0.30-0.42]), relative to inattention (hypomania at 15 years: 0.40 [0.34-0.47]; hypomania at 18 years: 0.24 [0.19-0.29]). Between 26%-28% of the genetic influences on ADHD accounted for hypomania with higher estimates detected for hyperactivity-impulsivity (23%-38%) compared to inattention (16%-29%). Environmental influences were found to play a negligible role in this context.

Conclusions: Up to a third of the genetic influences for ADHD traits across childhood and adolescence accounted for adolescent hypomania

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Bipolar Disord. 2019;21:18.

DO SHARED GENETIC FACTORS EXPLAIN THE PREDICTION OF BIPOLAR DISORDER BY CHILDHOOD PSYCHIATRIC SYMPTOMS?

Middeldorp CM, Akingbuwa O, Jarvelin M-R, et al.

Adult psychiatric disorders can be preceded by a broad range of childhood psychiatric symptoms. For schizophrenia, it has been suggested that this association is due to shared genetic risk factors. This is less well established for bipolar disorder. Given the large increase in genetic variants associated with bipolar disorder and the large increase in available genotypes in individuals with longitudinal data on childhood psychiatric symptoms, it is timely to test genetic associations. Comparing the genetic associations for several

adult psychiatric and related traits is also of relevance, as there is a large overlap in genetic variants influencing these phenotypes. Polygenic risk scores (PRS) are calculated based on the most recent results from Genome-Wide Association Meta-Analyses for schizophrenia, depression, bipolar disorder, wellbeing, neuroticism, BMI, height, educational attainment and insomnia. These risk scores reflect an individual's genetic vulnerability for a particular trait. The associations between the different PRS with internalizing, ADHD and social problems measured between age 7 and age 18 will be analysed in the cohorts participating in the CAPICE consortium (<http://www.capice-project.eu/>), total N = ~40,000. Preliminary analyses in the Netherlands Twin Register showed significant genetic associations between bipolar disorder PRS and internalizing problems, but no significant predictions for ADHD and social problems. This pattern of results was similar to the effects of schizophrenia PRS. In contrast, depression, neuroticism and wellbeing were also related to ADHD and social problems. Meta-regression analyses based on the results in all cohorts will also show whether these associations depend on age

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BMC Complement Altern Med. 2019 Mar;19:60.

MANUAL THERAPY FOR THE PEDIATRIC POPULATION: A SYSTEMATIC REVIEW.

Parnell PC, Gleberzon B, Carleo B, et al.

BACKGROUND: This systematic review evaluates the use of manual therapy for clinical conditions in the pediatric population, assesses the methodological quality of the studies found, and synthesizes findings based on health condition. We also assessed the reporting of adverse events within the included studies and compared our conclusions to those of the UK Update report.

METHODS: Six databases were searched using the following inclusion criteria: children under the age of 18 years old; treatment using manual therapy; any type of healthcare profession; published between 2001 and March 31, 2018; and English. Case reports were excluded from our study. Reference tracking was performed on six published relevant systematic reviews to find any missed article. Each study that met the inclusion criteria was screened by two authors to: (i) determine its suitability for inclusion, (ii) extract data, and (iii) assess quality of study.

RESULTS: Of the 3563 articles identified, 165 full articles were screened, and 50 studies met the inclusion criteria. Twenty-six articles were included in prior reviews with 24 new studies identified. Eighteen studies were judged to be of high quality. Conditions evaluated were: attention deficit hyperactivity disorder (ADHD), autism, asthma, cerebral palsy, clubfoot, constipation, cranial asymmetry, cuboid syndrome, headache, infantile colic, low back pain, obstructive apnea, otitis media, pediatric dysfunctional voiding, pediatric nocturnal enuresis, postural asymmetry, preterm infants, pulled elbow, suboptimal infant breastfeeding, scoliosis, suboptimal infant breastfeeding, temporomandibular dysfunction, torticollis, and upper cervical dysfunction. Musculoskeletal conditions, including low back pain and headache, were evaluated in seven studies. Twenty studies reported adverse events, which were transient and mild to moderate in severity.

CONCLUSIONS: Fifty studies investigated the clinical effects of manual therapies for a wide variety of pediatric conditions. Moderate-positive overall assessment was found for 3 conditions: low back pain, pulled elbow, and premature infants. Inconclusive unfavorable outcomes were found for 2 conditions: scoliosis (OMT) and torticollis (MT). All other condition's overall assessments were either inconclusive favorable or unclear. Adverse events were uncommonly reported. More robust clinical trials in this area of healthcare are needed.

TRIAL REGISTRATION: PROSPERA registration number: CRD42018091835

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BMC Psychiatry. 2019;19.

PREVALENCE OF BEHAVIORAL DISORDERS AND ATTENTION DEFICIT/HYPERACTIVE DISORDER AMONG SCHOOL GOING CHILDREN IN SOUTHWESTERN UGANDA.

Kivumbi A, Byansi W, Damulira C, et al.

Background: Disruptive Behavioral Disorders (DBDs) and Attention Deficit/Hyperactivity Disorder (ADHD) are chronic, impairing, and costly child and adolescent mental health challenges which, when untreated, can

result in disruptions in school performance, friendships and family relations. Yet, there is dearth of prevalence data on child and adolescent behavioral challenges within sub-Saharan Africa, including Uganda. This study aims to estimate the prevalence rate of behavioral challenges and ADHD among young school going children and early adolescents (ages 8-13 at study enrollment), utilizing a school-based sample in southwest Uganda.

Methods: We present screening results from a 5-year scale-up study titled SMART Africa-Uganda (2016-2021), set across 30 public primary schools located in the greater Masaka region in Uganda, a region heavily impacted by poverty and HIV/AIDS. Specifically, we draw on screening data from caregivers of 2434 children that used well-established standardized measures that had been pre-tested in the region. These were: 1) oppositional defiant disorder (ODD) and conduct disorder (CD) subscales of the Disruptive Behavior Disorders (DBD) scale; and 2) the Iowa Connors and Impairment scales. Slightly over half of the children in the sample were female (52%), with a mean age of 10.27 years.

Results: Of the 2434 participants screened for disruptive behaviors: 1) 6% (n = 136) scored positive on ODD and 2% (n = 42) scored positive on CD subscales of the DBD scale; 2) 9.61% (n = 234), and 2.67% (n = 65) were reported to have elevated symptoms of ODD and ADHD on the Iowa Connors caregiver report scale respectively. Twenty-five percent (n = 586) of children were described by their caregivers as having experienced some form of impairment in at least four domains of the Impairment scale.

Conclusion: The results indicate the presence of behavioral challenges and ADHD among school going children, aged 8-13 years, in Uganda. Given the negative outcomes associated with behavioral challenges as children transition to adolescence and adulthood, detecting these emerging behavioral challenges early is critical in developing appropriate interventions. School settings could be considered as one of the contextually-relevant, culturally-appropriate, and non-stigmatizing venues to implement screening procedures and to detect emerging behavioral challenges and to make necessary referrals

Brain Dev. 2019.

AGE-RELATED DIFFERENCES IN FRONTAL LOBE FUNCTION IN CHILDREN WITH ADHD.

Yasumura A, Omori M, Fukuda A, et al.

Background: The neural correlates of executive function disorders are thought to be predominantly localized within the prefrontal cortex (PFC). However, no study to date has investigated changes in this system across different age groups in children with attention deficit hyperactivity disorder (ADHD). Thus, this study aimed to explore changes in PFC function in children with ADHD.

Methods: Study participants included typically developing (TD) children (n = 140) and children with ADHD (n = 67) of primary school age. Behavioral executive functions and their neural basis were evaluated between the TD children and children with ADHD and also across different age periods (younger and older children). To examine executive function, inhibitory control was assessed using the reverse Stroop task, and PFC near-infrared spectroscopic measurements were used to investigate the neural mechanisms involved.

Results: Both ADHD symptoms and the ability to inhibit color interference improved with age. Compared to TD children, children with ADHD demonstrated decreased activation of the right and middle PFC across all age groups. Interestingly, the left PFC appeared to play a compensatory role.

Conclusion: Children with ADHD exhibited changes in PFC function that varied with age. Longitudinal studies are required to assess the potential of using PFC function as an early biomarker of ADHD

Brain Topogr. 2019 Mar;32:286-94.

TIME EFFECTS ON RESTING EEG IN CHILDREN WITH/WITHOUT AD/HD.

Zhang DW, Johnstone SJ, Li H, et al.

In this study we extend on behavioural evidence to examine the effect of time on EEG measures related to arousal and emotion/motivation in children with/without AD/HD. Thirty children with AD/HD and 30 age- and sex-matched controls participated. EEG was recorded during an eyes-closed resting condition and divided into three 2.5 min blocks after pre-processing. Time effects for absolute and relative alpha activity were found in healthy controls; these effects did not interact with AD/HD status. Interactions between time and AD/HD

status were found for absolute theta, relative theta, and theta/beta ratio (TBR), with these EEG indices increasing over time in children with AD/HD. Moreover, IQ played a role in the interaction between time and AD/HD status. These results are consistent with predictions from both the optimal stimulation model and the delay aversion model, and suggest important methodological considerations for future EEG research in children with/without AD/HD

Child's Nerv Syst. 2018;34:1353-59.

RISK OF MILD HEAD INJURY IN PRESCHOOL CHILDREN: RELATIONSHIP TO ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS.

Altun H, Altun.

AIM: To investigate whether there is an association between mild head injury (MHI) and attention deficit hyperactivity disorder (ADHD) symptoms in preschool children.

METHODS: The study included a patient group of 30 children aged 3-6 years with mild head trauma and a control group of 30 healthy and age- and sex-matched children. The symptoms of ADHD were evaluated using the Conners' Parent Rating Scale-Revised Long (CPRS-RL) form.

RESULTS: The mean age was 4.73 ± 1.13 years in the patient group and 4.65 ± 0.99 years in the control group. No significant differences were determined between the groups in terms of age, gender, parents' age and education ($p > 0.05$). The total subscale points as reported by the parents of the children with MHI were significantly higher than those for the control group in terms of the following subscales: oppositional, cognitive problems/inattention, hyperactivity, social problems, ADHD index, Conners' Global Index (CGI)-Irritability-Impulsiveness, CGI-Emotional Lability, CGI-Total and DSM-IV ADHD symptoms ($p < 0.05$). A history of previous trauma treated in emergency services was determined in eight of the 30 patients (26.7%).

CONCLUSIONS: The findings of this study suggest that preschool children with MHI have more pre-injury ADHD symptoms and oppositional and emotional-behavioural symptoms than healthy children without trauma. Clinicians should screen children with MHI for ADHD symptoms and refer them for treatment when necessary. Evaluation of children presenting with MHI by a child psychiatrist may prevent repetition of injuries

Child Adolesc Ment Health. 2019;24:133-41.

INVESTIGATING THE AGREEMENT BETWEEN THE CLINICIAN AND RESEARCH DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND HOW IT CHANGES OVER TIME; A CLINICAL COHORT STUDY.

Longridge R, Norman S, Henley W, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common reason for referral to Child and Adolescent Mental Health Services (CAMHS), but families experience long delays between first professional contact and diagnosis, which risks development of secondary impairments. This study explores the agreement between clinician and research diagnoses of ADHD among children attending CAMHS, and their access to interventions. From the limited literature, we anticipated fluctuation and delays, but no other study has focused prospectively on ADHD diagnoses.

Methods: This was a secondary analysis of a cohort of children attending two CAMHS between 2006 and 2009. The sample included 288 consecutive referrals of children aged between 5 and 11-áyears. Parents and teachers completed the Development and Well-Being Assessment (DAWBA) when the child was recruited to the study, which provided the research diagnosis of ADHD from the baseline. Clinicians reported no, possible, or definite diagnosis of ADHD and interventions provided at 6-monthly intervals for up to 2-áyears while the child attended CAMHS. We assessed agreement between the diagnoses using Kendall's Tau-B.

Results: Of the 101 children with a research diagnosis of ADHD, 26 received a definite clinician diagnosis during 2-year follow-up, and 47 received a possible clinician diagnosis. The chance-corrected agreement was poor at all time points (Kendall's Tau-B 0.14-0.48). Clinician diagnoses were unstable, particularly if possible ADHD was recorded at the initial assessment. Of those with a research diagnosis, 15 were prescribed medication and 11 were offered parent training.

Conclusions: The use of standardised-diagnostic assessments could reduce diagnostic uncertainty and increase access to evidence-based interventions

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Child Neuropsychol. 2019.

BRIEF REPORT: RELATIONSHIP BETWEEN PERFORMANCE TESTING AND PARENT REPORT OF ATTENTION AND EXECUTIVE FUNCTIONING PROFILES IN CHILDREN FOLLOWING PERINATAL ARTERIAL ISCHEMIC STROKE.

Krivitzky L, Bosenbark DD, Ichord R, et al.

Children with perinatal arterial ischemic stroke (PAIS) have increased rates of attention and executive functioning (EF) weaknesses. Research in other pediatric disorders has documented poor consistency between parent report of these skills and performance-based measures. We compared these data sources in children with PAIS. Forty full-term (≥37 weeks) children ages 3-16 (median = 7.2 years; 58% male) with PAIS completed neuropsychological testing and composite scores were created for seven attention and EF domains (Processing Speed; Attention; Working Memory; Verbal Retrieval; Inhibitory Control; Flexibility/Shifting; Planning). Parents completed "real-world" functioning questionnaires (ADHD Rating Scale-IV, BRIEF). Correlational analysis were used to compare parent and performance measures. Correlations between ADHD Rating Scale-IV scores and the performance-based Attention and Inhibition composite scores were nonsignificant. Significant negative correlations were found between the BRIEF GEC and performance-based Verbal Retrieval and Processing Speed composites, but remaining GEC/composite comparisons were nonsignificant. Analyses between parent report BRIEF index scores and the corresponding performance-based domain identified one significant negative correlation between the BRIEF Working Memory Index and the Working Memory composite score. While children with PAIS demonstrate difficulties in attention and EF on both parent report and performance measures, little significance was found in comparisons of these two types of measures. There may be several explanations for this dissociation: measures assessing different aspects of the same underlying construct; performance-based measures lacking ecological validity; and parents underestimating/underreporting their child's deficits. Thus, multiple sources of informant and performance data are necessary to make more accurate conclusions about functioning in these domains

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Child Psychiatry Hum Dev. 2019 Feb;50:35-44.

FATHERS WITH CHILDHOOD ADHD, PARENTING, AND THEIR YOUNG CHILDREN'S BEHAVIOR: OFFSPRING OF THE PITTSBURGH ADHD LONGITUDINAL STUDY (PALS).

Joseph HM, Kennedy TM, Gnagy EM, et al.

Despite high heritability, no research has followed children with ADHD to parenthood to study their offspring and parenting behaviors. Given greater prevalence of ADHD in males and lack of research involving fathers, this study evaluated offspring of fathers with and without ADHD histories for ADHD and disruptive behavior and compared fathers' parenting behaviors. Male fathers (N = 29) from the Pittsburgh ADHD Longitudinal Study (PALS) participated with their preschool-aged offspring. Fathers completed self-reported measures, and father-child dyads completed an interaction task. ADHD offspring had elevated ADHD symptoms and behavior dysregulation. All fathers displayed positive parenting. ADHD fathers reported lower supportive responses to their child's negative emotions than comparison fathers, yet rated their parenting as more efficacious. ADHD offspring were distinguishable as early as age 3; thus, earlier diagnosis and intervention may be feasible for this at-risk population. Future research should investigate the acceptability and efficacy of parent training for fathers with ADHD

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Clin Neuropharmacol. 2019;42:55-56.

ARIPIPRAZOLE-INDUCED HOARSENESS: A CASE REPORT.

Işık Ü, Çam Ray P.

Objectives Aripiprazole is an atypical antipsychotic drug that is commonly used in children and adolescents.

Methods The most common adverse effects of aripiprazole include fatigue, nausea, increased appetite, headache, sedation, and somnolence.

Results To our knowledge, there are no data regarding aripiprazole-induced hoarseness in the existing literature.

Conclusions We present a case of a preschool boy with attention-deficit/hyperactivity disorder and oppositional defiant disorder who displayed hoarseness after aripiprazole therapy

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Cortex. 2019;117:96-110.

OSCILLATORY NEURAL NETWORKS UNDERLYING RESTING-STATE, ATTENTIONAL CONTROL AND SOCIAL COGNITION TASK CONDITIONS IN CHILDREN WITH ASD, ADHD AND ASD+ADHD.

Shephard E, Tye C, Ashwood KL, et al.

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are common and impairing neurodevelopmental disorders that frequently co-occur. The neurobiological mechanisms involved in ASD and ADHD are not fully understood. However, alterations in large-scale neural networks have been proposed as core deficits in both ASD and ADHD and may help to disentangle the neurobiological basis of these disorders and their co-occurrence. In this study, we examined similarities and differences in large-scale oscillatory neural networks between boys aged 8-13 years with ASD (n = 19), ADHD (n = 18), ASD + ADHD (n = 29) and typical development (Controls, n = 26). Oscillatory neural networks were computed using graph-theoretical methods from electroencephalographic (EEG) data collected during an eyes-open resting-state and attentional control and social cognition tasks in which we previously reported disorder-specific atypicalities in oscillatory power and event-related potentials (ERPs). We found that children with ASD showed significant hypoconnectivity in large-scale networks during all three task conditions compared to children without ASD. In contrast, children with ADHD showed significant hyperconnectivity in large-scale networks during the attentional control and social cognition tasks, but not during the resting-state, compared to children without ADHD. Children with co-occurring ASD + ADHD did not differ from children with ASD when paired with this group and vice versa when paired with the ADHD group, indicating that these children showed both ASD-like hypoconnectivity and ADHD-like hyperconnectivity. Our findings suggest that ASD and ADHD are associated with distinct alterations in large-scale oscillatory networks, and these atypicalities present together in children with both disorders. These alterations appear to be task-independent in ASD but task-related in ADHD, and may underlie other neurocognitive atypicalities in these disorders

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Cyberpsychol Behav Soc Netw. 2019 Mar;22:198-204.

DEVELOPMENT OF VIRTUAL REALITY CONTINUOUS PERFORMANCE TEST UTILIZING SOCIAL CUES FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Eom H, Kim KK, Lee S, et al.

Virtual reality (VR) neuropsychological assessments have the potential for the ecological measurement of attention. We analyzed the newly developed VR continuous performance test (VR-CPT) for Korean children with attention-deficit/hyperactivity disorder (ADHD) and typically developing children (TDC). To identify specific features of a virtual environment that influence the attention performance of children, we investigated whether the presence of a virtual teacher and social cues in the VR environment affects their attention performance. A total of 38 participants (18 TDC and 20 ADHD children and adolescents) were recruited for VR-CPT testing. Bivariate correlational analysis was conducted to examine the associations between the results of the VR-CPT and ADHD questionnaires to determine the capacity of VR-CPT to mirror real-life attention behaviors. Mixed-design analysis of variables was conducted to compare the effects of the social aspects of the VR-CPT on attention performance in groups. There were significant associations between

ADHD rating scores and the omission error, commission error, reaction time (RT), reaction time variability (RTV), and total accuracy of the VR-CPT in the ADHD group. In addition, the ADHD group exhibited comparable performance with the TDC group for all measures of the VR-CPT. Also there seemed to be a trend of decreasing RTV when a virtual teacher with social cues was present compared with the equipment control condition in the ADHD group. Performance in the VR-CPT program was associated with behavioral measures of ADHD symptoms. Adding social aspects to a VR environment commonly encountered by children and adolescents has the potential to make a difference in the attention performance of youths with ADHD

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Dtsch Apoth Ztg. 2018;158.

AMPHETAMINES FOR ADULTS, METHYLPHENIDATE FOR CHILDREN: AGE-APPROPRIATE ADHD THERAPY.
Schmiedel K.

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Dev Neuropsychol. 2019 Mar;44:189-202.

TEST OF EVERYDAY ATTENTION FOR CHILDREN (TEA-CH): GREEK NORMATIVE DATA AND DISCRIMINATIVE VALIDITY FOR CHILDREN WITH COMBINED TYPE OF ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Malegiannaki AC, Aretouli E, Metallidou P, et al.

We examined the utility of the Test of Everyday Attention for Children (TEA-Ch) for Greek children. Discrete and regression-based norms, controlling for demographic characteristics and intelligence, were derived from the performance of 172 children. We also assessed the ability of the TEA-Ch to differentiate children with ADHD-Combined Type (ADHD-C) from healthy matched peers. Children with ADHD-C displayed dysfunction in multiple attentional domains. Discriminant function analysis indicated that two subtests (Sky Search and Walk, Don't Walk) correctly classified 84.2% of children with ADHD-C

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Dev Neuropsychol. 2019 Mar;44:159-71.

FURTHER EVIDENCE FOR EMBEDDED PERFORMANCE VALIDITY TESTS IN CHILDREN WITHIN THE CONNERS' CONTINUOUS PERFORMANCE TEST – SECOND EDITION.

Lichtenstein JD, Flaro L, Baldwin FS, et al.

Objective: To replicate previous research on Conners' Continuous Performance Test – Second Edition subscales as performance validity tests (PVTs) in children.

Method: Classification accuracy for the Omissions (OMI), Hit Reaction Time (HRT), and Perseverations (PER) subscales was computed for 414 children and adolescents.

Results: Overall, OMI, HRT, and PER demonstrated good specificity but low and variable sensitivity across cutoffs.

Conclusions: Results suggest that OMI, HRT, and PER can function as embedded PVTs in mixed clinical samples of children, although their clinical utility is limited by their low sensitivity. Implications for the use of these PVTs in the context of attention-deficit/hyperactivity disorder evaluations, medication-seeking patients, and sports concussion clinics are discussed

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Emot Behav Difficulties. 2019.

ATTACHMENT AND SENSITIVITY AMONG PARENTS WITH ADHD A MULTIPLE-CASE STUDY.

SyrjänenM, Hautamäki A, Pleshkova N, et al.

This study aimed to explore the self-protective strategies of six parents with ADHD and the sensitivity they displayed in dyadic interaction with their under 3-years-old children. The parents were interviewed using the

Adult Attachment Interview. Parental sensitivity was assessed using the CARE-Index. The study showed a variation of the parents self-protective strategies and sensitivity. The more complex the parents self-protective strategy was, the less sensitive was the interaction. Some parents need for self-protection compromised their ability to protect their child and decreased their sensitivity. All parents displayed indications of unresolved traumas, which also impaired their sensitivity to the signals of their child and ability to engage in mutual regulation of arousal and emotion with their child. Attachment-oriented family psychological assessment, including assessments of the self-protective strategies of each family member would make possible to design a treatment adapted to the unique family needs, also in order to alleviate early risk

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Eur Child Adolesc Psychiatry. 2019;28:531-42.

TRAJECTORIES OF BEHAVIOR, ATTENTION, SOCIAL AND EMOTIONAL PROBLEMS FROM CHILDHOOD TO EARLY ADULTHOOD FOLLOWING EXTREMELY PRETERM BIRTH: A PROSPECTIVE COHORT STUDY.

Linsell L, Johnson S, Wolke D, et al.

To investigate trajectories of behavior, attention, social and emotional problems to early adulthood in extremely preterm survivors compared to a term-born comparison group. Longitudinal analysis of a prospective, population-based cohort of 315 surviving infants born < 26 completed weeks of gestation recruited at birth in 1995, from the UK/Republic of Ireland, and a term-born comparison group recruited at age 6. The parent-report Strengths and Difficulties Questionnaire was completed at age 6, 11, 16 and 19-áyears. The Total Behavioral Difficulties Score was 4.81 points higher in extremely preterm individuals compared to their term-born peers over the period (95% CI 3.76-5.87, $p < 0.001$) and trajectories were stable in both groups. The impact of difficulties on home life, friendships, school or work and/or leisure activities was greater in the EPT group (RR 4.28, 95% CI 2.89-6.35, $p < 0.001$), and hyperactivity/inattention and peer problems accounted for the largest differences. A clinically significant behavioral screen at age 2.5 was associated with a higher Total Behavioral Difficulties Score from 6-áyears onwards in extremely preterm participants (Mean difference 6.90, 95% CI 5.01-8.70, $p < 0.001$), as was moderate/severe cognitive impairment at last assessment (Mean difference: 4.27, 95% CI 2.76-5.77, $p < 0.001$). Attention, social and emotional problems in extremely preterm individuals persist into early adulthood with significant impact on daily life. A positive behavioral screen in infancy and moderate/severe cognitive impairment are associated with early adult outcomes

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Eur Child Adolesc Psychiatry. 2019.

RESUMPTION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER MEDICATION IN EARLY ADULTHOOD: FINDINGS FROM A UK PRIMARY CARE PRESCRIBING STUDY.

Newlove-Delgado T, Ford TJ, Hamilton W, et al.

This study aimed to examine the resumption of attention-deficit hyperactivity disorder (ADHD) prescriptions in early adulthood in young people whose ADHD prescriptions stopped in adolescence. Whilst prescribing studies indicate that the proportion of those with ADHD stopping treatment in late adolescence remains in excess of the proportion expected to be symptom free, very few studies have examined patterns of resumption amongst young adults previously prescribed medication. Primary care records from the UK Clinical Practice Research Datalink from 2008 to 2013 were used to examine the outcome of resumption of ADHD prescriptions from age 20-áyears in a sample of cases with ADHD whose prescriptions stopped aged 14-á18-áyears. A Cox regression model was fitted to explore variables that could theoretically be associated with resumption of prescriptions. Of 1440 cases, 109 (7.6%) had their ADHD prescriptions resumed. Characteristics associated with an increased probability of resumption included female gender, learning disability, referral to adult mental health services, and prescription of antipsychotic medication. In this study, only a small proportion of adolescents who stopped ADHD medication subsequently resumed their prescriptions in primary care. Those that did resume were a more complex group. As many vulnerable individuals with ongoing ADHD symptoms may not have the resources required to surmount the barriers to

re-enter services, the implication is that not all those who could benefit from resuming medication are able to do so. The findings raise questions around whether current care models are flexible enough and whether primary care services are adequately supported in managing this group

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Eur Child Adolesc Psychiatry. 2019.

REPLY TO CRITICAL COMMENTS ON THE ARTICLE “INCREASED RISK OF DEVELOPING PSYCHIATRIC DISORDERS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD) RECEIVING SENSORY INTEGRATION THERAPY: A POPULATION-BASED COHORT STUDY”.

Tzang R-F, Kao K-L, Muo C-H, et al.

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European Journal of Neuroscience. 2019.

BETA BAND OSCILLATORY DEFICITS DURING WORKING MEMORY ENCODING IN ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVE DISORDER.

Zammit N, Muscat R.

Attention-deficit hyperactivity disorder (ADHD) is a neurobehavioural disorder, characterized by symptoms of inattention and/or hyperactivity/impulsivity, in addition to various cognitive deficits, including working memory impairments. This pathology arises from a complex constellation of genetic, structural and neurotransmission abnormalities, which give rise to the aberrant electrophysiological patterns evident in patients with ADHD. Among such, findings have consistently provided support in favour of weaker power across the beta frequency range. Evidence has also emerged that beta rhythmic decrements are linked to working memory encoding. The catecholaminergic modulation of both working memory and beta oscillations may suggest that the link between the two might be rooted at the neurotransmission level. Studies have consistently shown that ADHD involves significant catecholaminergic dysregulation, which is also supported by other clinical studies that demonstrate stimulant-induced amelioration of ADHD symptomology. In this study, we explore the possible ways that might relate ADHD, working memory, beta rhythms and catecholaminergic signalling altogether by investigating the integrity of encoding-relevant electroencephalographic beta rhythms in medication-na+»ve and stimulant-medicated adolescent patients. The aberrant parietal and frontal encoding-related beta rhythm revealed in the ADHD patients together with a working memory (WM) deficit as observed herein was reversed by methylphenidate in the latter case but not with regard to the beta rhythm. This finding per se raises the issue of the role played by beta rhythms in the WM deficits associated with ADHD

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Eur Neuropsychopharmacol. 2019;29:S811.

COMMON GENETIC RISK VARIANTS FOR ADHD CONTRIBUTE TO CHILDHOOD NEURODEVELOPMENTAL AND EXTERNALIZING TRAITS IN THE POPULATION.

Brikell I, Larsson H, Yi L, et al.

Background ADHD is a highly heritable disorder, marked by elevated levels of comorbidity across neurodevelopmental and externalizing conditions. Polygenic risk scores (PRS) for ADHD have previously been shown to predict ADHD clinical case status and ADHD traits in the general population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Stergiakouli et al., 2015). However, it is still unknown to what extent these genetic risk variants are disorder specific, and how they may influence neurodevelopmental and externalizing traits associated with ADHD.

Methods ADHD PRS were calculated using results from the latest iPSYCH/Psychiatric Genomics Consortium ADHD Genome-Wide Association (GWAS) meta-analysis for 13,471 children from the Child and Adolescent Twin Study in Sweden (CATSS). For replication, ADHD PRS were also calculated from the EAGLE consortia GWAS meta-analyses of ADHD traits. Phenotypes in CATSS were measured via parent-ratings using the Autism-Tics, ADHD, and Other Comorbidities inventory. To estimate the associations

between ADHD PRS and neurodevelopmental and externalizing traits, we used confirmatory factor analysis to fit a correlated factors model to the symptoms of trait inattention, impulsivity, autism, learning difficulties, oppositional-defiant and conduct problems. Each latent trait factor was then regressed on ADHD PRS in a structural equation modelling framework. In the second model, we included a latent general psychopathology factor to account for phenotypic associations among the traits. In this model, each item loaded on the latent general factor, in addition to the corresponding latent trait factor described above. Analyses were re-run using the EAGLE ADHD PRS.

Results ADHD PRS were significantly associated with elevated levels of trait inattention, impulsivity, autism, learning difficulties, oppositional-defiant and conduct problems. However, only unique associations with impulsivity and conduct problems remained after accounting for cross-trait covariance via a latent general psychopathology factor, on which all symptoms loaded positively (loadings=.31–.91, S.E.=.004–.028). ADHD PRS explained 1% ($\beta = .10$, $p < 0.001$) of the variance in the latent general factor, 0.5% ($\beta = .073$, $p < 0.001$) in impulsivity and 0.3% ($\beta = .052$, $p = .035$) in conduct problems. Similar results were found for the EAGLE ADHD PRS analyses, although significance and variance explained were attenuated.

Discussion Our results suggest that common genetic variants associated with clinically diagnosed ADHD have pleiotropic effects on neurodevelopmental and externalizing traits in the general population. These associations appear to be largely non-specific and reflect a general liability towards elevated childhood neurodevelopmental traits. Nonetheless, over and above predicting a general psychopathology factor, the ADHD PRS also seemed to capture genetic risk variants with unique effects on childhood externalizing traits of impulsivity and conduct problems.

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Eur Neuropsychopharmacol. 2019;29:S956.

A CASE-CONTROL GENOME WIDE ASSOCIATION STUDY OF CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Hawi Z, Yates H, Kent L, et al.

Background: Attention Deficit/Hyperactivity Disorder (ADHD) is the most prevalent mental disorder of childhood. Genetic influences are recognised as a major predisposing factor for ADHD with heritability estimated between 75-90% which is comparable to that of major psychiatric mental illnesses, such as autism and schizophrenia. Identifying the individual DNA variations that confer risk to ADHD has been a major scientific challenge over the last 20 years. In this investigation, we conducted a Genome-Wide Association Study (GWAS) involving 480 ADHD-DSM-IV diagnosed samples compared to 1207 ethnically notched controls.

Methods: Genotyping was conducted using Psych-Chip platform (Illumina, 2015). This array has been developed by Illumina in tandem with the Psychiatric Genomics Consortium for the purpose of large-scale genetic studies in psychiatry. The Psych-Chip contains a GWAS backbone of 588,628 markers enriched with 50,000 single nucleotide polymorphisms (SNPs) which have been implicated in psychiatric conditions and/or neurodevelopmental disorders. Quality control of the genotypic data was conducted as described in Anderson et al. [2010].

Results: Although no significant SNP association was observed at the GWAS level (5.0 8, several SNPs exhibited strong trends toward association. For example, association with rs6659350 which was mapped 22.8 kbp upstream of the Tenascin-R gene (TNR), was tantalizingly close to GWAS significance ($p=8.49\ 08$). In addition, rs2410116 (mapped 300.2kbp upstream of DLC1 Rho GTPase Activating Protein (DLC1)) also showed a strong trend toward association with ADHD ($p= 2.307$). Further, seven other SNPs (rs10006479, rs7007897, rs10835019, rs17772064, rs11788670, rs415300, rs2295135) showed strong trends (p -values ranged between 1.01 05 and 2.98 06).

Discussion: Although our sample has limited power to detect reliable genome wide association with ADHD, it represents a contribution of never before analysed (predominantly Australian) samples to the international GWAS effort. Although our analysis shows promising trends towards association, ultimately these results will need to be verified in the context of current international ADHD GWAS consortia

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Eur Neuropsychopharmacol. 2019;29:S868.

PHARMACOGENOMICS OF METHYLPHENIDATE TREATMENT OF DANISH CHILDREN WITH ADHD.

Madsen MB, Kaalund-Brok K, Jeppesen P, et al.

Background: The first choice drug for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Denmark and several other countries is Methylphenidate (MPH). More than 30% of the children treated with MPH have been reported to switch to another drug due to lack of efficacy or adverse reactions. Most likely, a significant fraction of this individual variation in treatment outcome is caused by genetic differences. Previous studies have not identified genes or genetic variants conclusively implicated in the response to MPH.

Methods: We performed a pharmacogenomics study of the efficacy and adverse reactions of MPH in a sample of 207 Danish children with ADHD, who were drug-naïve at baseline and were monitored for 12 weeks. Each week the ADHD symptom severity was scored on the ADHD-RS questionnaire, and any adverse reactions were recorded. We divided the ADHD symptom scores into inattention and hyperactivity/impulsive sub-scores, and performed GWAS on the outcome of MPH treatment defined as the difference in symptom severity from baseline to end of study. This was followed by calculation of pair wise epistatic interaction coefficients on the top SNPs from the GWAS. Moreover, we used functional principal component analysis to derive proxies that describe the longitudinal nature of the data for both the efficacy measurements and the adverse reactions. Subsequently, we performed GWAS using the proxies as phenotypes for the MPH outcome across the entire treatment period.

Results: None of the GWAS resulted in genome-wide associated hits. However, among the top SNPs for the inattention sub-score were some that fell in: RAS guanyl releasing protein 1 (RASGRP1), sodium/potassium transporting ATPase interacting 2 (NKAIN2) and tetratricopeptide repeat domain 12 (TTC12). For the hyperactivity/impulsive sub-score one of the top SNPs is in the vicinity of gamma-aminobutyric acid type A receptor gamma3 subunit (GABRG3). In the interaction analysis we identified the SNPs with the largest difference in connectivity between the inattention and hyperactivity/impulsive sub-scores and found that some of these were located in or near: myelin transcription factor 1 like (MYT1L), synaptotagmin 17 (SYT17), potassium voltage-gated channel subfamily Q member 5 (KCNQ5) and potassium voltage-gated channel modifier subfamily S member 3 (KCNS3).

Discussion: Despite the lack of genome-wide significant SNPs, some of the top hits from the GWAS reside in or near genes that could modulate the response to MPH. Some of these genes have previously been implicated in psychiatric disorders (RASGRP1, NKAIN2 and MYT1L), are involved in neurotransmission (GABRG3, KCNQ5, KCNS3 and NKAIN2) or has been implicated in substance abuse, e.g. TTC12 has been implicated in heroin dependence and SYT17 in alcoholism

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Eur Neuropsychopharmacol. 2019;29:S886-S887.

EXPLORING GENETIC VARIATION THAT INFLUENCES BRAIN METHYLPHENIDATE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Pineda-Cirera L, Shivalikanjli A, Cabana-Domínguez J, et al.

Background: Allele-Specific Methylation (ASM) is a common epigenetic mechanism that involves SNPs correlating with differential levels of methylation at CpG sites. Epigenetic changes play a crucial role in driving lasting changes in gene expression in several tissues, including the brain. As alteration of DNA methylation levels has recently been linked to ADHD symptoms, our aim is to explore the contribution of ASM to ADHD through a case-control association study using different GWAS datasets.

Methods: We performed a primary SNP selection based on two previous studies that identified ASM variants in different brain regions of post-mortem human samples. Subsequently, from those variants we selected a total of 3,896 SNPs following these criteria: associations in cis between the SNP and methylation at a CpG site, correlation of methylation levels with gene expression (R^2 0.2, tagSNPs for each CpG site (LD; r^2 0.85). These candidates were inspected in summary statistics data from the first GWAS meta-analysis of adult and childhood ADHD, performed by iPSYCH and the Psychiatric Genomics Consortium (PGC) in 20,183 cases and 35,191 controls. We applied False Discovery Rate (FDR) correction for multiple testing (5% FDR, corrected P 6.78e-05) to determine the top hits. These signals were followed-up to retrieve (i) SNPs located within the same CpG site and thereafter (ii) SNPs in high linkage disequilibrium with the associated SNPs

(using the same FDR threshold). Impact of the variants on gene expression levels were further explored in the GTEx database.

Results: The case-control association study identified eight tagSNPs surviving FDR, which correlate with differential methylation of six CpG sites. Top hits were followed-up to retrieve other SNPs that correlate with methylation of the same CpG sites, making a total of 39 candidate SNPs. The six CpG sites are located in the promoter regions of five genes, not previously related to ADHD. Notably, the risk SNPs associated with three of the genes are eQTLs for those genes in various brain tissues, including the cerebellar hemisphere and the cerebellum.

Discussion: We have directed existing knowledge of ASM to evaluate its possible contribution to ADHD both at genetic and epigenetic levels. We followed a systematic approach by employing cis-acting ASM variants to pinpoint candidate genes for ADHD. Interestingly, several of the identified variants are eQTLs for genes that are expressed in brain. Our aim is now to further investigate the role of these genes in the development of the ADHD phenotype

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Eur Neuropsychopharmacol. 2019;29:S1002.

INTEGRATIVE GENOMIC ANALYSIS OF METHYLPHENIDATE RESPONSE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Pagerols M, Richarte V, S+ínchez-Mora C, et al.

Background: Methylphenidate (MPH) is the most frequently used pharmacological treatment in children with Attention-Deficit Hyperactivity Disorder (ADHD). However, a considerable interindividual variability exists in clinical response, which may reflect underlying genetic influences.

Methods: We performed a Genome-Wide Association Study (GWAS) of MPH efficacy in 173 ADHD pediatric patients, considering the Clinical Global Impression-Improvement scale as the primary outcome measure of treatment success. For subsequent analyses, we prioritized the Single-Nucleotide Polymorphisms (SNPs) with P-values below 0.05 on the GWAS based on functional annotation and expression quantitative trait loci (eQTL) analysis in human brain. Ingenuity Pathway Analysis was used to assess the biological functions and pathways related to genes containing at least one SNP nominally associated with both MPH response and human cortical expression levels (eSNPs), and to test for over-representation of genes previously studied in either ADHD or treatment outcome. We subsequently meta-analyzed the association between clinical response and the eSNPs identified across the discovery sample and an independent cohort of 189 ADHD adult patients.

Results: Although no variant reached genome-wide significance, the set of genes containing SNPs nominally associated with MPH response was significantly enriched for genes previously studied in ADHD or treatment outcome ($P_{adjusted}=1.56e-31$). Considering these results, we prioritized the nominally significant markers by functional annotation and eQTL analysis in human brain, and we identified 33 SNPs tagging cis-eQTL in 32 different loci (eGenes). Pathway enrichment analyses revealed an over-representation ($P_{adjusted}<0.05$) of genes involved in morphology of neurons, neuroglia, white matter and brain regions important for motor control, attention and memory among the eGenes. Categories related to neuropsychiatric disorders and behavior were also significantly enriched, including learning deficit and hyperactive behavior. We subsequently meta-analyzed the 33 eSNPs nominally associated with treatment outcome across the discovery sample and an independent cohort and we detected 15 suggestive signals, with rs17685420 in the PEBP4 (phosphatidylethanolamine binding protein 4) gene surpassing Bonferroni correction ($OR=3.07$, $P=7.90e-05$).

Discussion: To our knowledge, this is the first study investigating the genetic basis of MPH response from an integrative perspective that combines GWAS data, functional annotation, eQTL in relevant tissues to ADHD and pathway enrichment analyses. Our results highlight genes related to nervous system development and function, neurological diseases and psychological disorders. Thus, this comprehensive strategy provides a better understanding of the molecular mechanisms implicated in MPH treatment effects and suggests promising candidates that may contribute to clinical outcome

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Eur Neuropsychopharmacol. 2019;29:S825.

GAENETICS OF WORKING MEMORY AND VIGILANCE ENDOPHENOTYPES IN ADHD.

Wilmot B, Bhatt P, Ryabinin P, et al.

Background: Joint genetic analysis of correlated endophenotypes markedly enhances insight into the relationships among them and the shared and distinct genetic influences on phenotypically related complex traits. In addition, identifying pleiotropic effects among endophenotypes can help improve our biological understanding of the genetic architecture of a complex disease, namely childhood Attention Deficit Hyperactivity Disorder (ADHD). Cognitive functions, in particular aspects of executive functioning, have long been proposed as endophenotypes for ADHD, in some cases with distinct components of ADHD emphasized (hyperactivity and inattention-disorganization). This study identifies and characterizes the individual and shared genetic variants associated with two major cognitive endophenotypes Working Memory (WM) and arousal in relation to both ADHD sub-dimensions.

Methods: Composite scores for working memory and arousal were created on the basis of a latent variable model using multiple laboratory-obtained measures of each construct. Inattention and hyperactivity were defined on the basis of a composite of parental and teacher ratings. A confirmatory factor model fit well, supporting the internal validity of the composite scores. Subjects included 656 unrelated community recruited volunteer children ranging 7 to 13 years old (n=435 ADHD, 221 non-ADHD). SNPs included in our analysis (n=193,657) were from a polygenic risk score (PGS) computed using the reported discovery sample of 20,183 ADHD cases and 35,191 controls from the Psychiatric Genetics Consortium. A linear regression analysis accounting for age, sex and population stratification was used to test for association to each endophenotype. Pleiotropic relationships were identified using linear regression analysis accounting for the correlation among all four phenotype measures. A likelihood ratio test framework was used for inferring the number of traits associated with a genetic variant and for partitioning traits associated with the different SNPs.

Results: The PGS was associated with ADHD diagnosis (Nagelkerke $R^2=0.04$, $p=0.0000006$) and multi-indicator dimensional ADHD latent variables by parent report ($\beta=0.196$, $SE=0.041$) and teacher report ($\beta=0.176$, $SE=0.040$). Univariate SNP associations ($p<0.0001$) were: WM=23, arousal=21, hyperactivity=20, and inattention=10. Two SNPs were significant in both hyperactivity and inattention, one located in EPHB1 which mediates axonal guidance. Hyperactivity was associated with genes involved in energy metabolism and signaling processes. Inattention was associated with genes involved in regulation of gene expression and GPCR signaling. WM was associated with genes involved in differentiation, genes expression regulation and mitochondrial transcription. Arousal was associated with genes involved in calcium binding, axon guidance and regulation of neurotransmitters. SNPs pleiotropic with WM (76 SNPs) or arousal (70 SNPs) were enriched for inorganic cation transmembrane transport ($p=0.000041$). SNPs pleiotropic with hyperactivity (133 SNPs) or inattention (142 SNPs) were enriched for phosphate-containing compound metabolic process ($p=0.027$).

Discussion: Our study provides motivation for pleiotropic effects in ADHD endophenotypes and helps begin to account for the mechanism by which cognitive endophenotypes participate in ADHD development

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Eur Neuropsychopharmacol. 2019;29:S891.

IDENTIFICATION OF GENES IN CHILD GENETIC RISK FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER THAT INTERACT WITH MATERNAL SYMPTOMS IN PREDICTION OF INTERNALIZING PROBLEMS.

Chen L, Bouvette-Turcot A-A, Garg E, et al.

Background: Maternal antenatal depression is associated with offspring socio-emotional problems. However, the impact varies across the population such that some individuals seem resilient. Genetic factors may define vulnerability/resilience to the environment, effects that likely span many molecular pathways. Despite moderate success in candidate gene approaches, genome-wide approaches in gene-environment interactions (GxE) have been under exploited. We sought to identify genes and biological pathways that moderate the relationship between Maternal Antenatal Depressive Symptoms (MADS) and child socio-emotional outcomes.

Methods: Our sample included 190 mother-child dyads from a Canadian longitudinal birth cohort. MADS was measured with the Center for Epidemiologic Studies IÇô Depression Scale. Child socio-emotional outcomes were mother-reported at 5 years with the Child Behavior Checklist. We constructed Genomic

Profile Risk Scores (GPRS) from the children's SNPs genome-wide that account for polygenic risk for Attention Deficit/Hyperactivity Disorder (ADHD) based on risk information from the genome-wide associations with ADHD by the Psychiatric Genomics Consortium and applied them in our GxE model. GPRS with the smallest p-value in the GxE model was defined as the best-fit GPRS. SNPs constituting the best-fit GPRS were used in a genome-wide by environment association analysis follow-up. We used MetaCore to examine the enriched gene ontology in a subset of SNPs in the GxE model with p-values less than .01.

Results: GPRS moderated the relationship between MADS and child internalizing problems ($p < .05$). A positive association between MADS and internalizing problems was found only in children with high GPRS. Among the SNPs that were included in the best-fit GPRS, 44 SNPs significantly interacted with MADS in predicting child internalizing problems after corrected for multiple testing (Benjamini & Hochberg FDR at 5%), including rs2239032 in CACNA1C ($p = 2.11 \times 10^{-5}$), which is shared risk factor in major psychiatric disorders. The top genes underlying the moderating effect of the GPRS were enriched in processes such as neuron development ($p = 1.56 \times 10^{-7}$) and synapse organization ($p = 5.58 \times 10^{-7}$), in molecular functions such as inositol 1,4,5-trisphosphate-sensitive calcium-release channel activity ($p = 3.66 \times 10^{-4}$) and retinoic acid receptor binding ($p = 4.49 \times 10^{-4}$), and in pathway networks such as synaptic contact ($p = 1.12 \times 10^{-4}$), synaptogenesis ($p = 2.90 \times 10^{-4}$), axonal guidance ($p = 1.11 \times 10^{-3}$), attractive and repulsive receptors ($p = 3.80 \times 10^{-3}$), and transmission of nerve impulse ($p = 1.60 \times 10^{-3}$).

Discussion: We used the GPRS for ADHD to facilitate our genome-wide approach in examining GxE and identified genes that have a moderating effect on the relationship between MADS and internalizing problems in children. The enriched biological pathways are implicated in axon development and synaptic functions, critically important in fetal neurodevelopment. These findings suggest that specific genes involved in the biological framework for antenatal neurodevelopment can confer sensitivity or resilience to the influences of MADS on mental health

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Eur Neuropsychopharmacol. 2019;29:S957-S958.

PHARMACOGENETICS PREDICTORS OF METHYLPHENIDATE EFFICACY RESPONSE IN CHILDHOOD ADHD.

Myer N, Boland J, Faraone S, et al.

Background: Stimulant medication has long been effective in treating Attention-Deficit Hyperactivity Disorder (ADHD) and is currently the first line pharmacological treatment for children. Both methylphenidate and amphetamine modulate extracellular catecholamine levels through interactions with dopaminergic, adrenergic, and serotonergic system components; it is therefore likely that catecholaminergic molecular components influence the effects of ADHD treatment.

Methods: We conducted a PubMed search to identify all peer-reviewed publications examining efficacy response to methylphenidate in the treatment of childhood ADHD. Using meta-analysis, we sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. We used meta-regression to examine the effects of gender ratios, cohort ethnicity, study quality, and mean participant age. Egger's test and Duval and Tweedie's 'trim and fill' were used to examine and correct for publication bias.

Results: We identified 35 studies (3,698 children) linking the efficacy of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between Single Nucleotide Polymorphisms (SNPs) rs1800544 ADRA2A (odds ratio: 1.69; confidence interval 1.12-2.55), rs4680 COMT (odds ratio: 1.40; confidence interval: 1.04-1.87), rs5569 SLC6A2 (odds ratio: 1.71; confidence interval 1.22-2.38), and, repeat variants VNTR 4 DRD4 (odds ratio: 1.64; confidence interval: 1.15-2.33), VNTR 7 DRD4 (odds ratio: 1.47; confidence interval: 1.00-2.15), and VNTR 10 SLC6A3 (odds ratio: 1.26; confidence interval: 1.11-1.67), whereas the following variants were not statistically significant: rs1947274 LPHN3 (odds ratio: 0.95; confidence interval: 0.71-1.26) and rs5661665 LPHN3 (odds ratio: 1.07; confidence interval: 0.84-1.37). Funnel plot asymmetry amongst SLC6A3 studies was identified and attributed largely to small study effects.

Discussion: This meta-analysis supports an association between genetic variants - within the ADRA2A, COMT, SLC6A2, and DRD4 genes - and efficacy response to methylphenidate for the treatment of childhood ADHD. These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment

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Eur Neuropsychopharmacol. 2019;29:S956-S957.

GENETIC OVERLAP BETWEEN ADHD AND ASD IN SHANK GENES IN CHINESE POPULATION.

Chen LH, Lee C-C, Ho T-P, et al.

Background: Attention Deficit/Hyperactivity Disorder (ADHD) is characterized with inattention, hyperactivity and impulsivity, while Autism Spectrum Disorder (ASD) is characterized with impaired social communication and interaction, restricted and repetitive patterns of behavior and activities. Phenotypically, both appear to be quite different. However, clinically it has been found that 20-50% ADHD children meet diagnostic criteria for ASD, while 30-80% ASD children meet diagnostic criteria for ADHD. These rates of comorbidity between the two disorders imply that they may share underlying etiologies. Although recent evidence has suggested a genetic overlap between ADHD and ASD, little progress has been made so far to identify the specific genes involved. The shank synaptic scaffold proteins, which are encoded by SHANK genes and located at the post-synaptic density of glutamatergic synapses, have been reported to be associated with a number of psychiatric disorders, including ADHD and ASD, separately. The aim of the current study is to investigate whether there is a genetic overlap between ADHD and ASD in SHANK genes.

Methods: In the present study, only male children with Chinese ethnicity, aged between 6 to 12 years, were included. 298 ADHD family trios (including ADHD children without ASD and their biological fathers and mothers), 134 ASD children without ADHD, and 109 children with both ASD and ADHD were recruited from public hospitals in Hong Kong. 232 normal control children were recruited from local primary schools. A number of single-nucleotide polymorphisms (SNPs) from SHANK2 and SHANK3 were selected for genotyping. After quality control, 14 SNPs from SHANK2 and 7 SNPs from SHANK3 were included for data analyses. For ADHD family trios data, we constructed ADHD cases and matched pseudo-control, which were based on transmitted and un-transmitted parental alleles using the Haplotype-Relative-Risk (HRR) principle. The pseudo-control supplemented the normal control to increase the statistical power. Likewise, ASD children with or without ADHD were also paired with samples of normal control and pseudo-control for association analysis. PLINK and KGG were used for statistical association analyses at SNP-level and gene-level, respectively.

Results: When association analysis was done between ADHD children without ASD and samples of normal control and pseudo-control, the T allele of rs7106631 of SHANK2 significantly decreased the ADHD risk ($p=0.001$, $OR=0.70$). When allele frequencies comparisons were conducted between ASD children with or without ADHD and samples of normal control and pseudo-control, the same protective effect of rs7106631 T allele was identified with $OR=0.74$ ($p=0.011$). Further association analysis conducted between all clinical children (i.e., ADHD children without ASD & ASD children with or without ADHD) and samples of normal control and pseudo-control yielded more significant results for rs7106631 ($p=0.0003$, $OR=0.72$). Additionally, significant associations were found for other SHANK2 SNPs, namely, rs7113016 ($p=0.027$), rs1073294 ($p=0.008$), rs11236616 ($p=0.003$), rs10899158 ($p=0.048$), and rs9888288 ($p=0.004$). However, no significant result was detected for SNPs of SHANK3. Subsequent gene-level analysis based on whole dataset suggested the significant role of SHANK2 in both ADHD and ASD (gene-level $p=0.003$).

Discussion: Consistent with previous findings in Western populations, this current study provides additional evidence for the significant association of SHANK2 with ASD from a Chinese population. A new finding rarely reported in previous studies is the association of SHANK2 with ADHD. This implies a shared genetic susceptibility between ADHD and ASD. Both disorders do share a number of characteristics, including male preponderance, increased level of oxidative stress, and abnormal neuronal connectivity, reflecting potentially common underlying neurodevelopmental abnormality. Speculatively, the identification of SHANK2 from this

current candidate gene study as associating to both ADHD and ASD may provide the common genetic etiology to explain their shared characteristics and higher-than-chance comorbidity. Further studies examining the functional abnormalities of the identified gene, SHANK2, are warranted in the future

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Eur Neuropsychopharmacol. 2019;29:S759.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND OBESITY: THE WEIGHT OF SHARED GENETIC RISK FACTORS.
Mota NR, Klein M, Galesloot TE, et al.

Apart from being highly comorbid with other psychiatric disorders, ADHD is also associated with the occurrence of certain somatic conditions. In particular, the relationship between ADHD and obesity has been receiving growing attention. Meta-analytic studies show increased prevalence of obesity in ADHD patients as well as higher rates of ADHD in individuals with obesity. However, the role of specific behavioural, neuropsychological, and genetic factors contributing to the development of such comorbidity deserves further investigation. Possible mechanisms underlying the comorbidity between ADHD and obesity have been suggested, including the dopaminergic neurotransmission and the circadian rhythm systems, which have both been associated with each condition individually. The recent success of ADHD GWAS and great increase in sample size enable us to explore the role of common genetic variants shared by these frequently co-occurring conditions. The findings that will be presented derive from a series of analyses, which take both hypothesis-free and hypothesis-driven approaches. We first examine the potential of polygenic risk scores (PRS) to predict ADHD symptoms and obesity-related traits in the general population. As discovery samples, this study makes use of the summary statistics from the latest ADHD GWAS from the Psychiatric Genomics Consortium (PGC)-iPSYCH collaboration, the first large-scale adult ADHD GWAS from the International Multicentre persistent ADHD CollaboraTion (IMpACT), and the latest publicly available GWAS on body mass index (BMI), a trait closely-related to obesity (Locke et al., 2015 - GIANT consortium). Our initial results, using as target sample the Dutch cohort from the Nijmegen Biomedical Study (NBS; N~3200 adults), show that ADHD-based PRS is associated with BMI ($P=8.7 \times 10^{-6}$, $R^2=0.59\%$) and with overweight/obesity ($P=0.007$, $R^2=0.3\%$); on the other hand, BMI-based PRS is associated with the presence of ADHD symptoms in childhood ($P=0.007$; $R^2=0.37\%$). The contribution of candidate pathways will also be discussed, where we examine the association of genes related to the dopaminergic and circadian rhythm systems with ADHD and obesity-related traits by conducting gene-set analyses using the aforementioned GWAS results. Finally, we will explore possible mediating roles of behavioural and neuropsychological traits and neuroimaging measures on the associations identified in more phenotypically characterized clinical and population samples. The great impact both ADHD and obesity have on an individual's life, as well as on society as a whole, emphasize the importance of pursuing a better understanding of the underlying mechanisms contributing to the co-occurrence of these phenotypes. A clearer picture of the factors involved in such comorbidity, as well as their effects on the general population, may provide relevant insights in terms of early treatment or even prevention guidelines

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Eur Neuropsychopharmacol. 2019;29:S918.

DIFFERENTIAL DNA METHYLATION AT BIRTH ASSOCIATED WITH MENTAL DISORDER IN INDIVIDUALS WITH 22Q11.2 DELETION SYNDROME.

Starnawska A, Hansen C, et al.

Background: Individuals with 22q11.2 Deletion Syndrome (DS) have an increased risk of comorbid mental disorders including schizophrenia, attention deficit hyperactivity disorder, depression, as well as intellectual disability. While most 22q11.2 deletion carriers have the long 3 Mb form of the hemizygous deletion, there remains a large variation in the development and progression of psychiatric disorders, which suggests that alternative factors contribute to the pathogenesis. In this study, we investigated whether neonatal DNA methylation signatures in individuals with the 22q11.2 deletion associate with mental disorder later in life.

Methods: Subjects with 22q11.2 deletion were selected from The Danish Cytogenetic Central Register. DNA methylation was measured genome-wide with the use of Infinium HumanMethylation450 BeadChip from

neonatal dried blood spots in a cohort of 164 individuals with 22q11.2DS, including 48 diagnosed with a psychiatric disorder. Epigenome-Wide Association Study (EWAS) was performed to determine differential DNA methylation among 22q11.2 deletion carriers diagnosed with mental disorder compared to carriers with no current or past mental disorder diagnosis. Most associated sites were used for Gene Ontology pathway enrichment analysis. Moreover, we evaluated four sub-classes of most commonly observed psychiatric diagnoses (intellectual disability: F70-79, behavioral disorders: F90-98, disorders of psychological development: F80-89 and schizophrenia spectrum disorders: F20-29) in the cohort and compared their methylome profiles to the non-psychiatric controls. Regression models, adjusted for sex, type of 22q11.2 deletion, and age of the blood spot card, were used for all EWAS analyses to identify differentially methylated sites.

Results: Among several CpG sites with p -value $< 10^{-6}$, we identified cg23546855 (p -value= 2.15×10^{-7}) mapping to STK32C to be associated with a later psychiatric diagnosis. Pathway analysis of the top findings resulted in the identification of several Gene Ontology pathways to be significantly enriched (p -value < 0.05 after BH correction), among them: neurogenesis, neuron development, neuron projection development, astrocyte development, axonogenesis, and axon guidance. Additionally, we identified differentially methylated CpG sites in LRP2BP (p -value= 5.37×10^{-8}) to be associated with intellectual disability, in TOP1 (p -value= 1.86×10^{-7}) with behavioral disorders, in NOSIP (p -value= 5.12×10^{-8}) with disorders of psychological development, and in SEMA4B (p -value= 4.02×10^{-7}) with schizophrenia spectrum disorders.

Discussion: In conclusion, our study suggests an association of DNA methylation differences at birth with development of mental disorder later in life in 22q11.2DS individuals. Differentially methylated sites were located in genes enriched in those involved in neurogenesis, nervous development, and neuron projection development, what supports previous studies that suggested mental disorders to have an early neurodevelopmental component

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Eur Neuropsychopharmacol. 2019;29:S888-S889.

GENOME-WIDE EXAMINATION OF PARENT-OF-ORIGIN EFFECTS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Smajlagić D, Connolly S, Hakonarson H, 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. Thus, we aimed at examining parent of origin effects (POE) together with maternal and additive 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 and Child Cohort, consisting of 2060 trios and 328 duos. Additional parent-offspring data is being added. ADHD was diagnosed based on DSM-IV, ICD-10 and child behavior checklist. POE, 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 (POE) and the largest ADHD Genome-Wide Association Study (GWAS) in children ($N=17666$). Gene based analyses are being performed using MAGMA software. Heritability estimates and genetic correlations of the examined effects are being calculated using LD score regression.

Results: Our preliminary results indicate the presence of non-additive genetic effects in the development of ADHD. Our preliminary strongest imprinting signal is located in CALD1 locus (rs11980823, effect=0.77, SE=0.14, $P=1.21 \times 10^{-7}$). This gene also revealed strong association signal in the previously reported large-scale childhood ADHD GWAS (rs79846815, $P=2.03 \times 10^{-6}$). CALD1 plays essential role in nerve regeneration, a function previously implicated in a number of neuropsychiatric disorders. Our preliminary gene-based analyses of the known imprinted genes revealed strong association with TP73 locus ($P=0.0034$), encoding a transcription factor implicated in disorders of nervous system (e.g. neuroblastoma). Additional hits were noted in the non-coding RNA genes, 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 first and the largest genome-wide parent-offspring study in ADHD, exploring its non-additive genetic effects by detecting and distinguishing between POE (imprinting), maternal

and child effects. As we increase our sample size, we will provide estimates of such effects as well as those of their heritability and genetic correlations

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Fortschritte der Neurologie Psychiatrie. 2019;87:47-56.

DETERMINANTS FOR THE DIAGNOSIS OF ADHD-AN ANALYSIS BASED ON SHI CLAIMS DATA.

Klora M, Zeidler J, Linder R, et al.

Background Up to now, there are only few studies on the influence of the sociodemographic factors on the diagnosis of ADHD in Germany, although the knowledge of these characteristics can be important for the design of prevention programs. Therefore, the aim of this study is to broaden the evidence on the factors influencing the diagnosis of ADHD in Germany. In addition, this study provides information on the influence of the familial predisposition with psychiatric diagnosis and the sociodemographic variables.

Methods Using a 3:1 control group design including claims data of a large German health insurance fund (Techniker Krankenkasse) psychosocial, regional and demographic factors were analyzed descriptively and by logistic regression models. The study variables consisted of the age, sex, region and comorbidities of the patients, the socioeconomic occupational status and the level of education of the members, the psychiatric diagnoses of the parents and the age of the parents at the birth of the patients (variables of the family background).

Results 9,881 ADHD patients with a mean age of 14.9 [SD: 12.6] years were analyzed. Based on this comprehensive sample, it was confirmed that ADHD risk is higher in male patients than in female patients (OR: 2.3 [95%-CI: 2.2-2.5]). In addition, a moderate or high educational status of the member had a significantly lower risk compared to a low education status (OR: 0.78 [95%-CI: 0.70-0.89] and OR: 0.55 [95%-CI: 0.47-0.63], respectively). In addition, the risk of ADHD increases with the parents' age, as well as with the presence of at least one psychiatric diagnosis (OR 1.02 [95%-CI: 1.01-1.03] and OR: 2.09 [95%-CI: 1.95-2.25], respectively). Regarding the socioeconomic index of occupational status, no clear correlation could be identified.

Conclusion Knowledge of sociodemographic risk factors facilitates the diagnosis and provides information on the development of individual therapy concepts

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Georgian Med News. 2018 Nov;88-92.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND HAIR HEAVY METAL AND ESSENTIAL TRACE ELEMENT CONCENTRATIONS. IS THERE A LINK?

Tabatadze T, Kherkheulidze M, Kandelaki E, et al.

The aim of our study was to assess hair micro-elemental status in children with attention deficit hyperactivity disorder, determine micro-elemental misbalances and heavy metal concentrations and evaluate its impact on child behavior. Case-control study was conducted at Child Development Center of M. Iashvili Children's Central Hospital in 2015-2017 years (Tbilisi, Georgia). We studied 70 children, mean age from 6 to 8 year. Target group involved 35 children with Attention Deficit Hyperactivity Disorder. Control group include 35 children of same age with normal behavior. Groups were homogenous based on different characteristics. To diagnose behavioral problems multi-profile group (pediatrician, neurologist, psychologist) assessment was used and final diagnostic was based on DSM V (Diagnostic and Statistical Manual of Mental Disorders from the American Psychiatric Association) and ICD-10 (International Classification of Disease-10) criteria. Micro-elemental status was detected in the hair, with roentgen-fluorescence spectrometer method (Method MBcapital I, Cyrillic 081/12-4502-000, Apparatus ELVAX-CIP, USA-UKRAIN). We study the content of 27 microelements (Zn, Fe, Cu, Mn, Co, Se, K, Cr, S, Cl, Ag, V, Ni, Rb, Sr, Mo, Sr., Pb, Hg, Br, Ti, Ba, As, Zr, Sb, Sn, Cd) in the hair in target and control groups. Computer program S

Georgian Med News. 2018 Nov;82-87.

VISUAL PROCESSING IN GEORGIAN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Parkosadze K, Kunchulia M, Kezeli A.

Neurodevelopmental disorders are disabilities that cause impairment in learning, language, or behaviour areas. ADHD and learning disabilities, namely dyslexia have the greatest prevalence among these disorders and very often co-occur together. As visual perception is essential for development of academic abilities, it is very important question whether visual processing is affected in children with neurodevelopmental disorders or not. There are controversial scientific evidences whether visual perceptual deficits are related to neurodevelopmental disorders or not. Here we investigated such aspects of visual processing as visual attention and visual working memory. Three groups of Georgian children participated in our study: children with dyslexia, children having ADHD and dyslexia together and typically developing children. Two types of attentions were evaluated with two different tasks: selective attention using visual search task and sustained attention using Go/NoGo tasks; short-term visual working memory was investigated using Visual N-back Test. We found that performances of all tasks were similar for dyslexia and control groups in simple conditions but performance deteriorated for all three groups as soon as task was complex. Children having ADHD and dyslexia together had worse performance. Our results showed no deficits for children with dyslexia in visual working memory or visual selective and sustained attention even when reaction times are prolonged. But we found deficits for children having more than one neurodevelopmental condition (ADHD+dyslexia). There was not found any correlation between performances of different tasks. We conclude that deficits of visual attention and visual working memory might not be related to impairment of reading skills in dyslexic children. Even when children with more than one neurodevelopmental disorders show some deficits in visual attention and visual working memory, those deficits alone cannot be accounted for specific deficits of complex neurobehavioral disorders

Indian Journal of Public Health Research and Development. 2019;10:179-84.

IMPACT OF ATTENTION DEFICIT DISORDER ON ACADEMIC PERFORMANCE OF CHILDREN.

Santosh BR, Rachana N.

Occasionally we all struggle to concentrate for a period of time, to sit still, focus on a particular activity, and have mood swings and social problems. At times we go out of control, unable to subdue our impulses. But children suffering from Attention Deficit Disorder (ADD) wrestle with these conditions every day. With the help of appropriate diagnosis and parent / teacher intervention this disorder can be out grown. Objective: The main objective of this study is to examine the prevalent conditions and indicators of ADD in children of the age group 6-13 years and how ADD factors and traits have an impact on the academics of the students. Method: Primary data was collected using a questionnaire distributed to parents and teachers. The data collected was analyzed using SPSS and Smart PLS. Results: The result of the study revealed that boys are generally more affected than girls in number. Further, the result revealed that there is an inverse relationship between ADD and academic performance. Conclusion: There is no doubt that if ADD symptoms are prevailing for a period of time one has to seek medical professional help. However, just medical attention may not be the solution to overcome ADD, teachers and parents have a significant role to play. Educating parents and teachers can lead to better parenting and teaching methods, which would improve the condition of children

Int J Eating Disord. 2019.

DSM-5 EATING DISORDER SYMPTOMS IN ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A POPULATION-BASED STUDY.

Bisset M, Rinehart N, Sciberras E.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is associated with increased eating disorder symptoms, yet little research examining this association has taken a diagnostic approach using a population-based sample. This cross-sectional study examined differences in DSM-5 eating disorder symptoms and

partial-syndrome diagnoses at 14-15 years of age in adolescents with and without ADHD in a population-based sample.

Method: This study uses data from waves 1, 5 and 6 of the Longitudinal Study of Australian Children (N = 2,672). ADHD (6.9%) was defined at 12-13 years of age by both parent- and teacher-reported hyperactivity-inattention scores 90th percentile on the Strengths and Difficulties Questionnaire, parent-reported ADHD diagnosis, and/or ADHD medication treatment. Adolescents reported eating disorder symptoms at 14-15 years of age via the Branched Eating Disorders Test.

Results: Boys with ADHD had greater odds of regular objective binge eating than boys without ADHD (OR: 9.4; 95% CI: 1.7-52.8; $p = .01$). Groups did not differ in prevalence of any other eating disorder symptoms or partial-syndrome diagnoses.

Discussion: Boys with ADHD appear to be at a greater risk of regular binge eating classified by DSM-5 criteria at 14-15 years of age. Overall, the risk for eating disorder symptoms and partial-syndrome diagnoses in adolescents with ADHD does not appear to be high at 14-15 years of age when using DSM-5 criteria with population-based sampling

Int J Environ Res Public Health. 2019;16.

SELF-REPORTED AND PARENT-REPORTED SCHOOL BULLYING IN ADOLESCENTS WITH HIGH FUNCTIONING AUTISM SPECTRUM DISORDER: THE ROLES OF AUTISTIC SOCIAL IMPAIRMENT, ATTENTION-DEFICIT/HYPERACTIVITY AND OPPOSITIONAL DEFIANT DISORDER SYMPTOMS.

Chou W-J, Hsiao RC, Ni H-C, et al.

The aim of this study was to examine the prevalence of self-reported and parent-reported bullying victimization, perpetration, and victimization-perpetration and the associations of autistic social impairment and attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms with bullying involvement in adolescents with high functioning autism spectrum disorder (ASD). A total of 219 adolescents with high functioning ASD participated in this study. The associations of sociodemographic characteristics, parent-reported autistic social impairment, and parent-reported ADHD and ODD symptoms with self-reported and parent-reported bullying victimization, perpetration, and victimization-perpetration were examined using logistic regression analysis. The results found that the agreement between self-reported and parent-reported bullying involvement was low. Compared with bullying involvement experiences reported by adolescents themselves, parents reported higher rates of pure bullying victimization (23.7% vs. 17.8%) and victimization-perpetration (28.8% vs. 9.1%) but a lower rate of pure bullying perpetration (5.9% vs. 9.1%). Deficit in socio-communication increases the risk of being pure victims and victim-perpetrators. Parent-reported victim-perpetrators had more severe ODD symptoms than did parent-reported pure victims

Int J Obes. 2019.

ASSESSING CAUSALITY IN THE ASSOCIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY: A MENDELIAN RANDOMIZATION STUDY.

Martins-Silva T, Vaz JS, Hutz MH, et al.

Background/Objectives: Attention-deficit hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders in childhood and adolescence, is associated with obesity in observational studies. However, it is unclear whether ADHD contributes to, results from or is merely correlated with obesity. This study evaluates the presence and direction of a causal effect between ADHD and obesity.

Subjects/Methods: We performed a bidirectional two-sample Mendelian randomization using summary data from consortia of genome-wide association studies to investigate if ADHD (N = 55,374) has a causal effect on body mass index (BMI) in childhood (N = 35,668) and adulthood (N = 322,154-500,000), and vice-versa. The main analysis was performed using the inverse variance weighted (IVW) method. As sensitivity analyses, we used other Mendelian randomization methods that are more robust to horizontal pleiotropy (i.e.,

MR-Egger, weighted mode, and penalized weighted median estimators), as well as stratified the analysis by the putative mechanisms of genetic instruments (i.e., pathways involved or not in neurological processes).

Results: The IVW method indicated a positive causal effect of BMI on ADHD: $\beta = 0.324$ (95% CI 0.198 to 0.449, $p < 0.001$; expressed as change in ln (odds ratio) of ADHD per each additional SD unit of BMI). IVW estimates were directionally consistent with other methods. On the other hand, we did not find consistent evidence for a causal effect of ADHD genetic liability on BMI.

Conclusions: The results suggested that higher BMI increases the risk of developing ADHD, but not the other way around

JAMA Psychiatry. 2019;76:306-13.

CHARACTERIZING DEVELOPMENTAL TRAJECTORIES AND THE ROLE OF NEUROPSYCHIATRIC GENETIC RISK VARIANTS IN EARLY-ONSET DEPRESSION.

Rice F, Riglin L, Thapar AK, et al.

Importance: Depression often first manifests in adolescence. Thereafter, individual trajectories vary substantially, but it is not known what shapes depression trajectories in youth. Adult studies suggest that genetic risk for schizophrenia, a psychiatric disorder with a neurodevelopmental component, may contribute to an earlier onset of depression.

Objective: To test the hypothesis that there are distinct trajectories of depressive symptoms and that genetic liability for neurodevelopmental psychiatric disorders (eg, schizophrenia, attention deficit/hyperactivity disorder [ADHD]), as well as for major depressive disorder (MDD), contribute to early-onset depression.

Design, Setting, and Participants: The Avon Longitudinal Study of Parents and Children is an ongoing, prospective, longitudinal, population-based cohort that has been collecting data since September 6, 1990, including data on 7543 adolescents with depressive symptoms at multiple time points. The present study was conducted between November 10, 2017, and August 14, 2018.

Main Outcomes and Measures: Trajectories based on self-reported depressive symptoms dichotomized by the clinical cutpoint; MDD, schizophrenia, and ADHD polygenic risk score (PRS) were predictors.

Results: In 7543 adolescents with depression data on more than 1 assessment point between a mean (SD) age of 10.64 (0.25) years and 18.65 (0.49) years (3568 [47.3%] male; 3975 [52.7%] female), 3 trajectory classes were identified: persistently low (73.7%), later-adolescence onset (17.3%), and early-adolescence onset (9.0%). The later-adolescence-onset class was associated with MDD genetic risk only (MDD PRS: odds ratio [OR], 1.27; 95% CI, 1.09-1.48; $P = .003$). The early-adolescence-onset class was also associated with MDD genetic risk (MDD PRS: OR, 1.24; 95% CI, 1.06-1.46; $P = .007$) but additionally with genetic risk for neurodevelopmental disorders (schizophrenia PRS: OR, 1.22; 95% CI, 1.04-1.43; $P = .01$; ADHD PRS: OR, 1.32; 95% CI, 1.13-1.54; $P < .001$) and childhood ADHD ($\beta_{21} = 6.837$; $P = .009$) and neurodevelopmental traits (pragmatic language difficulties: OR, 1.31; $P = .004$; social communication difficulties: OR, 0.68; $P < .001$).

Conclusions and Relevance: The findings of this study appear to demonstrate evidence of distinct depressive trajectories, primarily distinguished by age at onset. The more typical depression trajectory with onset of clinically significant symptoms at age 16 years was associated with MDD genetic risk. The less-common depression trajectory, with a very early onset, was particularly associated with ADHD and schizophrenia genetic risk and, phenotypically, with childhood ADHD and neurodevelopmental traits. Findings are consistent with emerging evidence for a neurodevelopmental component in some cases of depression and suggest that the presence of this component may be more likely when the onset of depression is very early

J Abnorm Child Psychol. 2019 Feb;47:245-57.

INATTENTIVENESS AND LANGUAGE ABILITIES IN PRESCHOOLERS: A LATENT PROFILE ANALYSIS.

Tambyraja SR, Rhoad-Drogalis A, Khan KS, et al.

Growing evidence suggests that early symptoms of inattentiveness may affect the language development and academic success of young children. In the present study, we examined the extent to which profiles of inattentiveness and language could be discerned within a heterogeneous group of preschoolers attending early childhood special education programs (n = 461). Based on parent-reported observations of children's symptoms of inattentiveness and direct assessments of children's language skills (grammar, vocabulary, and narrative ability), three distinct profiles were identified. The three groups, representing levels of severity (at risk, almost average, above average), differed not only by their end of year performance, but also with respect to which their abilities changed over the course of the academic year. Children in the poorest performing profile had poorer mean scores in the spring of their preschool year on all measures, but exhibited patterns of gain that exceeded or equaled their peers in higher-performing groups, in the domains of vocabulary and grammar. Examination of subsequent kindergarten reading skills suggested that profile differences remained consistent. Findings underscore the associations between early symptoms of inattentiveness and language difficulties, and further indicate that these relations extend to the acquisition of early reading skills. Future research is needed to corroborate these findings with more robust measures of attention, and to understand the long-term associations between inattentiveness, language and literacy, and potential effects on these associations from early intervention

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J Abnorm Child Psychol. 2019 Mar;47:405-19.

THE COURSE OF NEUROCOGNITIVE FUNCTIONING AND PREDICTION OF BEHAVIORAL OUTCOME OF ADHD AFFECTED AND UNAFFECTED SIBLINGS.

van Lieshout M, Luman M, Schweren LJS, et al.

Longitudinal studies on the course of neurocognitive functioning of children with ADHD and their unaffected siblings are scarce. Also, it is unclear to what extent that course is related to ADHD outcomes. A carefully phenotyped large sample of 838 Caucasian participants (ADHD-combined type: n = 339, unaffected siblings: n = 271, controls: n = 228; mean age at baseline = 11.4 years, mean age at follow-up = 17.3 years, SD = 3.2) was used to investigate differences in the course of neurocognitive functioning of ADHD affected and unaffected siblings versus controls, and to investigate the relationship between neurocognitive change and ADHD outcomes. At baseline, an aggregated measure of overall neurocognitive functioning and eight neurocognitive measures of working memory, timing (speed/variability), motor control, and intelligence were investigated. Outcomes at follow-up were dimensional measures of ADHD symptom severity and the Kiddie-Global Assessment Scale (K-GAS) for overall functioning. At follow up, affected and unaffected siblings trended to, or fully caught up with performance levels of controls on four (44.4%) and five (55.6%) of the nine dependent variables, respectively. In contrast, performance in remaining key neurocognitive measures (i.e. verbal working memory, variability in responding) remained impaired at follow-up. Change in neurocognitive functioning was not related to ADHD outcomes. Our results question the etiological link between neurocognitive deficits and ADHD outcomes in adolescents and young adults

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J Abnorm Child Psychol. 2019 Feb;47:259-71.

OBSERVED FREE-PLAY PATTERNS OF CHILDREN WITH ADHD AND THEIR REAL-LIFE FRIENDS.

Normand S, Soucisse MM, Melançon MPV, et al.

Previous observational studies conducted in highly structured, analog situations indicate that children with Attention-Deficit/Hyperactivity Disorder (ADHD) mismanage their relationships with same-age peers and friends. Such structured situations may not, however, fully represent the true nature of children's play, which is typically characterized by free choice, intrinsic motivation, and spontaneity. The unique objective of the current observational study was to describe how 87 children with ADHD and 46 comparison (76% boys) aged 7–13 years behave when interacting with their real-life dyadic friends during an unstructured, free-play

situation. Results indicate that dyads comprising one referred child with ADHD and an invited friend ('ADHD dyads') engaged in less cooperative play, displayed less companionship, and showed less sensitivity to friends than comparison dyads. ADHD dyads also engaged in more conflict and exhibited significantly more negative affect than comparison dyads. These findings complement and extend, possibly with somewhat enhanced ecological validity, results obtained in previous studies on the friendships of children with ADHD featuring closed-field observations and questionnaire methodology

J Abnorm Child Psychol. 2019 Feb;47:273-86.

EXECUTIVE FUNCTIONING HETEROGENEITY IN PEDIATRIC ADHD.

Kofler MJ, Irwin LN, Soto EF, et al.

Neurocognitive heterogeneity is increasingly recognized as a valid phenomenon in ADHD, with most estimates suggesting that executive dysfunction is present in only about 33%–50% of these children. However, recent critiques question the veracity of these estimates because our understanding of executive functioning in ADHD is based, in large part, on data from single tasks developed to detect gross neurological impairment rather than the specific executive processes hypothesized to underlie the ADHD phenotype. The current study is the first to comprehensively assess heterogeneity in all three primary executive functions in ADHD using a criterion battery that includes multiple tests per construct (working memory, inhibitory control, set shifting). Children ages 8–13 ($M = 10.37$, $SD = 1.39$) with and without ADHD ($N = 136$; 64 girls; 62% Caucasian/Non-Hispanic) completed a counterbalanced series of executive function tests. Accounting for task unreliability, results indicated significantly improved sensitivity and specificity relative to prior estimates, with 89% of children with ADHD demonstrating objectively-defined impairment on at least one executive function (62% impaired working memory, 27% impaired inhibitory control, 38% impaired set shifting; 54% impaired on one executive function, 35% impaired on two or all three executive functions). Children with working memory deficits showed higher parent- and teacher-reported ADHD inattentive and hyperactive/impulsive symptoms ($BF_{10} = 5.23 \times 10^4$), and were slightly younger ($BF_{10} = 11.35$) than children without working memory deficits. Children with vs. without set shifting or inhibitory control deficits did not differ on ADHD symptoms, age, gender, IQ, SES, or medication status. Taken together, these findings confirm that ADHD is characterized by neurocognitive heterogeneity, while suggesting that contemporary, cognitively-informed criteria may provide improved precision for identifying a smaller number of neuropsychologically-impaired subtypes than previously described

J Affective Disord. 2019 Feb;244:100-06.

LIGHT UP ADHD: II NEUROPHARMACOLOGICAL EFFECTS MEASURED BY NEAR INFRARED SPECTROSCOPY: IS THERE A BIOMARKER?

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

Background: Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by deficits in self-controlling attention, behavior, and emotions. In recent years, noninvasive optical techniques, such as near infrared spectroscopy (NIRS), have been used to measure the neural correlates of pharmacological-therapy outcomes in children and adolescents with ADHD.

Methods: We reviewed a short series of articles that investigated the results of functional NIRS (fNIRS) on developmental-age ADHD. The review was limited to fNIRS studies that investigated the cortical responses that occurred during neuropsychological tasks in ADHD patients who received methylphenidate or atomoxetine.

Results: The majority of the reviewed studies revealed the presence of increased oxygenated hemoglobin concentrations in the prefrontal cortex following pharmacotherapy in ADHD samples. A higher frequency of right-lateralized results was found. Limitations: The considered studies are characterized by substantial methodological heterogeneity in terms of the patients' medication status and washout period, explored cerebral regions, and neuropsychological tasks.

Conclusions: fNIRS seems to be a promising tool for the detection of pharmacological-treatment biomarkers in samples of children and adolescents with ADHD.

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J Autism Dev Disord. 2019.

BRIEF REPORT: NEUROPSYCHOLOGICAL TESTING AND INFORMANT-RATINGS OF CHILDREN WITH AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, OR COMORBID DIAGNOSIS .

Ng R, Heinrich K, Hodges EK.

This study aimed to examine the neuropsychological correlates of child patients diagnosed with ADHD, autism spectrum disorder (ASD), or comorbid ASD + ADHD through a multidisciplinary ASD evaluation clinic. Patients completed standardized tests of intellectual, attention, social-affective/cognitive, and executive functioning; and a semi-structured assessment commonly used for autism diagnosis. The majority of patients were medicated for ADHD concerns during testing. Parents and teachers also completed inventories of day-to-day social and attentional functioning. Group effects were found across objective social measures but not across related respondent-ratings. In contrast, group differences were observed in parent-ratings of attention difficulties, but not on standardized tests of attention or executive functioning. Findings underscore importance of integrating objective and functional measures when assessing ASD and/or ADHD

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J Child Adolesc Psychopharmacol. 2019;29:205-12.

CROCUS SATIVUS L. VERSUS METHYLPHENIDATE IN TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND PILOT STUDY.

Baziar S, Aqamolaei A, Khadem E, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood and adolescence. About 30% of patients do not respond to stimulants or cannot tolerate their side effects. Thus, alternative medication, like herbal medicine, should be considered. The aim of this trial is to compare the safety and efficacy of Crocus sativus (saffron) versus methylphenidate in improving symptoms of children with ADHD.

Methods: In a 6-week randomized double-blind study, 54 patients (children 6-17 years old) with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of ADHD were randomly assigned to receive either 20-30 mg/d (20 mg/d for <30 kg and 30 mg/d for >30 kg) methylphenidate (MPH) or 20-30 mg/d saffron capsules depending on weight (20 mg/d for <30 kg and 30 mg/d for >30 kg). Symptoms were assessed using the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and weeks 3 and 6.

Results: Fifty patients completed the trial. General linear model repeated measures showed no significant difference between the two groups on Parent and Teacher Rating Scale scores ($F = 0.749$, $df = 1.317$, $p = 0.425$, and $F = 0.249$, $df = 1.410$, $p = 0.701$, respectively). Changes in Teacher and Parent ADHD Rating Scale scores from baseline to the study end were not significantly different between the saffron group and the MPH group ($p = 0.731$ and $p = 0.883$, respectively). The frequency of adverse effects was similar between saffron and MPH groups.

Conclusion: Short-term therapy with saffron capsule showed the same efficacy compared with methylphenidate. Nevertheless, larger controlled studies with longer treatment periods are necessary for future studies

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J Child Adolesc Psychopharmacol. 2019;29:247-48.

EXFOLIATIVE SKIN REACTIONS WITH METHYLPHENIDATE AND DESENSITIZATION PROCEDURES IN TWO CASES.

Karakus Y, Cak ET.

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J Child Fam Stud. 2019 Mar;28:668-83.

PREDICTING CHILD BEHAVIOR: A COMPARATIVE ANALYSIS BETWEEN AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

McRae EM, Stoppelbein L, O'Kelley SE, et al.

Objective: Understanding factors that impact child adjustment is imperative. Parental adjustment, parenting behaviors, and environmental factors (e.g., child routines) have been linked to child behavior. In clinical child populations, these factors are particularly important given the increased demands the child's disorder often places on caregivers. Furthermore, children in clinical populations often engage in increased levels of internalizing and externalizing behaviors both related to and in addition to the core symptoms of their disorder. Two such clinical child populations are Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD).

Purpose: The first goal of the present study was to elucidate parental and environmental factors that predicted child behavior in ADHD and ASD. Based on Sameroff's Transactional Model of Development (2009), it was hypothesized that parental adjustment, parenting behaviors and child routines would collectively predict child behavior. A second goal was to examine differences in patterns of association between ADHD and ASD groups. Due to differences in the core symptoms of each disorder, it was hypothesized that the strength of associations would vary between groups.

Method: Researchers examined the impact of parental adjustment, parenting behaviors, and child routines on internalizing and externalizing child behavior using parent-report measures (CBCL, CRQ, HSCL-25, APQ) of children ages 6 to 12.

Results: Results indicated that for both groups, poor parental adjustment directly predicted externalizing child behavior and indirectly through harsh/disengaged parenting behavior. Fewer warm/supportive parenting behaviors predicted internalizing behavior, and more harsh/disengaged parenting predicted externalizing behavior. Higher levels of child routines predicted internalizing behavior for both groups but had a significantly stronger effect for children with ASD than ADHD.

Clinical Significance: Findings have important implications for interventions on several levels (e.g., parental adjustment, parenting behaviors, and environmental supports) in both the ADHD and ASD populations

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J Child Psychol Psychiatry. 2019 Apr;60:380-91.

ATTENTION DEFICIT HYPERACTIVITY DISORDER LATE BIRTHDATE EFFECT COMMON IN BOTH HIGH AND LOW PRESCRIBING INTERNATIONAL JURISDICTIONS: A SYSTEMATIC REVIEW.

Whitely M, Raven M, Timimi S, et al.

Background: Multiple studies have found that the youngest children in a classroom are at elevated risk of being diagnosed with, or medicated for, ADHD. This systematic review was conducted to investigate whether this late birthdate effect is the norm and whether the strength of effect is related to the absolute risk of being diagnosed/ medicated.

Methods: A literature search of the PubMed and ERIC databases and snowball and grey literature searching were conducted.

Results: A total of 19 studies in 13 countries covering over 15.4 million children investigating this relationship were identified. Three other studies exploring related topics were identified. The diversity of methodologies prevented a meta-analysis. Instead a systematic review of the 22 studies was conducted. A total of 17 of the 19 studies found that the youngest children in a school year were considerably more likely to be diagnosed and/or medicated than their older classmates. Two Danish studies found either a weak or no late birth date effect. There was no consistent relationship between per-capita diagnosis or medication rates and the strength of the relative age effect, with strong effects reported in most jurisdictions with comparatively low rates.

Conclusions: It is the norm internationally for the youngest children in a classroom to be at increased risk of being medicated for ADHD, even in jurisdictions with relatively low prescribing rates. A lack of a strong effect in Denmark may be accounted for by the common practice of academic 'redshirting', where children judged by parents as immature have a delayed school start. Redshirting may prevent and/or disguise late birthdate effects and further research is warranted. The evidence of strong late birthdate effects in

jurisdictions with comparatively low diagnosis/medication rates challenges the notion that low rates indicate sound diagnostic practices

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J Child Psychol Psychiatry. 2019 Feb;60:151-59.

INVESTIGATING THE EFFECTS OF CESAREAN DELIVERY AND ANTIBIOTIC USE IN EARLY CHILDHOOD ON RISK OF LATER ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Axelsson PB, Clausen TD, Petersen AH, et al.

Background: Increasing attention deficit hyperactivity disorder (ADHD) incidence has been proposed to be caused by factors influencing microbiota in early life. We investigated the potential causality between ADHD and two surrogate markers for changes in children's microbiota: birth delivery mode and early childhood antibiotic use.

Method: This population-based, prospective cohort study linked nationwide registers of data for native Danish singleton live births in Denmark from 1997 to 2010. Exposure variables were delivery mode and antibiotic use during the first 2 years of life. The main outcome measure was ADHD diagnosis or redeemed ADHD medication prescriptions. For statistical analysis, we used both advanced sibling models and a more traditional approach.

Results: We included 671,592 children, followed from their second birthday in the period 1999–2014 for 7,300,522 person-years. ADHD was diagnosed in 17,971. In total, 17.5% were born by cesarean delivery, and 72% received antibiotic treatment within their first 2 years of life. In the adjusted between-within sibling survival model, mode of delivery or antibiotics had no effect on ADHD when compared with vaginal delivery or no antibiotic treatment as hazard ratios were 1.09 (95% confidence interval 0.97–1.24) for intrapartum cesarean, 1.03 (0.91–1.16) for prelabor cesarean, 0.98 (0.90–1.07) for penicillin, and 0.99 (0.92–1.06) for broader spectrum antibiotics. In a sibling-stratified Cox regression, intrapartum cesarean was associated with increased ADHD risk, but other exposures were not. In a descriptive, nonstratified Cox model, we found increased risk for ADHD for all exposures.

Conclusions: Detailed family confounder control using the superior between-within model indicates that cesarean delivery or use of antibiotics during the first 2 years of life does not increase ADHD risk. Therefore, our study suggests that changes in children's microbiota related to cesarean delivery or antibiotic use, do not cause ADHD

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J Clin Child Adolesc Psychol. 2019 Mar;48:228-37.

HONING IN ON THE SOCIAL DIFFICULTIES ASSOCIATED WITH SLUGGISH COGNITIVE TEMPO IN CHILDREN: WITHDRAWAL, PEER IGNORING, AND LOW ENGAGEMENT.

Becker SP, Garner AA, Tamm L, et al.

Sluggish cognitive tempo (SCT) symptoms are associated with social difficulties in children, though findings are mixed and many studies have used global measures of social impairment. The present study tested the hypothesis that SCT would be uniquely associated with aspects of social functioning characterized by withdrawal and isolation, whereas attention deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms would be uniquely associated with aspects of social functioning characterized by inappropriate responding in social situations and active peer exclusion. Participants were 158 children (70% boys) between 7–12 years of age being evaluated for possible ADHD. Both parents and teachers completed measures of SCT, ADHD, ODD, and internalizing (anxiety/depression) symptoms. Parents also completed ratings of social engagement and self-control. Teachers also completed measures assessing asociality and exclusion, as well as peer ignoring and dislike. In regression analyses controlling for demographic characteristics and other psychopathology symptoms, parent-reported SCT symptoms were significantly associated with lower social engagement (e.g., starting conversations, joining activities). Teacher-reported SCT symptoms were significantly associated with greater asociality/withdrawal and ratings of more frequent ignoring by peers, as well as greater exclusion. ODD symptoms and ADHD hyperactive-impulsive symptoms were more consistently associated with other aspects of social behavior, including peer exclusion, being

disliked by peers, and poorer self-control during social situations. Findings provide the clearest evidence to date that the social difficulties associated with SCT are primarily due to withdrawal, isolation, and low initiative in social situations. Social skills training interventions may be effective for children displaying elevated SCT symptomatology

J Clin Rheumatol. 2019;25:S75.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AMONG PATIENTS WITH FIBROMYALGIA (FM).

Moyano S, Berrios W, Gandino I, et al.

Objectives: To evaluate ADHD in patients with FM and to assess its association with functional disability, disease impact, level of perceived pain and fatigue, severity of perceived cognitive symptoms and vitamin D levels.

Methods: Consecutive patients, older than 18 years, with diagnosis of FM (2010 ACR criteria) seen at the outpatient Rheumatology Unit between May 2016 and April 2017, were included. During the inclusion visit the following data were collected: Revised Fibromyalgia Impact Questionnaire (FIQ-R), HAQ-A (Health Auto Questionnaire-simplified, Argentinian validation); pain (Visual Analogue Scale, VAS), fatigue (VAS) and serum 25-hydroxyvitamin D (25(OH)D) level. During the Neurology visit, the following tests were performed: Conners Continuous Performance Test II (CPT II), Wender-Utah Rating Scale (WURS) and Structured Clinical Interview for Personality Disorders (SCID-II). Descriptive statistics were calculated. Correlations were calculated between CPT II and pain, fatigue, FIQ-R, HAQ-A and 25 (OH)D, using Spearman's test.

Results: 37 patients with FM were included. 73% (n=27) of the patients tested positive for adult ADHD. In 40.7% (11/27) of them, the diagnosis had been missed in childhood. Participants with both FM and a positive adult ADHD screening test did not score significantly higher on the FIQ-R (54.9, SD= 16.3 vs 48.8, SD= 11.3; $p=0.3320$) and did not have lower vitamin D levels (27.4 ng/ml, SD= 13.1 vs 36.7 ng/ml, SD= 9.6; $p=0.1050$). There was a very good positive correlation between ADHD and fatigue ($r=-0.9607$; $p=0.0086$). No association was found between ADHD and severity of perceived cognitive symptoms ($p=0.673$). There was no correlation with pain ($r=0.1688$ $p=0.3325$), HAQ-A ($r=0.1340$; $p=0.4429$) or vitamin D level ($r=-0.3211$; $p=0.1176$). No correlation was observed between vitamin D levels and FIQ-R ($r=-0.1848$; $p=0.3662$). The most frequent personality disorders found were narcissism and obsessive-compulsive disorder (35.1%).

Conclusions: The co-occurrence of adult ADHD in FM was highly prevalent. The diagnosis had been often overlooked in childhood. ADHD was associated with fatigue but not with pain, disease impact or functional capacity. Vitamin D levels were not associated with disease impact or dysfunction. Patients with FM should be assessed for the presence of adult ADHD. More investigations are needed to understand the impact of cognitive disorders in FM

J Dev Behav Pediatr. 2019 Feb;40:81-91.

THE ASSOCIATION BETWEEN RACE/ETHNICITY AND SOCIOECONOMIC FACTORS AND THE DIAGNOSIS AND TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Bax AC, Bard DE, Cuffe SP, et al.

Objective: Assessing race/ethnicity and socioeconomic status (SES) relationships with Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosis, treatment, and access to care has yielded inconsistent results often based only on parent-report. In contrast, this study used broader ADHD diagnostic determination including case-definition to examine these relationships in a multisite elementary-school-based sample.

Method: Secondary analysis of children with and without ADHD per parent and teacher-reported Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria evaluated SES, race/ethnicity, and other variables through simple bivariate/multivariable models within and across: parent-reported diagnosis, medication treatment, and meeting ADHD study case-definition.

Results: The total sample included 51.9% male, 51.3% White, and 53.1% with private insurance; 10% had parent-reported ADHD diagnoses while 8.3% met ADHD study case-definition. In multivariable models,

White children had higher odds of parent-reported diagnoses than Black, Hispanic, and Other Race/Ethnicity children ($p < 0.05$), but only Hispanic children had lower odds of being case-positive (< 0.05); males and children in single-parent households had higher odds of parent-reported diagnoses and being case-positive ($p < 0.05$); and children who were White, male, and had health insurance had higher odds of taking medication ($p < 0.05$). Among children who were case-positive, those with Medicaid, White, and 2-parent statuses had higher odds of parent-reported diagnoses ($p < 0.05$).

Conclusion: Children with underlying ADHD appear more likely to have assessment/medication treatment access if they are White, male, have health insurance (particularly Medicaid), and live in 2-parent households. While boys and children raised by single parents may have higher rates of ADHD diagnoses, false-positive diagnostic risk also appeared higher, inviting further investigation

Journal of Dual Diagnosis. 2019.

COMORBIDITY PATTERNS AMONG PATIENTS WITH OPIOID USE DISORDER AND PROBLEM GAMBLING: ADHD STATUS PREDICTS CLASS MEMBERSHIP.

Silbernagl M, Yanagida T, Slamanig R, et al.

Objective: Psychiatric comorbidities are highly prevalent among individuals affected by substance use disorders and those with non-substance-related addictive disorders such as gambling disorder. More recently, the frequent co-occurrence of substance use disorders and attention-deficit hyperactivity disorder (ADHD) has received particular attention. The aim of our study was to identify patterns of psychiatric comorbidity and to examine associations between patient group and ADHD status with class membership.

Methods: Participants were patients with opioid use disorder enrolled in opioid maintenance treatment (OMT), either recruited from the community ($n = 142$; M age = 35.8 years; 38.7% female) or prison ($n = 133$; M age = 35.7 years; 21.8% female), and patients undergoing treatment for problem gambling (PrG; $n = 80$; M age = 43.1 years; 20% female). To enable direct comparisons, the following instruments were applied: Mini International Neuropsychiatric Interview, Adult ADHD self-report scale, Wender Utah Rating Scale, and European Addiction Severity Index. We used a latent class analysis (LCA) to identify psychiatric comorbidity patterns and a multinomial logistic regression to examine associations between patient group, ADHD status, age, and gender with class membership.

Results: The LCA resulted in a three-class solution: (1) a class of individuals with a relatively low probability of current psychiatric comorbidities, except for a high probability of substance use disorders; (2) a class with markedly increased probabilities of current and recurrent psychiatric comorbidities, especially for major depression; and (3) a class with very low probabilities of psychiatric comorbidities, except for moderate probabilities of substance use disorders and antisocial personality disorder. Both OMT patients recruited from the community and those in prison were less likely than PrG patients to be assigned to the most burdened class with respect to psychiatric comorbidity (class 2). Further, both individuals with ADHD in childhood and those with adult ADHD were more likely members of class 2.

Conclusions: PrG patients seem to be at an even higher risk for psychiatric comorbidities compared to OMT patients. Raising awareness among practitioners for the high prevalence of psychiatric comorbidities among patients with gambling disorder and individuals with ADHD is crucial to initiate adequate treatment and to improve response

J Invest Med. 2019;67:373-74.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ARE RESIDENTS FOLLOWING GUIDELINES?

Bradham K, Trimm R, Darden AG.

Purpose of study Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common pediatric neurobehavioral disorder. Although the American Academy of Pediatrics (AAP) have published guidelines about the diagnosis, evaluation, and treatment of ADHD, it is not clear if resident education prepares trainees to apply the guidelines to their practice. The supervising faculty at the University of South Alabama and senior residents express concerns that the care and management of patients with ADHD does not follow the AAP

guidelines. This study allowed for significant and meaningful evaluation of gaps in residents' knowledge in an effort to work toward more efficient education of residents and quality of patient care in the area of ADHD. **Methods** used Retrospective chart review of 50 charts of children ages 4-18 years seen April-June 2015. Charts were selected if (1) the child was age 4-18 years, (2) the ICD 9 diagnosis code was related to ADHD (314.00 or 314.01), and (3) if the pediatric resident completed the chart. A single reviewer audited and analyzed the charts using a checklist based on the AAP practice guidelines for clinical diagnosis, evaluation, and treatment of ADHD. Summary of results Findings indicate that a majority of patient encounters were follow up visits (96%), of which 19% had medication adjustment(s). Symptoms of inattention (19%) and hyperactivity/impulsivity (21%) were addressed at the follow up visits. Academic performance (56%) was the most commonly addressed behavioral component. Co-morbidities were documented 20% of the time. At least one component of the medications side effect profile was mentioned (92%). Many physical examination measurements such as height (66%), weight (100%), blood pressure (96%) were addressed.

Conclusions A majority of the patient encounters were for follow up visits including medication management. Documentation of the discussion of side effects from stimulant medication was a relative strength of residents. Documentation of core symptoms of ADHD was a relative weakness of the residents. The chart review revealed that documentation rates of co-morbidities in this study were below rates documented in the literature. An educational intervention will be developed to improve residents' documentation of core symptoms and co-morbidities of ADHD

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J Invest Med. 2019;67:587-88.

FECAL INCONTINENCE IN CHILDREN WITH ADHD, BEFORE AND AFTER ADHD TREATMENT: THE ROLE OF STIMULANT MEDICATION.

McCann L.

Purpose of study The aim of this study is to compare the resolution of FI in children with ADHD before and after treatment with ADHD stimulants. We hypothesize that FI will be higher prior to initiation of ADHD stimulants and lower after initiation.

Methods used A retrospective chart review from 2011-2017, using ICD 9-10 codes for FI, constipation, and ADHD. Children aged 5yo-19yo were included. Patients excluded if deceased, severe neurological diagnoses, anorectal malformations, or previous GI surgery. Statistical analysis was done using Fisher's exact test and logistic regression analysis. Summary of results This study included 174 patients with ADHD. There were 106 males (61%) and 68 females (39%). Data showed 171 of 174 patients (98%) had constipation and 22 patients (12%) had FI and ADHD. Of these 22 patients, all were currently being treated for FI with laxatives. Among the 19 patients with results, 14 (73%, 95% CI[48%, 89%]) did not have recurrence of FI after stimulants. 18 (82%) were on stimulants, and 4 (18%) were not. The effect of stimulant on FI is not significant ($p=0.15$) with an odd ratio of 0.13. 133 patients out of 174 patients (76%) were currently on ADHD stimulant medications. Mean length of constipation treatment and ADHD stimulant treatment were similar, at 3 years. Fisher's exact test and logistic regression analysis were used.

Conclusions Children with ADHD have a higher incidence of FI. Treatment of ADHD with stimulants helps in resolution of FI

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Journal of Mazandaran University of Medical Sciences. 2019;28:107-19.

EFFECT OF MINDFULNESS-BASED EDUCATION ON PSYCHOLOGICAL CAPITAL OF PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Talebi S, Lolaty HA, Shafaat A, et al.

Background and purpose: Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in children that affects the health of parents. The aim of this study was to determine the effect of mindfulness education on psychological capital of parents of ADHD children.

Materials and methods: This semi-experimental study was of pretest-posttest control group design which was carried out in 80 parents of ADHD children. The participants were selected using convenience sampling

from Sari Zare Clinic, Iran, 2018. They were randomly divided into intervention group (n=40) or control group (n=40). Mindfulness education was done in 8 sessions of 90 minutes twice a week for the intervention group. Data were collected using demographic questionnaire and Luthans psychological capital questionnaire. Data were analyzed using Chi-square, t-test and covariance test.

Results: Before and after the intervention, significant differences were found between the mean values for psychological capital (60.65 ± 7.61 vs. 80.58 ± 7.59), hope (15.86 ± 3.37 vs. 21.36 ± 3.37), resilience (14.34 ± 2.85 vs. 19.34 ± 2.68), optimism (15.65 ± 2.70 vs. 20.22 ± 2.76), and self-efficacy (15.2 ± 2.35 vs. 19.89 ± 2.59) in intervention group. The scores after the intervention showed the significant effect of mindfulness education on psychological capital of parents of children with ADHD ($P < 0.05$).

Conclusion: Mindfulness education is recommended to increase the psychological capital and its dimensions in the parents of ADHD children

J Neural Transm. 2019.

ASSOCIATION STUDY AND A SYSTEMATIC META-ANALYSIS OF THE VNTR POLYMORPHISM IN THE 3' UTR OF DOPAMINE TRANSPORTER GENE AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Grünblatt E, Werling AM, Roth A, et al.

Attention-deficit hyperactivity disorder (ADHD) has been postulated to associate with dopaminergic dysfunction, including the dopamine transporter (DAT1). Several meta-analyses showed small but significant association between the 10-repeat allele in the DAT1 gene in 3'-untranslated region variant number tandem repeat polymorphism and child and adolescent ADHD, whereas in adult ADHD the 9-repeat allele was suggested to confer as risk allele. Interestingly, recent evidence indicated that the long-allele variants (10 repeats and longer) might confer to lower expression of the transporter in comparison to the short-allele. Therefore, we assessed here the association in samples consisting of families with child and adolescent ADHD as well as a case-control sample, using either the 10- versus 9-repeat or the long- versus short-allele approach. Following, we conducted a systematic review and meta-analysis, including family and case-control studies, using the two aforementioned approaches as well as stratifying to age and ethnicity. The first approach (10-repeat) resulted in nominal significant association in child and adolescent ADHD (OR 1.1050 $p = 0.0128$), that became significant stratifying to European population (OR 1.1301 $p = 0.0085$). The second approach (long-allele) resulted in significant association with the whole ADHD population (OR 1.1046 $p = 0.0048$), followed by significant association for child and adolescent ADHD (OR 1.1602 $p = 0.0006$) and in Caucasian and in European child and adolescent ADHD (OR 1.1310 $p = 0.0114$; OR 1.1661 $p = 0.0061$; respectively). We were not able to confirm the association reported in adults using both approaches. In conclusion, we found further indication for a possible DAT1 gene involvement; however, further studies should be conducted with stringent phenotyping to reduce heterogeneity, a limitation observed in most included studies

Journal of Neuro-Oncology. 2019.

CLINICAL DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SURVIVORS OF PEDIATRIC BRAIN TUMORS.

Shabason EK, Brodsky C, Baran J, et al.

PURPOSE: Survivors of pediatric brain tumors often have neurodevelopmental late effects, such as inattention. Symptoms may mirror those of attention-deficit/hyperactivity disorder (ADHD), which affects ~5-8% of the general population. This retrospective study of survivors followed at a large tertiary care center examined the prevalence of a clinical diagnosis of ADHD, and risk factors associated with ADHD diagnosis and ADHD-related medication use.

METHODS: A retrospective chart review of brain tumor survivors ($n = 528$), diagnosed between 2000 and 2015, who were at least 6 years old and 2 years from the end of tumor-directed therapy or from diagnosis, if no interventions were received. Clinical and demographic data were extracted from the medical record.

RESULTS: Survivors were 55.7% male with mean age 8.15 ± 4.4 (0.0-16.0) years at brain tumor diagnosis. The most common diagnoses were low-grade glioma, medulloblastoma, and craniopharyngioma, with 52.5%

of tumors supratentorial. Of the survivors, 81.3% received surgery, 40.0% radiation therapy, and 36.6% chemotherapy. Sixty-nine survivors (13.1%) had ADHD diagnoses, 105 (19.9%) had symptoms of ADHD without diagnoses, and 64 (12.1%) had ADHD medication use. ADHD diagnosis was associated with younger age at tumor diagnosis ($p = 0.05$) and supratentorial tumor location ($p = 0.001$). ADHD diagnosis was not associated with gender, tumor type, or treatment type.

CONCLUSIONS: Survivors of brain tumors are at increased risk of ADHD and related symptoms. The greatest increase in risk occurs for survivors with diagnoses at younger ages and supratentorial tumors. Additional research is warranted, as select survivors may benefit from behavioral or pharmacologic ADHD treatments to optimize functioning

J Am Acad Child Adolesc Psychiatry. 2019 Feb;58:256-66.

BRAIN STRUCTURE AND FUNCTION IN SCHOOL-AGED CHILDREN WITH SLUGGISH COGNITIVE TEMPO SYMPTOMS.

Camprodon-Rosanas E, Pujol J, Martínez-Vilavella G, et al.

Objective: Sluggish cognitive tempo (SCT) is a cluster of symptoms associated with poor function in various domains of major life activities that may comprise a novel attention disorder distinct from attention-deficit/hyperactivity disorder (ADHD). Nevertheless, very little is known about the neural substrate of SCT in children. The present study aimed to examine associations between SCT symptoms and brain structure and function in school-aged children.

Method: We performed a cross-sectional MRI study in 178 children 8 to 12 years old from primary schools in Barcelona, Spain. Data were collected between January 2012 and March 2013. Parents completed the Sluggish Cognitive Tempo–Child Behavior Checklist (SCT-CBCL). Participants underwent magnetic resonance imaging to assess regional brain volume, white matter integrity using diffusion tensor imaging, and functional connectivity in major neural networks.

Results: SCT symptoms were associated with altered anatomy of the frontal lobe in the form of increased regional volume. The anomalously large cortical regions were less mature in terms of functional connectivity. Importantly, all the anatomical and functional anomalies identified remained significant after adjusting the analyses for ADHD symptom scores.

Conclusion: Our results suggest that SCT symptoms are associated with distinct features of brain structure and function that differ from the classical neural substrates described in ADHD

J Am Acad Child Adolesc Psychiatry. 2019 Feb;58:164-66.

EDITORIAL: NEURAL CORRELATES OF SLUGGISH COGNITIVE TEMPO: BIOLOGICAL EVIDENCE OF A DISTINCT CLINICAL ENTITY?

Sussman TJ, Posner J.

Comments on an article by E. Camprodon-Rosanas et al. (see record [rid]2019-08925-016[/rid]). Camprodon-Rosanas et al. examined associations between sluggish cognitive tempo (SCT) symptoms and brain morphometry, functional connectivity, and white matter microstructure in a large sample from the general population. Perhaps the most striking finding was that as SCT symptoms increased, volumes within the frontal lobe increased, including the right prefrontal and premotor cortices. Furthermore, similar to studies of ADHD, SCT symptoms were associated with altered functional connectivity of the brain's default mode network (DMN), a neural circuit implicated in inattention and mind-wandering. More specifically, less pronounced anti-correlations between a key node of the DMN and nodes of a task-positive network were found. These decreases in anti-correlations between the DMN and taskpositive nodes persisted after accounting for ADHD symptoms, suggesting that these neural correlates of SCT are distinct from those of ADHD. These findings raise important questions about the relation between the DMN and attentional symptoms. The results from Camprodon-Rosanas et al. build on emerging evidence of brain differences related to SCT. Camprodon-Rosanas et al. further these results by demonstrating neural correlates of SCT in a general population, thereby providing further support SCT as a distinct clinical entity

J Am Acad Child Adolesc Psychiatry. 2019;58:423-32.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, SCHOOL PERFORMANCE, AND EFFECT OF MEDICATION.

Jangmo A, et al.

Objective: Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for poor school performance, and pharmacological treatment of ADHD may have beneficial effects on school performance. Conclusions from previous research have been limited by small sample sizes, outcome measures, and treatment follow-up. The current study analyzed school performance in students with ADHD compared to students without ADHD, and the association between pharmacological treatment of ADHD and school performance.

Method: A linkage of Swedish national registers covering 657,720 students graduating from year 9 of compulsory school provided measures of school performance, electronically recorded dispensations of ADHD medication, and potentially confounding background factors such as parental socioeconomic status. Primary measures of school performance included student eligibility to upper secondary school and grade point sum.

Results: ADHD was associated with substantially lower school performance independent of socioeconomic background factors. Treatment with ADHD medication for 3 months was positively associated with all primary outcomes, including a decreased risk of no eligibility to upper secondary school, odds ratio = 0.80, 95% confidence interval (CI) = 0.76-0.84, and a higher grade point sum (range, 0.0-320.0) of 9.35 points, 95% CI = 7.88-10.82; standardized coefficient = 0.20.

Conclusion: ADHD has a substantial negative impact on school performance, whereas pharmacological treatment for ADHD is associated with higher levels in several measures of school performance. Our findings emphasize the importance of detection and treatment of ADHD at an early stage to reduce the negative impact on school performance

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J Med Assoc Thailand. 2018;101:S34-S40.

THE PREVALENCE AND PATTERNS OF SLEEP PROBLEM IN CHILDREN WITH ADHD.

Hosiri T, Punyapas S, Sawangsri W.

Objective: To determine the prevalence and patterns of sleep problems in children with Attention deficit/hyperactivity disorder [ADHD] as well as to identify several factors associated sleep problems.

Materials and Methods: This present study was a cross-sectional, descriptive study. Ninety- six parents whose children were diagnosed with ADHD in their first visit responded to a questionnaire. The items in the questionnaire included questions about demographic data and questions related to sleep problems chosen from a Child Behavior Checklist (Thai version) and the literature review. The prevalence and patterns of sleep problem are presented as descriptive statistics. Factors associated with sleep problems were analyzed by Chi-square test and logistic regression.

Results: The prevalence of sleep problems was found to be 72.9%. Their patterns were the following: needing the parents to stay with them at bedtime (38.5%); fear of sleeping in the dark (30.2%); and hard to fall asleep (24%). The factors associated with the sleep problems were the age of the children, adjusted OR = 7.47 (1.97 to 28.34), and the perception of the parents on their child's sleep problems, adjusted OR = 7.80 (1.92 to 31.68). Namely, children under 11 years old were more likely to have a sleep problem than children over 11 years old. Children whose parents had been aware of some signs of their sleep problems were more likely to have a real sleep problem than those whose parents had not been aware.

Conclusion: The prevalence of sleep problems in ADHD children before coming for treatment was high. Most sleep problems occurred at the time they were going to bed. For these reasons, it is essential to identified children's sleep problems before an ADHD treatment is prescribed

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J Trauma Dissociation. 2019.

DISSOCIATION AND PSYCHOPATHOLOGY IN RESIDENTIAL YOUTH: A BRIEF REPORT.

Fragkaki I, Weijman EL, Cima M.

Although dissociative symptoms are observed in several psychiatric disorders and linked to antisocial behavior and offending, the relation between dissociation and psychopathology or comorbidity has not been consistently investigated in residential youth yet. This brief report documented prevalence and comorbidity rates of several psychiatric disorders and examined their relation to dissociation in residential youth. The study included 100 male adolescents (Mean age=16.51) admitted to residential youth care facilities. Psychopathology was assessed with the Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) and dissociation was measured with the Adolescent Dissociative Experiences Scale (A-DES). Externalizing problems (conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder) were the most prevalent (81%) followed by substance abuse/dependence (71%), manic/hypomanic symptoms (40%), anxiety (35%), and depression (33%). High comorbidity was also observed in externalizing problems with alcohol/substance abuse/dependence (67%), manic/hypomanic symptoms (35%), depression (31%), and anxiety (30%). Logistic regression analyses revealed a significant link between dissociation and externalizing problems, depression, and manic/hypomanic symptoms, as well as comorbid externalizing problems and depression or manic/hypomanic symptoms. The findings highlight the need to assess dissociation in order to better understand the multifaceted individual profile of residential youth and incorporate it in the treatment plan

Koomesh. 2019;21:292-97.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS IN FIRST TO THIRD GRADES PRIMARY SCHOOL STUDENTS IN SEMNAN, IRAN.

Sadolahi A, Ghorbani R, Bakhtiyari J, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is a developmental behavioral disorder. Children with ADHD do not have the ability to concentrate on a subject due to the unusual and extremely high physical activity. In spite of the negative effects of the ADHD, the epidemiological studies in this field seem to be limited. The aim of the present study was to report the prevalence of ADHD in the first to third grade elementary school students of Semnan, Iran.

Materials and Methods: Twenty out of 69 primary schools were selected through the cluster random sampling procedure. The Conner's questionnaire (teachers' version) was handed in to the teachers. After three working days, the completed forms were collected. Each child's score was calculated. The cutoff point for the diagnosis of ADHD was considered 60.

Results: The results of the present study indicated that 44.5% of the students showed some degrees of the ADHD that 10.9% of them scored as severe (they scored at or above 60). Thirteen percent of the boys and 8.6% of the girls showed severe symptoms of ADHD, this difference was statistically significant ($p = 0.049$). In the subdivisions of the Conner's questionnaire, the girls scored better than the boys in the "Behavior in Class" section ($p = 0.014$).

Conclusion: About half of the primary school students in Semnan city showed different degrees of ADHD in the first to third grades, of which 10.9% were severe. Therefore, performing diagnostic screening of ADHD at the beginning as well as in the middle of the school year can be an effective way to identify children with ADHD earlier, provide extra educational and rehabilitation services and support, with priority in boys, and to be able to prevent the consequences and disadvantages of ADHD in students

Medicine (Baltimore). 2019 Apr;98:e15097.

THE EFFECTS OF PHYSICAL ACTIVITY ON EXECUTIVE FUNCTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL.

Zhang MQ, Liu Z, Ma HT, et al.

BACKGROUND: The effects of physical activity on executive function are well documented, but whether physical activity contributes to the executive function of attention deficit hyperactivity disorder (ADHD) children are still inconclusive.

METHODS: The study is guided by the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). We will search the following databases PubMed, EMBASES, the Cochrane Library, CNKI, and Wanfang-Data to identify the Randomized Controlled Trials evaluating the effects of physical activity on executive function among ADHD children. The language of literature restricted in Chinese and English, which published from inception to January 2019. Two reviewers will screen the studies independently, while risk of bias assessment, data extraction, and inconsistent results will be discussed by the third reviewer. Revman 5.3 and Stata 12 software will be used to complete data analysis and synthesis.

CONCLUSION: This study will be based on findings of previous studies, thus the ethics approval is not required. The final results will be presented at an international conference and submitted to a peer-reviewed journal of relative field for consideration of publication.

PROSPERO REGISTRATION NUMBER: CRD42019118622

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Nan Fang Yi Ke Da Xue Xue Bao. 2019 Jan;39:30-34.

RESPONSE INHIBITION AND EMOTIONAL RESPONDING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH COMORBID DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS.

Jiang X, Liu L, Ji H, et al.

OBJECTIVE: To characterize the traits of neuropsychological functioning deficits in patients with attention-deficit/ hyperactivity disorder (ADHD) with comorbid disruptive, impulse-control, and conduct disorders (DICCD).

METHODS: Twenty out-patients with ADHD, 20 with ADHD with comorbid DICCD, and 20 with DICCD, all aged 6-16 years, were enrolled in this study, with 20 healthy subjects matched for age, gender and IQ serving as the healthy controls. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5). All the subjects were assessed with Golden Stroop test and emotional Stroop test to evaluate their response inhibition and emotional responding. **RESULTS:** In Golden Stroop test, the interference scores (IGs) of errors and reaction time both differed significantly among the groups ($P < 0.05$), and were the highest in patients with ADHD only. In emotional Stroop test, the mean reaction time (MRT) showed significant differences among the groups ($P < 0.05$); the MRT of positive-congruent trials in ADHD with comorbid DICCD group was shorter than that in ADHD group but longer than that in group DICCD; the MRT in the 3 case groups were all longer than that in the control group. The MRT of both positive-incongruent trials and negative-congruent trials in ADHD with comorbid DICCD group and DICCD group was shorter than that in ADHD group but longer than that in the control group. The MRT of negative- incongruent trials in DICCD group was shorter than that in ADHD group and ADHD with comorbid DICCD group but longer than that in the control group.

CONCLUSIONS: The response inhibition deficit and abnormal emotional responding are the core symptoms of ADHD. Bias emotional stimuli may render response inhibitory dysfunction in patients with DICCD with callous-unemotional traits of emotional responding disorder, especially in dealing with negative emotional trials, while the comorbidity of ADHD and DICCD tends to have the emotional response trait of DICCD

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Neuropsychopharmacology. 2019.

WHITE MATTER MICROSTRUCTURE IS ASSOCIATED WITH HYPERACTIVE/INATTENTIVE SYMPTOMATOLOGY AND POLYGENIC RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A POPULATION-BASED SAMPLE OF ADOLESCENTS.

Albaugh MD, Hudziak JJ, Ing A, et al.

Few studies have investigated the link between putative biomarkers of attention-deficit/hyperactivity disorder (ADHD) symptomatology and genetic risk for ADHD. To address this, we investigate the degree to which ADHD symptomatology is associated with white matter microstructure and cerebral cortical thickness in a large population-based sample of adolescents. Critically, we then test the extent to which multimodal correlates of ADHD symptomatology are related to ADHD polygenic risk score (PRS). Neuroimaging, genetic, and behavioral data were obtained from the IMAGEN study. A dimensional ADHD composite score was derived from multi-informant ratings of ADHD symptomatology. Using tract-based spatial statistics, whole brain voxel-wise regressions between fractional anisotropy (FA) and ADHD composite score were calculated. Local cortical thickness was regressed on ADHD composite score. ADHD PRS was based on a very recent genome-wide association study, and calculated using PRSice. ADHD composite score was negatively associated with FA in several white matter pathways, including bilateral superior and inferior longitudinal fasciculi ($p < 0.05$, corrected). ADHD composite score was negatively associated with orbitofrontal cortical thickness ($p < 0.05$, corrected). The ADHD composite score was correlated with ADHD PRS ($p < 0.001$). FA correlates of ADHD symptomatology were significantly associated with ADHD PRS, whereas cortical thickness correlates of ADHD symptomatology were unrelated to ADHD PRS. Variation in hyperactive/inattentive symptomatology was associated with white matter microstructure, which, in turn, was related to ADHD PRS. Results suggest that genetic risk for ADHD symptomatology may be tied to biological processes affecting white matter microstructure

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Neuroscience. 2019;406:444-56.

EEG CHARACTERISTICS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Chen H, Chen W, Song Y, et al.

The electroencephalogram (EEG) is an informative neuroimaging tool for studying attention-deficit/hyperactivity disorder (ADHD); one main goal is to characterize the EEG of children with ADHD. In this study, we employed the power spectrum, complexity and bicoherence, biomarker candidates for identifying ADHD children in a machine learning approach, to characterize resting-state EEG (rsEEG). We built support vector machine classifiers using a single type of feature, all features from a method (relative spectral power, spectral power ratio, complexity or bicoherence), or all features from all four methods. We evaluated effectiveness and performance of the classifiers using the permutation test and the area under the receiver operating characteristic curve (AUC). We analyzed the rsEEG from 50 ADHD children and 58 age-matched controls. The results show that though spectral features can be used to build a convincing model, the prediction accuracy of the model was unfortunately unstable. Bicoherence features had significant between-group differences, but classifier performance was sensitive to brain region used. rsEEG complexity of ADHD children was significantly lower than controls and may be a suitable biomarker candidate. Through a machine learning approach, 14 features from various brain regions using different methods were selected; the classifier based on these features had an AUC of 0.9158 and an accuracy of 84.59%. These findings strongly suggest that the combination of rsEEG characteristics obtained by various methods may be a tool for identifying ADHD

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Nutrients. 2019;11.

THE RELATIONSHIP BETWEEN FOOD INSECURITY AND SYMPTOMS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN: A SUMMARY OF THE LITERATURE.

Lu S, Perez L, Leslein A, et al.

Food insecurity is a major public health concern characterized by an individual or household lacking access to adequate food to support a healthy lifestyle. Food insecurity has been associated with predisposing or exacerbating mental health symptoms in children. However, the evidence is scarce with regards to Attention-Deficit Hyperactivity Disorder (ADHD) symptoms in children. The purpose of this review is to summarize and identify gaps in the existing literature, as well as to explore associations between food insecurity and symptoms of childhood ADHD. Literature for this review was pulled from Ovid MEDLINE and PubMed library databases, with a focus on food insecurity, food insufficiency, hunger, and ADHD symptoms such as inattention, hyperactivity, and impulsivity in children. The limited evidence to date shows a predictive and inverse relationship between childhood experience of food insecurity and symptoms of ADHD, with lasting impacts into adulthood. Evidence exists to hypothesize that childhood food insecurity is associated with predisposing or exacerbating ADHD symptoms in children, yet the literature needed to confirm this relationship is scarce and utilizes inconsistent methodology. Future research is needed to further characterize this complex relationship and inspire community or public health interventions addressing food insecurity in children with ADHD. Additionally, it may be clinically useful to routinely screen for food insecurity when assessing pediatric ADHD symptoms

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Paediatr Croat. 2018;62:151-55.

CORRELATIONS BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER, OBSESSIVE-COMPULSIVE DISORDER AND TICS IN CHILDREN AND ADOLESCENTS: CASE REPORT.

Klobu-iar A, Prv-ii-ç I, Jaku+ii-ç N, et al.

The relationship between the attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and tics is primarily discussed through genetic, neurobiological, neurocognitive and neurochemical substrates of reduced impulse control. The comorbidity of these disorders in children and adolescents is not a rarity. In our 14-year-old patient, ADHD and simple motor tics were diagnosed at pre-school age and OCD at the age of 10. We diagnosed these disorders by DSM-IV criteria and semi-structured interviews based on it. In a multimodal treatment we used techniques from cognitive behavioural psychotherapy, psychoeducation and parental support, sensory integration therapy with a assistance dog, neurofeedback, medication therapy (methylphenidate, fluvoxamine), group therapy aimed at enhancing social skills and expressing emotions, individualized approach to learning in school with a personal assistant. We discuss the complexity of treatment of clinical presentation complicated by comorbidity and emotional distress, and some known and possible links between these disorders. Treatment of ADHD demands multimodal approach and cooperation of different professionals. Among other things, timely recognition of associated symptoms and other psychiatric disorders and their linkage is very important to prevent intensification of symptoms and signs of the disorder and to determine therapeutic guidelines. Further investigation is needed

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PLoS ONE. 2019;14.

RISK AND PROTECTIVE FACTORS FOR THE DEVELOPMENT OF ADHD SYMPTOMS IN CHILDREN AND ADOLESCENTS: RESULTS OF THE LONGITUDINAL BELLA STUDY.

Wüstner A, Otto C, Schlack R, et al.

Background Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood worldwide, and causes significant impairments in overall functioning. In order to develop effective prevention and intervention programs, knowledge of the determinants that have an impact on the onset and development of ADHD symptoms is essential. So far, little is known about factors affecting ADHD symptoms in children and adolescents over time. Therefore, this study investigates potential

psychosocial risk and protective factors for ADHD symptoms based on cross-sectional and longitudinal data of a German population-based study.

Methods Data on children and adolescents ($n = 1,384$ aged 11 to 17 years) were collected at three measurement points (baseline, 1-year and 2-year follow-ups) covering a period of two years. We used latent growth modelling to investigate effects of parental mental health problems (risk factor) and self-efficacy, family climate and social support (protective factors) on symptoms of ADHD based on cross-sectional as well as longitudinal data. Sociodemographic factors, pre- and postnatal factors, and comorbid symptoms of internalizing and externalizing mental health problems were considered as covariates.

Results At baseline, male gender, younger age, stronger aggressive behavior, and stronger parental mental health problems were related to more ADHD symptoms. Longitudinal analyses showed that female gender, migration status, increasing symptoms of generalized anxiety, increasing aggressive behavior and increasing parental mental health problems were associated with stronger increase of ADHD symptoms over time. However, improving family climate was related to decreasing ADHD symptoms over time. We further found moderator effects for social support.

Conclusion The findings of the study provide important information concerning risk and protective factors in the context of ADHD. Hence, the results may be integrated into the planning and implementation of future prevention and early intervention strategies that target affected children and adolescents

Psychiatry Res. 2019 Jan;271:726-31.

THE IMPACT OF DEPRESSION, ANXIETY, NEUROTICISM, AND SEVERITY OF INTERNET ADDICTION SYMPTOMS ON THE RELATIONSHIP BETWEEN PROBABLE ADHD AND SEVERITY OF INSOMNIA AMONG YOUNG ADULTS.

Evren B, Evren C, Dalbudak E, et al.

The aim of the present study was to evaluate the impact of depression, anxiety, neuroticism, and severity of Internet addiction symptoms (IAS) on the relationship between probable attention deficit/hyperactivity disorder (ADHD) and severity of insomnia among young adults. The study was conducted with online survey among 1010 volunteered university students in Ankara, people who are in the e-mail database of a company located in Istanbul that organizes e-sports tournaments and Turkish gamers from gaming forums. Scale scores were higher among the group with high probability of insomnia ($n=200$, 19.8%). Also risk of high probability of insomnia was 2.7 times higher among those with probable ADHD. In linear regression analysis, both inattentiveness and hyperactivity/impulsivity dimensions of ADHD were related with the severity of insomnia, together with severities of anxiety, depression, neuroticism and IAS. Similarly, presence of probable ADHD was related with the severity of insomnia in ANCOVA, together with severities of anxiety, depression, neuroticism and IAS. These findings suggest that the presence of probable ADHD and the severity of ADHD symptoms are related with the severity of insomnia, even after controlling the depression, anxiety, neuroticism and IAS, which are all related with the severity of insomnia, among young adults

Psychiatry Res. 2019 Mar;273:753-58.

Construct validity and diagnostic accuracy of the Italian translation of the 18-Item World Health Organization Adult ADHD Self-Report Scale (ASRS-18) Italian translation in a sample of community-dwelling adolescents.

Somma A, Borroni S, Fossati A.

Aim of this prospective study was to evaluate the factor structure, internal consistency, and diagnostic efficacy of the Italian translation of the Adult ADHD Self-Report Scale (ASRS-18; Kessler et al., 2005, 2007) in a sample of community-dwelling sample of adolescents. Three hundred eight Italian adolescents attending professional high schools were administered the ASRS-18; the adolescence ADHD module of the MINI interview was administered to obtain ADHD criterion diagnoses. Robust maximum likelihood confirmatory factor analysis results identified a bifactor model of the ASRS-18 items as the best-fitting model, RMSEA = 0.029, $p > 0.99$, TLI = 0.93, CFI = 0.95. Further analyses showed that 77.9% of the ASRS-18 reliable (? = 0.78) score variance was due to the total score. In our study the ASRS-18 proved to be able to effectively

differentiate adolescents who received a MINI ADHD diagnosis (n = 80) from adolescents who did not receive a MINI ADHD diagnosis (n = 163), area under the curve = 0.80, 95% confidence interval = 0.74, 0.86. Our data suggest that the ASRS-18 may represent an effective self-report measure to screen for ADHD in community-dwelling adolescents, at least in its Italian translation

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Psychiatry Res. 2019 Apr;274:75-90.

ARE SUBSYNDROMAL MANIFESTATIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER MORBID IN CHILDREN? A SYSTEMATIC QUALITATIVE REVIEW OF THE LITERATURE WITH META-ANALYSIS.

Kirova AM, Kelberman C, Storch B, et al.

We conducted a qualitative review (n = 15 manuscripts) and meta-analysis (n = 9 manuscripts) of the extant literature to evaluate the prevalence and morbidity of subthreshold Attention Deficit Hyperactivity Disorder (ADHD). Our qualitative review showed that a sizable minority (mean: 17.7%) of clinically referred and non-referred children met a priori definitions of subthreshold ADHD. Those affected exhibited significantly higher rates of family dysfunction, cognitive impairment, executive dysfunction, interpersonal and school deficits, temperament problems, psychiatric comorbidity, and juvenile delinquency compared to children with no ADHD symptoms. These deficits were highly consistent with those observed in children with full threshold ADHD. These findings indicate that children with subthreshold ADHD symptoms are at significantly greater risk for negative outcomes in a wide range of non-overlapping functional domains worthy of further clinical and scientific consideration

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Psychiatry Res. 2019;275:212-20.

AUTONOMIC AROUSAL PROFILES IN ADOLESCENTS AND YOUNG ADULTS WITH ADHD AS A FUNCTION OF RECORDING CONTEXT.

Du RE, James S-N, Banaschewski T, et al.

A recent study (James et al. 2016) found that attention-deficit/hyperactivity disorder (ADHD) was associated with hypo-arousal, indexed by low electrodermal activity, during a low-demand reaction-time task, which normalized in a fast-incentive condition. We now investigate if (1) autonomic arousal in individuals with ADHD changes over a long testing session and (2) across time, to clarify if arousal profiles are context-dependent. We also examine (3) how autonomic arousal relates to each ADHD symptom domain, and specificity of arousal profiles to ADHD, by controlling for oppositional defiant/conduct disorder (ODD/CD) symptoms. Skin conductance level and non-specific fluctuations were measured during four successive resting-state and cognitive conditions (Resting-state time 1, Continuous Performance Task, Fast Task: Baseline and Fast-Incentive conditions, Resting-state time 2) from 71 adolescents/young adults with ADHD and 140 controls. Lower arousal was observed in individuals with ADHD only during a slow, low-demanding task, and more fluctuating arousal was observed towards the end of assessment. Both inattentive and hyperactive-impulsive symptoms were associated with arousal levels and fluctuations, independently from ODD/CD. Overall, we extend previous findings showing that under-arousal, but also fluctuating arousal, are context-specific rather than stable impairments in ADHD

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Psychol Assess. 2019.

SCREENING WITH AN ADHD-SPECIFIC RATING SCALE IN PRESCHOOLERS: A CROSS-CULTURAL COMPARISON OF THE EARLY CHILDHOOD INVENTORY-4.

Overgaard KR, Oerbeck B, Friis S, et al.

The Early Childhood Inventory-4 (ECI-4) Hyperactivity-Impulsivity (HI) and Inattention (IA) subscales are screeners for attention-deficit/hyperactivity disorder (ADHD). There have been few studies of the screening properties of these subscales, particularly outside the United States. We investigated the classification accuracy of the parent and teacher versions of the HI and IA subscales and the crosscultural validity of the

cutoff values based on norms from a United States sample. The present study was part of the Norwegian Mother and Child Cohort Study. Parents and teachers rated boys ($n = 332$) and girls ($n = 319$) with the ECI-4 (mean Age 3.5 years). Interviewers who were blind to the ratings used the Preschool Age Psychiatric Assessment Interview to assign ADHD diagnoses. The ECI-4 HI and IA subscales showed acceptable accuracy in identifying ADHD in boys and girls (areas under the curve ranged from .67 to .85). In a multivariate regression analysis, the parent and teacher HI subscale scores significantly contributed to ADHD identification, but not the IA subscale scores. To achieve the necessary sensitivity to detect children with ADHD, lower cutoff levels than those specified by the United States ECI-4 norms were needed. For screening purposes, the parent and teacher ECI-4 showed acceptable accuracy in identifying preschoolers at risk for ADHD, and it may be sufficient to use the HI subscale scores. The suggested cutoff values provided by the United States ECI-4 norms had limited cross-cultural validity

Rev Neurol. 2019;68:7-10.

NEUROFIBROMATOSIS TYPE 1 AND ATTENTION-DEFICIT DISORDER. OUR CURRENT EXPERIENCE.

Sanchez-Marco SB, Lopez-Pison J, et al.

Introduction. Patients with neurofibromatosis type 1 (NF1) have a high predisposition to develop attention-deficit disorder. The aim of this study is to determine the prevalence of NF1 patients with attention-deficit/hyperactivity disorder (ADHD) diagnosis attending our Child Neurology Department. We assess patient adherence and medical treatment outcomes.

Patients and methods. Identification of patients with NF1 being followed up from December 31 2015 to June 31 2017 with ADHD diagnosis. Clinical and treatment data were collected.

Results. 56 patients with NF1 were enrolled in the study with a mean age of 9.83 \pm 4.17 years. 23 patients (41%) were diagnosed with ADHD, mean age at ADHD diagnosis of 7.53 \pm 2.46 years. School-age children with ADHD represented 48.8% of cases. All but one of the children received treatment, mean duration of treatment was 3.85 \pm 3.04 years. 19 out of 22 patients (86%) continue medical treatment. Positive effects were reported by eleven patients with a moderate response in eight patients.

Conclusions. Prevalence of ADHD in patients with NF1 is high. Early diagnosis and treatment of ADHD in patients with NF1 is highlighted by this study. Our study reveals good patient adherence and medical treatment outcomes in most patients

Scand J Psychol. 2019 Apr;60:138-44.

AN EXAMINATION OF THE PSYCHOMETRIC PROPERTIES OF SCORES ON THE FAMILY STRAIN INDEX (FSI) IN A GENERAL COMMUNITY SAMPLE.

Lambek R, Lange AM, Petersen N, et al.

Given the potentially harmful effects of parenting stress on parents, children, and their relationship, it is critical to have a reliable and valid measure of parenting stress in clinical and community samples. The Family Strain Index (FSI) is a brief questionnaire designed to measure stress and demand on parents of children with ADHD. The present study is the first to evaluate the psychometric properties of scores on the FSI in a general community sample. Parents (89% mothers) of 550 preschool children (aged 2-5 years; 50% boys) sampled through 17 kindergartens located in Danish cities and villages completed the FSI, the ADHD Rating Scale (RS)-IV Preschool Version, and a background questionnaire. FSI scores were characterized by restricted range and floor effects. The scale's construct validity was not supported and the measurement repeatability after 1 month was low. The scale did have convergent validity as levels of parenting stress were associated with perceived ADHD behavior in off-spring, but overall, results did not encourage the use of the FSI as a measure of parenting stress in the general population. Measures that include more normative events may be more appropriate when attempting to capture parenting stress in general community samples

Lancet Psychiatry. 2017;4:437-38.

SUBCORTICAL BRAIN VOLUME DIFFERENCES IN PARTICIPANTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADULTS.

Poulton A, Nanan R.

Trauma Violence Abuse. 2019 Apr;20:149-67.

A SYSTEMATIC REVIEW OF RISK AND PROTECTIVE FACTORS FOR EXTERNALIZING PROBLEMS IN CHILDREN EXPOSED TO INTIMATE PARTNER VIOLENCE.

Fong VC, Hawes D, Allen JL.

Intimate partner violence (IPV) is a serious public health issue with innumerable costs to the victims, children, and families affected as well as society at large. The evidence is conclusive regarding a strong association between exposure to IPV and children's externalizing problems. Moving forward, the next step is to enhance our understanding of risk and protective factors associated with these outcomes in order to tailor treatments to meet the needs of both parents and children. The databases Medline, PubMed, and PsylNFO were searched combining variations of the key words such as parent*, child*, mother, partner abuse, domestic abuse, spousal abuse, interpersonal violence, domestic violence, or intimate partner violence. This search were combined with child externalizing behaviors specifically conduct*, oppositional defiant disorder, externaliz*, aggress*, hyperactivity, and ADHD. A total of 31 studies from all three databases were reviewed following application of inclusion and exclusion criteria. The main findings were that child age and gender, callous-unemotional traits, cognitive appraisals, maternal mental health, and quality of parenting emerged as key mediating and moderating factors of the relationship between IPV exposure and child externalizing problems. These findings suggest that interventions provided to families exposed to IPV need to target both maternal and child risk factors in order to successfully reduce child externalizing problems

World J Biol Psychiatry. 2019.

THE AMYGDALA IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: STRUCTURAL AND FUNCTIONAL CORRELATES OF DELAY AVERSION.

Van DJ, Sonuga-Barke E, Moerkerke M, et al.

Objectives: Recent magnetic resonance imaging (MRI) studies implicate structural alterations of amygdala, a brain region responsible for processing and experiencing negative emotions, in adolescents with attention-deficit/hyperactivity disorder (ADHD). Here we examined ADHD-related structural correlates of amygdala functional activity elicited during a functional MRI task designed to test behavioural and brain responses to the imposition of delay-related event known to both elicit amygdala hyperactivation and aversity in ADHD.

Methods: Structural MRI scans from 28 right-handed male adolescents with combined type ADHD and 32 age-matched controls were analysed. Regional grey matter volumes of ADHD and control participants ($P[FWE] < 0.05$) were correlated with delay aversion self-ratings and neural activity in response to delay-related cues on the Escape Delay Incentive fMRI task.

Results: ADHD was associated with significantly reduced volumes in bilateral amygdala, parahippocampal and temporal gyrus ($P[FWE] < 0.05$), greater basolateral amygdala activation to delay-related cues ($P[FWE] < 0.05$) and higher delay aversion self-ratings. Amygdala volume reductions were significantly correlated with, and statistically mediated the pathway from ADHD to, delay-cue-related amygdala hyperactivity ($P < 0.01$) and self-reported delay aversion ($P < 0.01$).

Conclusions: We provide the first evidence of the functional significance of reduced amygdala volumes in adolescents with ADHD by highlighting its relation to delay-induced brain activity that is linked to delay aversion

Zh Vyssh Nerv Deiat Im I P Pavlova. 2016 May;66:289-301.

NEUROBIOLOGICAL MARKERS OF AUTISM SPECTRUM DISORDERS IN INFANCY.

Pereverzeva DS, Gorbachevskaya NL.

The article aims to systematically review recent studies on early symptoms of autism developmental disorders. Autism spectrum disorders is a group of neurodevelopmental disorders that is characterized by impairment of communication and social interaction. Nevertheless, the earliest detected features of ASD are impairments of attention disengagement and orientation to novel stimulus, perception abnormalities of stimuli of magnocellular visual pathway and executive control deficit. The role of attention impairment for manifestation of other symptom of ASD including social deficit is discussed. Early executive control deficit may in its turn be associated with symptoms of hyperactivity

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Zhongguo Dang Dai Er Ke Za Zhi. 2019 Mar;21:229-33.

CLINICAL EFFECT OF PSYCHOLOGICAL AND BEHAVIORAL INTERVENTION COMBINED WITH BIOFEEDBACK IN THE TREATMENT OF PRESCHOOL CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

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

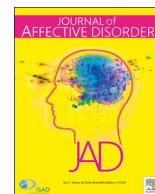
OBJECTIVE: To study the clinical effect of psychological and behavioral intervention combined with biofeedback in the treatment of preschool children with attention deficit hyperactivity disorder (ADHD).

METHODS: Sixty children each with inattentive, hyperactive/impulsive or combined type ADHD were enrolled. According to the intervention measure, they were randomly divided into 4 groups: control, psychological and behavioral intervention, biofeedback treatment and comprehensive treatment (psychological and behavioral intervention + biofeedback). Attention concentration time and impulse/hyperactivity and hyperactivity index scores of the Conners Parent Symptom Questionnaire (PSQ) were evaluated after 4 months of treatment.

RESULTS: The attention concentration time increased in all types children with ADHD after psychological and behavioral intervention, biofeedback treatment or comprehensive treatment ($P < 0.05$). In children with inattentive ADHD, hyperactive/impulsive ADHD or combined-type ADHD, biofeedback or comprehensive treatment reduced the impulse/hyperactivity index score ($P < 0.05$). In children with inattentive or combined-type ADHD, psychological and behavioral intervention or comprehensive treatment reduced the hyperactivity index score ($P < 0.05$). In children with hyperactive/impulsive ADHD, biofeedback treatment, psychological and behavioral intervention or comprehensive treatment reduced the hyperactivity index score ($P < 0.05$).

CONCLUSIONS: In children with ADHD, psychological and behavioral intervention combined with biofeedback treatment can improve the attention concentration and impulsive/hyperactive and hyperactive symptoms. The treatment strategies are slightly different for children with different types of ADHD

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Review article

Light up ADHD: II. Neuropharmacological effects measured by near infrared spectroscopy: is there a biomarker?



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ABSTRACT

Background: Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by deficits in self-controlling attention, behavior, and emotions. In recent years, noninvasive optical techniques, such as near infrared spectroscopy (NIRS), have been used to measure the neural correlates of pharmacological-therapy outcomes in children and adolescents with ADHD.

Methods: We reviewed a short series of articles that investigated the results of functional NIRS (fNIRS) on developmental-age ADHD. The review was limited to fNIRS studies that investigated the cortical responses that occurred during neuropsychological tasks in ADHD patients who received methylphenidate or atomoxetine.

Results: The majority of the reviewed studies revealed the presence of increased oxygenated hemoglobin concentrations in the prefrontal cortex following pharmacotherapy in ADHD samples. A higher frequency of right-lateralized results was found.

Limitations: The considered studies are characterized by substantial methodological heterogeneity in terms of the patients' medication status and washout period, explored cerebral regions, and neuropsychological tasks.

Conclusions: fNIRS seems to be a promising tool for the detection of pharmacological-treatment biomarkers in samples of children and adolescents with ADHD.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequently diagnosed neurodevelopmental disorders in childhood, and its worldwide prevalence among children and adolescents is about 5% (Faraone et al., 2015). ADHD's heterogeneous phenotypes are characterized by inattention, excessive motor activity, and high levels of impulsivity (American Psychiatric Association, 2013); these symptoms seem to arise from neurotransmission dysregulation or insufficient production of catecholamines within the prefrontal cortex (PFC) and subcortical regions (Arnsten, 2006; Del Campo et al., 2011).

Though the etiology of this neurodevelopmental disorder is not fully understood, empirical evidence has shown that the symptoms improve following pharmacological treatment. The first-line drug therapies currently approved for treating ADHD are psychostimulants such as amphetamines and methylphenidate (MPH) (Kempton et al., 1999). Atomoxetine (ATX) was the first nonstimulant pharmacotherapy approved for ADHD (Hazell et al., 2011).

Amphetamines and MPH are catecholamine agonists, and they block dopamine (DA) and norepinephrine (NE) transporters, that modulate

the normal reuptake of neurotransmitters. Stimulant drugs increase extracellular levels of DA and NE at synaptic sites in both the PFC and the striatum (Berridge & Devilbiss, 2011; Makris et al., 2009), thereby restoring executive functioning (Arnsten, 2006).

ATX, the alternative prescription to psychostimulant drugs, is a selective NE reuptake inhibitor with little affinity for other monoamine transporters. Studies have shown that following ATX treatment, the extracellular levels of NE and DA increase in the PFC but not in the striatum (Bymaster et al., 2002).

Near infrared spectroscopy (NIRS) is a noninvasive optical technique that uses specific wavelengths of light to probe over time the changes in concentrations of oxygenated and deoxygenated hemoglobin (Oxy-Hb and Deoxy-Hb, respectively). The measurement of these changes is closely related with functional brain activation, thus providing reliable clinical indicators (Scholkmann et al., 2014).

The NIRS technique has clear advantages in the context of studying children with ADHD symptoms: it is silent, it does not require many body fixities, and its acquisition environment is not intrusive. Studies

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Table 1
Selection of studies comprising samples of patients treated with methylphenidate.

Study	Sample and design	Treatment	fNIRS measures	Analysis	Main findings
Ishii-Takahashi et al., 2015 – Neuroimaging-aided prediction of the effect of methylphenidate in children with attention-deficit hyperactivity disorder: a randomized controlled trial	<p>Sample: 30 ADHD, 26 males, mean age 8.6 ± 1.4 y, 22 drug naïve.</p> <p>20 TDC, 14 males, mean age 8.1 ± 1.6 y.</p> <p>Design: RCT</p> <p>Phase 1: Baseline NIRS acquisition for each group (naïve ADHD, non-naïve ADHD, TDC), wash-out for non-naïve ADHD: 1 week.</p> <p>Phase 2: Randomized, double-blind, placebo-controlled crossover with NIRS acquisition (ADHD, TDC) within 5 h of treatment.</p> <p>Phase 3: 4–8 weeks follow-up NIRS acquisition in continuous MPH treatment (ADHD, TDC).</p> <p>Phase 4: 1 year follow-up NIRS acquisition in continuous MPH treatment, wash-out: 1 week (naïve ADHD, TDC)</p> <p>Task: SST.</p>	<p>MPH: Mean maintenance dose for naïve and non-naïve group 25.4 ± 5.9 mg/day, mean treatment duration 14.7 ± 2.3 months.</p> <p>Concurrent medications suspended for a minimum of 7 days before NIRS.</p> <p>Wash-out period: 1 week.</p>	<p>Measures: Oxy-Hb task-related mean concentration changes (task period data linear fitted on between pre-task and post-task baselines data).</p> <p>Areas: 24 CHs on bilateral inferior frontal areas (IFC) according to 10–20 international system (Jaspers, 1958).</p>	<p>Naïve ADHD vs non-naïve ADHD vs TDC: Repeated measures ANOVA: between subjects variable: group (naïve, non-naïve, TDC); within subjects variables: Phase (1 and 3) and hemisphere (left-IFC and right-IFC).</p> <p>Intra-medication: Repeated measures ANOVA (Phase 2): between subjects variable: group (naïve vs non-naïve); within subjects variables: treatment (MPH vs placebo) and hemisphere. Naïve ADHD vs TDC: Repeated measures ANOVA: (naïve vs TDC); within subjects variables: Phase (1 and 4) and hemisphere.</p> <p>Medication response prediction (naïve ADHD): Stepwise regression analysis: Independent variables: Oxy-Hb at Phase 1 and Oxy-Hb at Phase 2 minus Oxy-Hb at Phase 1; dependent variables: CGI-S scores at Phase 3 or 4.</p> <p>Intra-medication: Two tailed paired t test: MPH-off vs MPH-on conditions.</p>	<p>Naïve ADHD vs non-naïve ADHD vs TDC: Phase 1: naïve < TDC in right IFC; non naïve = TDC.</p> <p>Phase 3: naïve = non naïve = TDC.</p> <p>Intra-medication: Naïve: MPH > placebo in right-IFC; Non-naïve: MPH = placebo. Naïve ADHD vs TDC: Phase 1: naïve < TDC in bilateral IFC; Phase 4: naïve = TDC.</p> <p>Medication response prediction: Oxy-Hb in left IFC predict CGI-S scores at Phase 3 and 4.</p>
Matsuura et al., 2014 – Effects of methylphenidate in children with attention deficit hyperactivity disorder: a near-infrared spectroscopy study with CANTAB*	<p>Sample: 11 ADHD, 10 males, mean age 10.8 ± 1.8 y (range 10–15 y).</p> <p>Design: Clinical trial: single arm NIRS acquisition within 4 h of MPH intake and after 24 h wash-out. Conditions counterbalanced across participants, second acquisition one month after the first.</p> <p>Task: SWM (2 levels: 6 and 8 box) and spatial span.</p>	<p>MPH: Mean maintenance dose 33.6 mg/kg.</p> <p>Wash-out period: 24 h.</p>	<p>Measures: Oxy-Hb task-related concentration integral value for each CH (task period data corrected on between pre-task and post-task baselines data).</p> <p>Areas: 16 CHs on bilateral frontal areas according to 10–20 international system (Jaspers, 1958).</p>	<p>SWM 6-box: MPH-off > MPH-on in 10 CHs on bilateral PFC.</p> <p>SWM 8-box: MPH-off < MPH-on bilaterally in 8 CHs; MPH-off > MPH-on in 8 CHs on bilateral PFC.</p> <p>Spatial span: MPH-off > MPH-on in 15 CHs on bilateral PFC.</p>	<p>SWM 6-box: MPH-off > MPH-on in 10 CHs on bilateral PFC.</p> <p>SWM 8-box: MPH-off < MPH-on bilaterally in 8 CHs; MPH-off > MPH-on in 8 CHs on bilateral PFC.</p> <p>Spatial span: MPH-off > MPH-on in 15 CHs on bilateral PFC.</p>
Monden et al., 2012a – Clinically-oriented monitoring of acute effects of methylphenidate on cerebral hemodynamics in ADHD children using fNIRS.	<p>Sample: 12 ADHD, 11 males, mean age 9.7 ± 2.4 y (range 7–14 y). Co-diagnosis: 2 Asperger syndrome, 1 Epilepsy.</p> <p>Design: Clinical trial: single arm NIRS acquisition pre- and 1.5 h post-MPH intake.</p> <p>Task: Go / No Go.</p>	<p>MPH: mean maintenance dose 26.2 mg/kg (range 18–45 mg/day), range treatment duration 1 week–3.6 years.</p> <p>Wash-out period: 24 h.</p>	<p>Measures: Oxy-Hb concentration changes (inter trial mean of differences between task peaks and pre task baselines)</p> <p>Areas: 44 CHs on bilateral cortices.</p> <p>ROI: 4 CHs on right hemisphere (located on MFG, IFG and AG according with MNI coordinates).</p> <p>Measures: Oxy-Hb concentration changes (intertrial mean of differences between task peaks and post task baselines).</p> <p>Areas: 44 CHs on bilateral</p>	<p>Intra-medication: Two tailed paired t test: MPH-off vs MPH-on.</p>	<p>MPH-off < MPH-on in 2 of the selected CHs, located on right MFG and IFG.</p>
Monden et al., 2012b – Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study.	<p>Sample: 16 ADHD, mean age 8.8 ± 2.2 y (range 6–13 y), 7 drug naïve.</p> <p>16 TDC, mean age 8.9 ± 2.4 y (range 6–13 y).</p>	<p>MPH: mean maintenance dose range treatment duration naïve–3.4 years.</p> <p>Concurrent medications: 1</p>	<p>Measures: Oxy-Hb concentration changes (intertrial mean of differences between task peaks and post task baselines).</p> <p>Areas: 44 CHs on bilateral</p>	<p>ADHD vs TDC: Independent two sample t test: a) Pre-medicated ADHD vs TDC, b) Post-placebo ADHD vs TDC, c) Post-MPH ADHD vs TDC.</p>	<p>a) Pre-medicated ADHD < TDC, b) Post-placebo ADHD < TDC, c) Post-MPH ADHD = TDC.</p> <p>Intra-medication: MPH-ADHD > Placebo-ADHD.</p>

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Table 1 (continued)

Study	Sample and design	Treatment	fNIRS measures	Analysis	Main findings
Negashima et al., 2014a – Neuropharmacological effect of methylphenidate on attention network in children with attention deficit hyperactivity disorder during oddball paradigms as assessed using functional near-infrared spectroscopy	<p><i>Design:</i> RCT Randomized, double-blind, placebo-controlled, crossover with NIRS acquisition. <i>Task:</i> Go / No Go.</p> <p><i>Sample:</i> 22 ADHD, 19 males, mean age 9.5 ± 2 y (range 6–14 y). Co-diagnosis: 1 epilepsy, 12 ASD.</p> <p>22 TDC, 15 males, mean age 9.8 ± 2 y (range 6–13 y). <i>Design:</i> RCT Randomized, double-blind, placebo-controlled, crossover with NIRS acquisition pre- and 1.5 h post-treatment. <i>Task:</i> oddball paradigms.</p>	<p>carbamazepine and risperidone; 1 valproic acid. Wash-out period: 4 days.</p> <p>MPH: mean maintenance dose 27 mg/day (range 18 - 54 mg/day), range treatment duration 1–61 months. Concurrent medications: 1 valproic acid. Wash-out period: 4 days.</p>	<p>lateral PFC ROI: 1 CH on right hemisphere (located between MFG and IFG according with MNI coordinates). <i>Measures:</i> Oxy-Hb concentration changes (intertrial mean of differences between the peak Hb signals and baseline periods). <i>Areas:</i> 44 CHs on bilateral prefrontal and inferior parietal cortices. ROI: 1 CH on right hemisphere (located between MFG and IFG according with MNI coordinates).</p>	<p>ADHD: Paired <i>t</i>-test: Intra-medication: pre- vs. post-placebo, pre- vs post-MPH, Intra-medication: intra-MPH vs intra-placebo. ADHD vs TDC: Independent two sample <i>t</i> test: a) Post-placebo ADHD vs TDC, Intra-medication: MPH-ADHD vs TDC. ADHD: Paired <i>t</i>-test: Intra-medication: pre- vs. post-placebo, pre- vs post-MPH, Intra-medication: intra-MPH vs intra-placebo.</p>	<p>a) Post-placebo ADHD < TDC, b) Post-MPH ADHD = TDC. Intra-medication: MPH-ADHD > Placebo-ADHD.</p>
Nakanishi et al., 2017 – Differential therapeutic effects of atomoxetine and methylphenidate in childhood attention deficit/hyperactivity disorder as measured by near-infrared spectroscopy.	<p><i>Sample:</i> 30 CEHD, 25 males, age range 6–14 y, all drug naïve. <i>Design:</i> Open label clinical trial (a) 14 ATX, 11 males, mean age 9.5 ± 2 y. (b) 16 MPH, 14 males, mean age 8.2 ± 2.4 y. NIRS acquisition pre- and post-treatment. <i>Task:</i> Stroop color-word task.</p>	<p>ATX: Mean maintenance dose 1.3 ± 0.44 mg/kg/day. MPH: Mean maintenance dose 0.87 ± 0.23 mg/kg/day. Treatment duration: 12 weeks.</p>	<p><i>Measures:</i> Grand average waveforms of Oxy-Hb task-related concentration changes. <i>Areas:</i> 24 CHs on bilateral PFC according to 10–20 international system (Jaspers, 1958).</p>	<p><i>Intra-medication:</i> Two-tailed paired <i>t</i>-test: pre- vs post-MPH. <i>Inter-medication:</i> Interaction effect measured with ANOVA: between subjects variable: treatment (MPH vs ATX); within subjects variable: condition (pre- vs post-treatment).</p>	<p><i>Intra-medication:</i> MPH: post-treatment = pre-treatment. <i>Inter-medication:</i> Post-MPH < Post-ATX.</p>
Öner et al., 2011 – Association Among SNAP-25 Gene Ddel and MnlI polymorphisms and hemodynamic changes during methylphenidate use: A functional near-infrared spectroscopy study.	<p><i>Sample:</i> 15 ADHD adults, 8 males, mean age 26.1 ± 7.7 y (range 18–43 y), 12 drug-naïve. Co-diagnosis: 1 social phobia, 3 major depression (lifetime). 16 ADHD children, 13 males, mean age 9.7 ± 4.5 y (range 7–14 y), all drug-naïve. Co-diagnosis: 6 (anxiety disorder, elimination disorder, depression, conduct disorder). <i>Design:</i> Open label clinical trial (NIRS acquisition with (half of the sample) or without MPH intake. Conditions counterbalanced across participants. <i>Task:</i> Stroop color-word task.</p>	<p>MPH: 10 mg of short-acting treatment (fixed dose). Wash-out period: 24 h.</p>	<p><i>Measures:</i> ΔOxy-Hb and ΔDeoxy-Hb mean concentration changes (MPH-on minus MPH-off) measured during interference condition (incongruent stimulus minus neutral stimulus parameters). <i>Areas:</i> 16 CHs on bilateral DLPFC.</p>	<p>MANCOVA: Within subjects factors: SNAP-25 gene Ddel and MnlI polymorphisms; covariates: age and gender. Ddel and MnlI polymorphisms: 4 groups: (1) Ddel C/C or T/C and MnlI G/G or T/G, (2) Ddel T/T and MnlI T/T, (3) Ddel C/C or T/C and MnlI T/T, (4) Ddel T/T and MnlI G/G or T/G</p>	<p><i>Deoxy-Hb</i> Ddel: C/C or T/C: †in right PFC T/T: †in right PFC. <i>MnlI:</i> T/G and G/G: †in left PFC T/T: †in left PFC. MnlI T/G or G/G) ≠ [Ddel T/T and MnlI T/T] or [Ddel T/T and MnlI T/G or G/G] in right PFC. <i>Oxy-Hb</i> Ddel: no significant results. <i>MnlI:</i> T/G and G/G: †in right PFC. T/T: †in right PFC. [Ddel T/T and MnlI T/T] ≠ [Ddel C/C or T/C and MnlI T/G or G/G] or [Ddel T/T and MnlI G/G or T/G] in right PFC.</p>

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Table 1 (continued)

Study	Sample and design	Treatment	fNIRS measures	Analysis	Main findings
Sanefuji et al., 2014 – Altered strategy in short-term memory for pictures in children with attention-deficit/hyperactivity disorder: A near-infrared spectroscopy study	<p>Sample: 10 ADHD, 9 males, mean age 10.4 ± 1.6 y (range 8.2–12.3 y), 2 drug-naïve, 13 TDC, 9 males, mean age 8.4 ± 2 (range 5.4–11).</p> <p>Design: Open label clinical trial NIRS acquisition with and without MPH intake. Drug-naïve ADHD underwent only MPH-off acquisition.</p> <p>Task: Short-term memory task; non-phonological (visual stimuli) and phonological (auditory stimuli) conditions.</p>	<p>MPH: optimal maintenance dose (18 or 27 mg/day). Wash-out period: 24 h.</p>	<p>Measures: Total-Hb concentration changes for visual (ΔCv), auditory (ΔCa) and visual-auditory conditions. Visual Index (VI) = ΔCv / (ΔCv + ΔCa). Auditory Index (AI) = ΔCa / (ΔCv + ΔCa). Visual-Auditory Index (VAI) = (ΔCv - ΔCa) / (ΔCv + ΔCa). Areas: 4 CHs on bilateral DLPFC and VLPFC, according to 10–20 international system (Jaspers, 1958). ROI: 1 CH on left VLPFC.</p>	<p>Two-tailed Spearman's rank correlation between VAI and Digit Span score. ADHD vs TDC: Fisher's r to z transformation: dependent variable: coefficients of correlation. Intra-medication: One-tailed paired t-test: MPH-on vs MPH-off.</p>	<p>TDC: significant positive correlation in left VLPFC. ADHD: no significant correlation. Fisher's Z: ADHD < TDC. Intra-medication: VAI MPH-on > VAI MPH-off.</p>

Note: ADHD = Attention Deficit Hyperactivity Disorder, y = years, TDC = Typically Developing Controls, RCT = Randomized Controlled Trial, fNIRS = functional Near Infrared Spectroscopy, MPH = Methylphenidate, SST = Stop Signal Task, Oxy - Hb = Oxygenated Hemoglobin, CH = Channel, IFC = Inferior Frontal Cortex, ANOVA = Analysis of Variance, CGI-S = Clinical Global Impressions-Severity, CANTAB = Cambridge Automated Neuropsychological Testing Battery, SWM = Spatial Working Memory, VLPFC = Ventro Lateral Prefrontal Cortex, DLPFC = Dorsal Lateral Prefrontal Cortex, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, AG = Angular Gyrus, MNI = Montreal Neurological Institute, ROI = Region of Interest, ATX = Atomoxetine, MANCOVA = Multivariate Analysis of Covariance, Deoxy-Hb = deoxygenated hemoglobin, AUC = Area Under the Curve, TC = Temporal cortex.

on functional NIRS (fNIRS) reported that peculiar cortical activation occurred during the execution of neuropsychological and emotional tasks in children and adolescents with ADHD (Mauri et al., 2017). Recently, fNIRS was used to investigate the effects of pharmacological treatment on cortical hemodynamics and to detect a biological marker of pharmacotherapy outcome.

The present brief review summarizes the results of studies published between January 2010 and March 2018, that investigated the hemodynamic responses of pharmacological treatments using NIRS technology in children and adolescents with ADHD. Our final aim is to examine whether NIRS could be used as an objective marker to identify the effects of drug administration.

The bibliographic research was conducted on PubMed, and the following search criteria were used: “((NIRS AND ADHD) AND treatment) OR ((NIRS AND ADHD) AND efficacy)” and “((fNIRS AND ADHD) AND treatment) OR ((fNIRS AND ADHD) AND efficacy).” This search was supplemented with other publications from the personal-reference databases of the authors (Matsuura et al., 2014; Ota et al., 2015).

We limited our review to MPH and ATX studies, which are the most frequently prescribed drugs. All of the studies that used the fNIRS technique to investigate the effects of nonpharmacological treatments and those that used samples comprising adults only were excluded. Because ADHD symptoms affect executive functions primarily, we focused our review on studies that used fNIRS to investigate hemodynamic signals during neuropsychological tasks. In Schecklmann et al. (2011) study, they investigated the hemodynamic signals during odor stimulation; thus, it was not included in the present review.

Twelve articles that met our inclusion criteria are summarized in Table 1, which describes MPH studies; Table 2 summarizes the ATX studies. Nakanishi et al. (2017) examined the effects of both MPH and ATX; their study's results are reported in each table, respectively.

Some preliminary suggestions can be drawn from the reviewed studies.

First, it should be noted that all but one study (Nakanishi et al., 2017) found that fNIRS is an effective indicator of hemodynamic response to pharmacotherapy. The majority of the studies reported changes in Oxy-Hb and Deoxy-Hb signals, and Sanefuji et al. (2014) identified changes in total Hb concentrations. Öner et al. (2011) study is the only genetic-imaging study, and its results did not report the effect of treatment regardless of participants' genotypes. Nakanishi et al. (2017) did not find that MPH treatment significantly influenced hemoglobin concentrations.

All of the studies included in the present review investigated PFC activation, regardless of therapy. In addition, Nagashima et al. (2014b) measured activation of the parietal and temporal areas. The findings of studies that investigated stimulant medication effects were diffused on bilateral PFC surfaces, but most of the studies found right-hemisphere lateralization. This lateralization trend was even more evident in studies that accounted for ATX treatment.

In particular, Monden et al., (2012a; 2012b) and Nagashima et al., (2014a;2014b; 2014c) found increased Oxy-Hb concentrations after drug intake in the right dorsolateral (DL) and ventrolateral (VL) PFC (i.e., in the middle frontal gyrus and in the inferior frontal gyrus, respectively). In addition, Nagashima et al. (2014b) found increased Oxy-Hb concentrations in the right temporoparietal cortex (i.e., in the angular gyrus and in the supramarginal gyrus, whose activity is involved in the bottom-up attentional system).

Two studies (Nakanishi et al., 2017; Sanefuji et al., 2014) found a left-lateralized effect of pharmacotherapy on the fNIRS signal. In particular, Sanefuji et al. (2014) found that the total Hb concentration in the ventrolateral PFC had increased. This left-lateralization effect could be attributable to the verbal components of the tasks.

In five works (Öner et al., 2011; Matsuura et al., 2014; Araki et al.,

Table 2
Selection of studies comprising samples of patients treated with atomoxetine.

Study	Sample and design	Treatment	fNIRS measures	Analysis	Main findings
Araki et al., 2015 – Improved prefrontal activity in AD/HD children treated with atomoxetine: A NIRS study.	Sample: 12 ADHD, 6 males, mean age 9.8 ± 2.3 y (range 6–13 y) in part drug naïve. 14 TDC, 5 males, mean age 9.7 ± 2.8 y (range 6–15 y). Design: Clinical trial single arm NIRS acquisition pre- (naïve or ATX starting dosage) and post-ATX treatment (at least 6 months of maintenance dose). Task: CPT.	ATX: Mean maintenance dose 1.6 mg/kg/day, twice/day.	Measures: ΔOxy-Hb mean concentration changes (task period minus pre-task baseline). Areas: 24 CHs on bilateral PFC according to 10–20 international system (Jaspers, 1958).	TDC: Two way repeated measures ANOVA: within subject variables: hemisphere and period (baseline vs task). Three way repeated measures ANOVA: within subject variables: condition (pre-vs post-ATX), hemisphere and period.	TDC: ↑ Oxy-Hb during CPT in bilateral DLPFC. ADHD: Pre-ATX: ↓ Oxy-Hb during CPT in left VLPFC. Post-ATX: ↑ Oxy-Hb during CPT in right DLPFC; ↓ Oxy-Hb during CPT in left VLPFC disappeared.
Nagashima et al., 2014b – Neuropharmacological effect of atomoxetine on attention network in children with attention deficit hyperactivity disorder during oddball paradigms as assessed using functional near-infrared spectroscopy.	Sample: 15 ADHD, 12 males, mean age 9.9 ± 2.1 y (range 6–14 y). Co-diagnosis: 9 ASD. 15 TDC, 12 males, mean age 10.1 ± 1.7 (range 7–13 y). Design: RCT Randomized, double-blind, placebo-controlled, crossover with NIRS acquisition. Task: Oddball.	ATX: Mean maintenance dose 27 mg/day, mean treatment duration 16.1 ± 12.2 months. Concurrent medication: 1 Risperidone. Wash-out period: 2 days.	Measures: Oxy-Hb concentration changes (inter trial mean of differences between task peaks and pre-task baselines). Areas: lateral PFC and inferior parietal lobe. ROI: 2 CHs on right hemisphere (CH10 located between MFG and IFG; CH22 located between AG and SMG) according with MNI coordinates.	ADHD vs TDC: Independent two sample t test: (a) Pre-medicated ADHD vs TDC, (b) Post-placebo ADHD vs TDC, (c) Post-ATX ADHD vs TDC. ADHD: Paired t-test: Intra-medication: pre- vs. post-placebo, pre- vs post-ATX, Inter-medication: intra-ATX vs intra-placebo.	CH10: (a) Pre-medicated ADHD < TDC, (b) Post-placebo ADHD < TDC, (c) Post-ATX ADHD = TDC. CH22: (a) Pre-medicated ADHD < TDC, (b) Post-placebo ADHD = TDC, (c) Post-ATX ADHD = TDC. Inter-medication: ATX-ADHD > Placebo-ADHD. (a) Pre-medicated ADHD < TDC, (b) Post-placebo ADHD < TDC, (c) Post-ATX ADHD = TDC. Inter-medication: ATX-ADHD > Placebo-ADHD.
Nagashima et al., 2014c – Acute neuropharmacological effects of atomoxetine on inhibitory control in ADHD children: A fNIRS study.	Sample: 16 ADHD, 14 males, mean age 8.9 ± 2.2 y (range 6–14 y). Co-diagnosis: 13 ASD 16 TDC, 14 males, mean age 8.9 ± 2.2 y (range 6–13 y). Design: RCT Randomized, double-blind, placebo-controlled, crossover with NIRS acquisition. Task: Go / No Go.	ATX: mean maintenance dose 23.1 ± 13.6 mg/day, mean treatment duration 10 ± 8 months. Concurrent medication: 1 Valproic acid. Wash-out period: 2 days.	Measures: Oxy-Hb concentration changes (inter trial mean of differences between task peaks and pre task baselines). Areas: lateral PFC and inferior parietal lobe. ROI: 1 CH on right hemisphere (located between MFG and IFG) according with MNI coordinates.	ADHD vs TDC: Independent two sample t test: (a) Pre-medication ADHD vs TDC, (b) Post-placebo ADHD vs TDC, (c) Post-ATX ADHD vs TDC. ADHD: Paired t-test: Intra-medication: pre- vs post-placebo, pre- vs post-ATX, Inter-medication: intra-ATX vs intra-placebo.	ADHD < TDC, Post-placebo ADHD < TDC, Post-ATX ADHD = TDC. Inter-medication: ATX-ADHD > Placebo-ADHD.
Nakanishi et al., 2017 – Differential therapeutic effects of atomoxetine and methylphenidate in childhood attention deficit/hyperactivity disorder as measured by near-infrared spectroscopy.	Sample: 30 ADHD, 25 males, age range 6–14 y, all drug naïve. (a) 14 ATX, 11 males, mean age 9.5 ± 2 y. (b) 16 MPH, 14 males, mean age 8.2 ± 2.4 y. Design: Open label clinical trial NIRS acquisition pre- and post-treatment. Task: Stroop color-word task.	ATX: mean maintenance dose 1.3 ± 0.44 mg/kg/day. Treatment duration: 12 weeks. MPH: mean maintenance dose 1.34 ± 0.75 mg/kg/day. Treatment duration: 8 weeks.	Measures: Grand average waveforms of task-related Oxy-Hb concentration changes. Areas: 24 CHs on bilateral PFC according to 10–20 international system (Jaspers, 1958).	Two-tailed paired t test: pre- vs post-ATX. Inter-medication: Interaction effect measured with ANOVA: between subjects variable: treatment (MPH vs ATX); within subjects variable: condition (pre- vs post-treatment).	Intra-medication: ATX: Post-treatment > pre-treatment in left lateral frontal cortex. Inter-medication: Post-ATX > Post-MPH.
Ota et al., 2015 – Increased prefrontal hemodynamic change after atomoxetine administration in pediatric attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy.	Sample: 10 ADHD, 7 males, mean age 9.9 ± 2.4 y (range 7–13 y), all drug naïve. Design: Open label clinical trial NIRS acquisition pre- and post-treatment. Task: Stroop Color-Word Task.	ATX: mean maintenance dose 1.34 ± 0.75 mg/kg/day. Treatment duration: 8 weeks.	Measures: grand average waveforms of task-related Oxy-Hb concentration changes. Areas: 24 CHs on bilateral PFC according to 10–20 international system (Jaspers, 1958).	Intra-medication: Two-tailed paired t test: pre- vs post-ATX.	Post-ATX > Pre-ATX.

Note: ADHD = Attention Deficit Hyperactivity Disorder, y = years, fNIRS = functional Near InfraRed Spectroscopy, ATX = Atomoxetine, TDC = Typically Developing Controls, CPT = Continuous Performance Task, Oxy-Hb = Oxygenated Hemoglobin, CHs = Channels, PFC = Prefrontal Cortex, ANOVA = Analysis of Variance, DLPFC = Dorsal Lateral Prefrontal Cortex, VLPFC = Ventro Lateral Prefrontal Cortex, ASD = Autism Spectrum Disorder, ROI = Region of Interest, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, AG = Angular Gyrus, SMG = Supramarginal Gyrus, MNI = Montreal Neurological Institute, MPH = Methylphenidate.

2015; Ishii-Takahashi et al., 2015; Ota et al., 2015) a bilateral and a partially overlapping pattern was found.

In particular, Ishii-Takahashi et al. reported bilateral increases of Oxy-Hb concentrations in the VLPFC. Araki et al. (2015) found the same result in the left VLPFC and in the right DLPFC. Ota et al. (2015) found that the Oxy-Hb concentrations in the left DLPFC and in the right PFC had increased.

Öner et al. (2011) study is the only imaging-genetic study included in the present review. The neurophysiological findings detected bilaterally were connected to SNAP-25 gene polymorphisms. This gene is involved in both dopaminergic and serotonergic pathways in the PFC; thus, depending on the allele that patients carry, those with ADHD may show different responses to MPH. In other words, the authors found associations between genotypes and task-related Oxy-Hb and Deoxy-Hb concentration changes due to MPH intake in the bilateral DLPFC.

Bilateral DL and VLPFC functional activities are linked to a broad range of executive-task performances—in particular, the top-down attentional system, response inhibition, and working memory.

It is relevant to note some limitations that might have contributed to the heterogeneity of the abovementioned studies' results.

First, a high heterogeneity of the studies' samples, the patients' medication statuses, and the studies' designs are evident. Only five of the revised works had randomized, double-blind, placebo-controlled, crossover designs (Ishii-Takahashii et al., 2015; Monden et al., 2012a; Monden et al., 2012b; Nagashima et al., 2014a; Nagashima et al., 2014b; Nagashima et al., 2014c). Approximately half of the considered works compared ADHD patients with typically developing children.

The majority of the studies recruited mixed samples of patients, including both naïve and non-naïve children with ADHD. In addition, the washout periods varied significantly across the considered studies. It is worth mentioning that the presence or absence of pharmacotherapy and its duration affected the cortical hemodynamics in ADHD patients (Frodl & Skokauskas, 2012).

Two out of the 12 studies recruited only drug-naïve patients (Nakanishi et al., 2017; Ota et al., 2015). Five of the studies reported results from groups comprising entirely premedicated children with different washout periods (Matsuura et al., 2014; Monden et al., 2012a; Nagashima et al., 2014a; Nagashima et al., 2014b; Nagashima et al., 2014c). Five out of the 12 studies used mixed samples of children: drug-naïve patients and children previously medicated with MPH (Ishii-Takahashi et al., 2015; Monden et al., 2012b; Öner et al., 2011; Sanefuji et al., 2014) or ATX (Araki et al., 2015). In addition, the washout periods were heterogeneous.

Last, it is worth mentioning that the significant heterogeneity of the neuropsychological tasks used in the considered studies (see Tables 1 and 2) could have led to partly mixed results. Indeed, cortical activation was registered while subjects were performing a broad range of tasks so that the executive components could be evaluated. These components included sustained attention (Araki et al., 2015), stimulus-driven attention (Nagashima et al., 2014a; Nagashima et al., 2014b), inhibition (Ishii-Takahashi et al., 2015; Monden et al., 2012a; Monden et al., 2012b; Nagashima et al., 2014c; Nakanishi et al., 2017; Öner et al., 2011; Ota et al., 2015), visual working memory (Matsuura et al., 2014; Sanefuji et al., 2014), and auditory working memory (Sanefuji et al., 2014). All of those tasks were reported to recruit DA or NE circuits, though in different cortical and subcortical prefrontal loci within these networks (Stahl, 2013).

Even in consideration of the early point of scientific literature and the heterogeneous, methodological aspects previously stated, an interpretation of the results presented here is possible. The present review suggests that pharmacological treatment with MPH or ATX in developmental-aged individuals with ADHD is linked to a peculiar cortical response, as measured by fNIRS, during neuropsychological tasks. Most of the considered studies found increased oxygenated hemoglobin concentrations in the DL and/or VLPFC following drug treatment in ADHD samples.

The literature is still too limited to allow for definitive conclusions; in particular, protocols that investigate the same neuropsychological functions in a specific cerebral region of interest in homogeneous samples are urgently needed.

In conclusion, the present review confirms the results of our previous work (Mauri et al., 2017), which showed that fNIRS represents a promising tool for investigating the changes in cerebral hemoglobin concentrations in children and adolescents with ADHD; furthermore, fNIRS is an effective imaging technique for evaluating the cortical effects of pharmacotherapy.

Contributors

Silvia Grazioli, Maddalena Mauri and Maria Nobile wrote the first version of the manuscript, Alessandro Crippa and Eleonora Maggioni contributed on the discussion of the results. All the authors agreed on the final version of the review.

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Ethical statement

The authors declare that no human or animal experimentation was conducted for this work.

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None

Conflict of Interest

None

References

- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. 5 DSM, Washington, DC.
- Araki, A., Ikegami, M., Okayama, A., Matsumoto, N., Takahashi, S., Azuma, H., Takahashi, M., 2015. Improved prefrontal activity in AD/HD children treated with atomoxetine: a NIRS study. *Brain Dev.* 37, 76–87.
- Arnsten, A.F., 2006. Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology* 31, 2376.
- Berridge, C.W., Devilbiss, D.M., 2011. Psychostimulants as cognitive enhancers: the prefrontal cortex, catecholamines, and attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69, e101–e111.
- Bymaster, F.P., Katner, J.S., Nelson, D.L., Hemrick-Luecke, S.K., Threlkeld, P.G., Heiligenstein, J.H., ..., Perry, K.W., 2002. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27, 699–711.
- Del Campo, N., Chamberlain, S.R., Sahakian, B.J., Robbins, T.W., 2011. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69, e145–e157.
- Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J., Rohde, L.A., Sonuga-Barke, J.S., Tannock, R., Franke, B., 2015. Attention-deficit/hyperactivity disorder. *Nat. Rev. Dis. Primers* 1, 1–23.
- Frodl, T., Skokauskas, N., 2012. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatr. Scand.* 125, 114–126.
- Hazell, P.L., Kohn, M.R., Dickson, R., Walton, R.J., Granger, R.E., van Wyk, G.W., 2011. Core ADHD symptom improvement with atomoxetine versus methylphenidate: a direct comparison meta-analysis. *J. Atten. Disord.* 15, 674–683.
- Ishii-Takahashi, A., Takizawa, R., Nishimura, Y., Kawakubo, Y., Hamada, K., Okuhata, S., ..., Igarashi, T., 2015. Neuroimaging-aided prediction of the effect of methylphenidate in children with attention-deficit hyperactivity disorder: a randomized controlled trial. *Neuropsychopharmacology* 40, 2676–2685.
- Jasper, H.H., 1958. The ten-twenty electrode system of the International Federation. *Electroencephalogr. Clin. Neurophysiol.* 10, 371–375.
- Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., Pantelis, C., 1999. Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychol. Med.* 29, 527–538.

- Makris, N., Biederman, J., Monuteaux, M.C., Seidman, L.J., 2009. Towards conceptualizing a neural systems-based anatomy of attention-deficit/hyperactivity disorder. *Dev. Neurosci.* 31, 36–49.
- Matsuura, N., Ishitobi, M., Arai, S., Kawamura, K., Asano, M., Inohara, K., ..., Kosaka, H., 2014. Effects of methylphenidate in children with attention deficit hyperactivity disorder: a near-infrared spectroscopy study with CANTAB®. *Child Adolesc. Psychiatry Mental Health* 8, 273–283.
- Mauri, M., Nobile, M., Bellina, M., Crippa, A., Brambilla, P., 2017. Light up ADHD: I. cortical hemodynamic responses measured by functional Near Infrared Spectroscopy (fNIRS). *J. Affect. Disord.* 234, 358–364.
- Monden, Y., Dan, H., Nagashima, M., Dan, I., Kyutoku, Y., Okamoto, M., ..., Watanabe, E., 2012a. Clinically-oriented monitoring of acute effects of methylphenidate on cerebral hemodynamics in ADHD children using fNIRS. *Clin. Neurophysiol.* 123, 1147–1157.
- Monden, Y., Dan, H., Nagashima, M., Dan, I., Tsuzuki, D., Kyutoku, Y., ..., Momoj, M.Y., 2012b. Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: an fNIRS study. *NeuroImage* 1, 131–140.
- Nagashima, M., Monden, Y., Dan, I., Dan, H., Mizutani, T., Tsuzuki, D., ..., Shimoizumi, H., 2014a. Neuropharmacological effect of atomoxetine on attention network in children with attention deficit hyperactivity disorder during oddball paradigms as assessed using functional near-infrared spectroscopy. *Neurophotonics* 1 025007-1-14.
- Nagashima, M., Monden, Y., Dan, I., Dan, H., Tsuzuki, D., Mizutani, T., ..., Shimoizumi, H., 2014b. Acute neuropharmacological effects of atomoxetine on inhibitory control in ADHD children: a fNIRS study. *NeuroImage* 6, 192–201.
- Nagashima, M., Monden, Y., Dan, I., Dan, H., Tsuzuki, D., Mizutani, T., ..., Yamagata, T., 2014c. Neuropharmacological effect of methylphenidate on attention network in children with attention deficit hyperactivity disorder during oddball paradigms as assessed using functional near-infrared spectroscopy. *Neurophotonics* 1 015001-1-15.
- Nakanishi, Y., Ota, T., Iida, J., Yamamuro, K., Kishimoto, N., Okazaki, K., Kishimoto, T., 2017. Differential therapeutic effects of atomoxetine and methylphenidate in childhood attention deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Child Adolesc. Psychiatry Mental Health* 11, 26–36.
- Öner, Ö., Akın, A., Herken, H., Erdal, M.E., Çiftçi, K., Ay, M.E., ..., Yazgan, Y., 2011. Association among SNAP-25 gene Dde I and Mnl I Polymorphisms and Hemodynamic changes during methylphenidate use: a Functional Near-Infrared Spectroscopy Study. *J. Atten. Disord.* 15, 628–637.
- Ota, T., Iida, J., Nakanishi, Y., Sawada, S., Matsuura, H., Yamamuro, K., ..., Kishimoto, T., 2015. Increased prefrontal hemodynamic change after atomoxetine administration in pediatric attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Psychiatry Clin. Neurosci.* 69, 161–170.
- Sanefuji, M., Yamashita, H., Torisu, H., Takada, Y., Imanaga, H., Matsunaga, M., ..., Hara, T., 2014. Altered strategy in short-term memory for pictures in children with attention-deficit/hyperactivity disorder: a near-infrared spectroscopy study. *Psychiatry Res.* 223, 37–42.
- Scheckmann, M., Schaldecker, M., Aucktor, S., Brast, J., Kirchgäßner, K., Mühlberger, A., ..., Romanos, M., 2011. Effects of methylphenidate on olfaction and frontal and temporal brain oxygenation in children with ADHD. *J. Psychiatr. Res.* 45, 1463–1470.
- Scholkmann, F., Kleiser, S., Metz, A.J., Zimmermann, R., Pavia, J.M., Wolf, U., Wolf, M., 2014. A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. *NeuroImage* 85, 6–27.
- Stahl, S.M., 2013. *Stahl's Essential psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge university press.



Construct validity and diagnostic accuracy of the Italian translation of the 18-Item World Health Organization Adult ADHD Self-Report Scale (ASRS-18) Italian translation in a sample of community-dwelling adolescents.



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ABSTRACT

Aim of this prospective study was to evaluate the factor structure, internal consistency, and diagnostic efficacy of the Italian translation of the Adult ADHD Self-Report Scale (ASRS-18; Kessler et al., 2005, 2007) in a sample of community-dwelling sample of adolescents. Three hundred eight Italian adolescents attending professional high schools were administered the ASRS-18; the adolescence ADHD module of the MINI interview was administered to obtain ADHD criterion diagnoses. Robust maximum likelihood confirmatory factor analysis results identified a bifactor model of the ASRS-18 items as the best-fitting model, RMSEA = 0.029, $p > 0.99$, TLI = 0.93, CFI = 0.95. Further analyses showed that 77.9% of the ASRS-18 reliable ($\omega = 0.78$) score variance was due to the total score. In our study the ASRS-18 proved to be able to effectively differentiate adolescents who received a MINI ADHD diagnosis ($n = 80$) from adolescents who did not receive a MINI ADHD diagnosis ($n = 163$), area under the curve = 0.80, 95% confidence interval = 0.74, 0.86. Our data suggest that the ASRS-18 may represent an effective self-report measure to screen for ADHD in community-dwelling adolescents, at least in its Italian translation.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is currently conceived as a childhood-onset neurodevelopmental disorder, characterized by the presence of developmentally inappropriate and impairing levels of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013; Asherson et al., 2016). Although the latent distribution of ADHD is likely to be dimensional in nature (Coghill and Sonuga-Barke, 2012), epidemiological studies indicate that 5–6% of children meet DSM-IV criteria for ADHD (e.g., Willcutt et al., 2005). Meta-analysis of follow-up studies of children with ADHD found that 15% of children retained the full diagnostic criteria by the age of 25 years, with a further 50% of those meeting subthreshold criteria with persistence of ADHD symptoms causing continued impairments (Faraone et al., 2006).

In the transitional period between childhood and adulthood, adolescents with ADHD continue to display the impairments of children with ADHD (Sibley et al., 2012). Functional impairments and behavior problems associated with ADHD included low school grades, defiance of authority, poor peer relationships, and family conflict (see, for a review, Sibley et al., 2012). Moreover, adolescents with ADHD begin to

experience the impairments that characterize adults suffering from this disorder, such as substance use (Molina et al., 2007), and driving problems (Thompson et al., 2007). Finally, there are impairments associated with ADHD that are specific to adolescence – delinquency (Sibley et al., 2011), school drop-out (Kent et al., 2011), and early initiation of sexual behavior (Flory et al., 2006).

The availability of short, self-report screening measures would greatly enhance the likelihood of adolescent and adult ADHD subjects to be correctly diagnosed and treated, although ADHD adolescent and adults are known to underreport their symptoms (Asherson et al., 2016). Against this background, Kessler et al. (2005, 2007) developed the Adult ADHD Self-Report Scale (ASRS-18), a short self-report measure that includes also a six-item screener (ASRS-6), which was developed selecting the six items that were most effective in discriminating ADHD adults from non-ADHD adults in several independent samples. However, recent data based on Rasch models of the Spanish version of the ASRS-18 proposed six different items for the ASRS-6 in substance use disorder subjects (Sanchez-Garcia et al., 2015). Recently, Ustun et al. (2017) proposed a revised version of the ASRS-6 that included two non-symptom items reflecting executive dysfunction. The ASRS-18 provides nine hyperactivity items and nine attention-deficit

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items that map onto *DSM-IV* (APA, 2000) ADHD criteria. The ASRS has been translated and validated in a number of different languages and cultures, ranging from Spanish language (Sanchez-Garcia et al., 2015) to Japanese language (Takeda et al., 2017). To our knowledge, the ASRS has never been validated in Italy.

Starting from these premises, we aimed at testing the factor structure, internal consistency, and diagnostic efficacy of the Italian translation of the ASRS-18. Since early diagnosis is crucial for preventing long-term negative outcomes of adult ADHD and screening instruments are particularly relevant for non-psychiatric subjects, we administered the ASRS to a sample of community-dwelling adolescents who were receiving professional education at a large institute in the North of Italy.

2. Methods

2.1. Participants

Three hundred eight community dwelling adolescents ($M = 177$, 57.5%, $F = 131$, 42.5%; mean age = 14.91, $SD = 2.70$ years) who were receiving professional education at a large institute in the North of Italy. After obtaining Institutional Review Board approval from the university and the principals of the schools, researchers recruited adolescents from classrooms (data were collected in Winter 2016–Spring 2017). Written informed parent consent and adolescent assent were obtained prior to study participation. In order to participate in the present study, participants were required to speak Italian as their first language in order to avoid cultural and lexical bias in questionnaire responses; to maximize the likelihood of including adolescents potentially meeting *DSM-IV* ADHD criteria in our sample, only adolescents who were reported by their teachers as manifesting externalizing problem behaviors (e.g., truancy, anger outbursts at school, calling teacher names, restless behavior during classroom time, reckless behavior at school, drug misuse, etc.) were allowed to participate in this study. A subsample of 243 (79.9%) adolescents agreed to be administered a diagnostic interview for assessing *DSM-IV* ADHD and CD; 21.1% of the adolescents declined to participate due primarily (98.5%) to the time commitment the study required. Notably, adolescents who were administered the MINI were not significantly different from adolescents who were not administered the MINI on gender, $\chi^2(1) = 0.03$, $p > 0.80$, $\phi = 0.01$, and average ASRS-18 mean score, $t(306) = 0.38$, $p > 0.70$, $d = 0.00$. Fig. 1 showed the flow of participants through the study. The interview was administered by trained research fellows blind to ASRS-18 scores, as well as to adolescents' grades.

2.2. Measures

2.2.1. Adult ADHD Self-Report Scale (ASRS-18; Kessler et al., 2005)

The ASRS is made up of two parts—the first one (Part A, screening) includes six items that, according to the authors, best predict the presence or absence of ADHD; Part B is made up of the remaining 12 items. Consistent with the other existing translations of the ASRS-18, the scale has been translated into Italian using the standard WHO translation and back-translation protocol (National Comorbidity Survey, 2005).

Each question asked how often a symptom occurred over the past 6 months on a 0–4 scale with responses of never = 0, rarely = 1, sometimes = 2, often = 3, and very often = 4. The ASRS-18 items are summed to yield a total score but may also be grouped into two subscales: Inattentive (INA) and Hyperactive/Impulsive (H/I), each one comprised of nine items. Thus, the scale permits a global ADHD diagnosis (the higher the ASRS-18 total score, the higher the intensity of ADHD symptoms), as well as the assessment of INA and H/I symptomatology.

2.2.2. MINI International Neuropsychiatric Interview, Plus, Version 5.00 (MINI; Sheehan et al., 1997)

The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in *DSM-IV* and ICD-10. This interview was chosen because it includes an ADHD Module specifically designed for assessing adolescent ADHD and because the inter-rater reliability of the Italian version of the MINI was previously established (Rossi et al., 2004). Consistent with previous studies (Kumar et al., 2011), our adolescents were administered only the adolescent ADHD Module from the MINI to obtain *DSM-IV* categorical diagnoses of ADHD. The MINI adolescent ADHD Module yields 9 questions (rated yes/no) for *DSM-IV* ADHD inattention symptoms and 9 questions (rated yes/no) for *DSM-IV* ADHD hyperactive/impulsive symptoms. We could assess the inter-rater reliability of MINI adolescent ADHD dimensional scores (i.e., number of symptoms) on 34 adolescent participants; one-way, random effect ANOVA intraclass r value was 1.00.

2.3. Data analysis

Cronbach α values and Haberman's (2008) H reliability estimates were computed; to the degree that α coefficients are larger than H coefficients, subscale scores provide a relatively better indicator of subscale true score standing, and, thus, can be reported (Reise et al., 2013). Robust maximum likelihood confirmatory factor analysis (MLR CFA) was used to assess the factor structure of the ASRS. The following models were tested: a) a unidimensional model, with a single latent

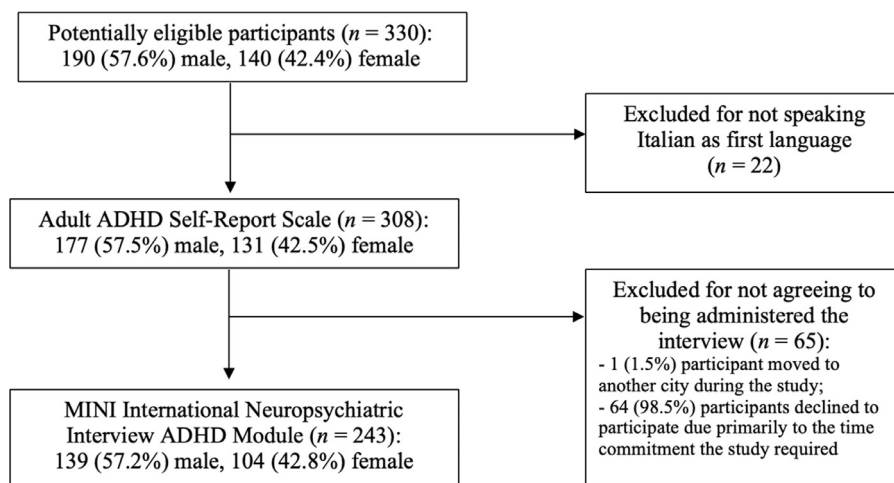


Fig. 1. Flow chart of participant recruitment and exclusion.

factor underlying all the ASRS items; b) a two-factor model based on the a priori item allocation rule to an ASRS INA factor (items 1, 2, 3, 4, 7, 8, 9, 10, and 11) and to a H/I factor (items 5, 6, 12, 13, 14, 15, 16, 17, and 18); c) a CFA bi-factor model, with all ASRS items loading on the general factor, and two specific factors corresponding to the INA factor and the H/I factor, respectively. Following Hu and Bentler's (1999) suggestions and cut-off scores, we used several measures to identify model fit.

The reliability of the factors was assessed by computing omega-hierarchical (ω_H) and omega-specific (ω_S) coefficients (Reise et al., 2013). The ω coefficient is an estimate of the percentage of variance in observed total scores due to all sources of common variance (Reise et al., 2013). The ω_H coefficient is an estimator of the percentage of test score variance accounted for by variation on the general factor (Reise et al., 2013). The ω_S coefficient estimates the reliability of a subscale (e.g., ASRS-18 INA or H/I subscales) after controlling for the general factor (Reise et al., 2013).

Mann-Whitney tests and *t*-tests were computed in order to compare the median/mean scores of the ASRS items and total scores, respectively, between ADHD adolescents and non-ADHD adolescents. Forward logistic regression analysis was used to evaluate if the ASRS items may be sufficient to summarize the information that is necessary to effectively discriminate ADHD adolescents from non-ADHD adolescents, and to identify the ASRS items that best discriminated ADHD adolescents from non-ADHD adolescents.

In the present study, the area under the curve (AUC; i.e., the probability that a randomly selected clinical case would score higher on the ASRS than a randomly selected non-case; Kessler et al., 2005) was used as a measure of the overall ability of the ASRS to predict the presence or absence of ADHD diagnosis. The AUC of a perfect measure is expected to be 1.0, whereas it is expected to be 0.5 for a useless instrument. AUC based on 10-fold cross-validated (CV) receiver operating characteristic (ROC) analysis (LeDell et al., 2014) was used to identify the best balance between sensitivity and specificity with respect to MINI ADHD diagnosis. For all possible cut-off scores provided by ROC analysis, cut-off scores with sensitivity close to or higher than 0.70, and specificity close to or higher than 0.70 were identified for detection purposes for the ASRS, with no differentiation between boys and girls. Cohen κ value was used to evaluate the diagnostic agreement between the ASRS and the MINI ADHD diagnoses. Cohen κ values ranging from 0.21 to 0.40 were considered suggestive of fair agreement, values ranging from 0.41 to 0.60 of moderate agreement, and values ranging from 0.61 to 0.80 of substantial agreement (Cohen, 1988). In the present study, sensitivity, specificity, positive predictive power (PPP), negative predictive power (NPP) and likelihood ratio values were computed (e.g., Grimes and Schulz, 2005).

3. Results

3.1. Descriptive statistics and reliability estimates

Descriptive statistics, Cronbach α values and Haberman's *H* reliabilities based on total score rather than subscales for ASRS-18 dimensions are summarized in Table 1. No significant difference between male and female adolescents was observed on ASRS-18 INA, *t*(306) = 1.54, $p > 0.10$, $d = 0.18$, H/I, *t*(306) = 0.77, $p > 0.40$, $d = 0.09$, and total score, *t*(306) = 1.86, $p > 0.05$, $d = 0.21$.

3.2. Factor analysis results

MLR CFA findings for the one-factor model of the ASRS-18 items were sub-optimal, $\chi^2(135) = 249.67$, $p < 0.001$, root mean square error of approximation (RMSEA) = 0.053, $p > 0.30$, Tucker-Lewis index (TLI) = 0.78, comparative fit index (CFI) = 0.80, standardized root mean square residual (SRMSR) = 0.058, sample size adjusted Bayesian information criterion (SABIC) = 15,832.01. The two-factor

Table 1

Adult ADHD Self-Report Scale: Descriptive statistics, Cronbach α s, and Haberman's *H*s in the full sample ($N = 308$).

	<i>M</i>	<i>SD</i>	Pearson <i>r</i> s			Reliabilities	
			1	2	3	α	<i>H</i>
1. Inattention	15.20	4.98	–			0.71	0.65
2. Hyperactivity/Impulsivity	14.03	4.90	0.44	–		0.62	0.63
3. Total Score	29.23	8.37	0.85	0.85	–	0.76	–

Note. All *r* coefficient *p*s < 0.001.

model of the ASRS-18 items showed marginal fit in MLR CFA, $\chi^2(134) = 206.50$, $p < 0.001$, RMSEA = 0.042, $p > 0.80$, TLI = 0.86, CFI = 0.88, SRMSR = 0.053, SABIC = 15,791.10. When we tested in MLR CFA a confirmatory bifactor model with a general ADHD factor, which all ASRS-18 items were expected to load on, and two orthogonal specific factors that were defined according to the a priori ASRS-18 item allocation rule to an INA factor and to a H/I factor, respectively, an adequate fit was observed, $\chi^2(117) = 147.72$, $p < 0.05$, RMSEA = 0.029, $p > 0.99$, TLI = 0.93, CFI = 0.95, SRMSR = 0.041, SABIC = 15,775.81.

Standardized factor loadings for MLR CFA best-fitting (i.e., bifactor) model of the ASRS-18 items are listed in Table 2. ω , ω_H , and ω_S coefficient values based on MLR CFA bifactor model of the ASRS-18 items were 0.78, 0.61, 0.26, and 0.42 for ASRS-18 scale as a whole, ASRS-18 item general factor (i.e., ASRS-18 total score), ASRS-18 INA subscale, and ASRS-18 H/I subscale, respectively. The ratio of the ω_H coefficient value to the ω coefficient value was 0.779, indicating that 77.9% of the reliable variance in the ASRS-18 was due to the total score (Reise et al., 2013).

3.3. Diagnostic accuracy statistics

According to MINI interview, 80 (32.9%) adolescents received a DSM-IV ADHD diagnosis. Adolescents who received a MINI ADHD diagnosis showed significantly lower average school grades¹ ($M = 6.74$, $SD = 0.94$) than non-ADHD adolescents ($M = 7.13$, $SD = 0.99$), $t(241) = -2.92$, $p > 0.01$, $d = -0.40$. ADHD adolescents received lower average behavior grade ($M = 7.96$, $SD = 0.89$) than non-ADHD adolescents ($M = 8.41$, $SD = 0.82$), $t(241) = -3.92$, $p < 0.001$, $d = -0.54$.

Descriptive statistics, bivariate associations (i.e., Mann-Whitney tests and *t*-tests), and logistic regression analysis results for ASRS-18 item and total scores, including the total scores based on the six-item screener and on the six best performing items in forward logistic regression, are summarized in Table 3. The 10-fold CV, ROC AUC analysis of the ASRS-18 total score was 0.80, $SE = 0.03$, 95% CI = 0.74, 0.86. When we considered the 6-item screener total score 10-fold CV, ROC AUC was 0.75, $SE = 0.04$, 95% CI = 0.68, 0.81. Finally, when we carried out 10-fold CV ROC analysis of the sum of the six ASRS-18 items that best discriminated ADHD adolescents from non-ADHD adolescents in forward LR analysis the corresponding AUC was 0.84, $SE = 0.03$, 95% CI = 0.78, 0.89.

Ten-fold CV ROC analysis results suggested an ASRS-18 total score ≥ 31 , an ASRS-6 score ≥ 11 , and a score ≥ 12 for the sum of the six ASRS-18 items that best discriminated ADHD adolescents from non-ADHD adolescents in LR analysis (ASRS-6-LR), yielded the best balance between sensitivity and specificity in predicting MINI ADHD diagnosis. Cohen κ value, sensitivity, specificity, PPP and NPP values for these cut-off scores are listed in Table 4. When we relied on an ASRS-18 total

¹ Schools in Italy use a 10-point scale that can be divided into failing (0 to 5) and passing (6 to 10) grades. A behavior grade lower than 8 indicates severe problem behavior at school and in the case of 6 grade, or even 7 grade in behavior, failure may occur.

Table 2
Robust maximum likelihood confirmatory bifactor model of the adult ADHD Self-Report Scale Items: Standardized factor loadings ($N = 308$).

Adult ADHD Self-Report Scale Items	<i>M</i>	<i>SD</i>	Standardized factor loadings		
			ADHD	INA	H/I
1. Wrapping up the final details	1.48	0.82	0.28***	0.21*	–
2. Difficulty getting things in order	1.40	1.04	0.37***	0.16	–
3. Remembering appointments	1.27	1.07	0.35***	0.20	–
4. Avoid or delay getting started	1.87	0.99	0.32***	0.31***	–
5. Fidget or squirm	2.04	1.27	0.29***	–	0.36***
6. Feel overly active and compelled	1.76	1.10	0.18	–	0.66***
7. Make careless mistakes	2.20	0.97	0.38***	0.51***	–
8. Difficulty keeping your attention	2.25	1.04	0.32***	0.52***	–
9. Difficulty concentrating	0.99	0.91	0.43***	0.28**	–
10. Difficulty finding things	1.82	1.11	0.47***	0.05	–
11. Distracted by activity or noise	1.91	1.10	0.41***	0.26**	–
12. Leave seat in meetings	0.85	0.95	0.43***	–	0.15
13. Feel restless or fidgety	1.95	1.06	0.35***	–	0.37***
14. Difficulty unwinding and relaxing	1.54	1.27	0.30***	–	0.21*
15. Talking too much	1.85	1.13	0.29***	–	0.21*
16. Finishing the sentences	1.30	1.08	0.29***	–	0.21*
17. Difficulty waiting turn	1.34	1.06	0.44***	–	0.00
18. Interrupt others	1.40	0.89	0.41***	–	0.06

Note.

ADHD: ADHD general factor; INA: inattentive specific factor; H/I: hyperactive/impulsive specific factor.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

score ≥ 31 to consider a possible ADHD diagnosis with MINI ADHD diagnosis, a significantly higher proportion of false positives (FP; 18.5%) than of false negatives (FN; 7.4%) was observed, McNemar $\chi^2(1) = 10.73$, $p < 0.01$. Similar considerations held for an ASRS-6 score ≥ 11 (FP = 18.1%, FN = 10.3%, McNemar $\chi^2(1) = 4.70$, $p < 0.05$), and an ASRS-6-LR score ≥ 12 (FP = 16.0%, FN = 8.2%, McNemar $\chi^2(1) = 5.49$, $p < 0.05$).

4. Discussion

Consistent with previous reports in adult samples (e.g., Kessler et al., 2005, 2007), the Italian translation of the ASRS-18 seemed to represent a reliable and valid self-report measure to screen for ADHD symptomatology also in a sample of community dwelling adolescents. This finding may have relevant clinical implications because could allow for early identification of adolescents needing for accurate ADHD assessment to start early treatment of long-term sequelae of childhood ADHD, or even rapid diagnosis and treatment of adult-onset ADHD (e.g., Agnew-Blais et al., 2016). It should be stressed that our adolescent sample did not aim to be representative of the Italian adolescent population; rather, inclusion criteria (i.e., presence of problem behavior) aimed at maximizing the likelihood of including ADHD adolescents. This sampling strategy may explain the large ADHD base rate (32.9%) that was observed in our adolescent sample.

Confirming and extending previous studies based on adult samples (e.g., Kessler et al., 2005, 2007; Sanchez-Garcia et al., 2015), our findings based on Haberman's (2008) approach and Reise et al. (2013) method to dimensionality assessment seemed to indicate that the correlations among the ASRS-18 items were explained by a single, common latent dimension, purportedly corresponding to ADHD symptomatology. Thus, clinicians and researchers should focus mainly (not to say exclusively) on the ASRS-18 total score to evaluate the likelihood of ADHD problems.

Although ASRS-18 Inattention subscale yielded reliable scores

according to Haberman's (2008) criteria, MLR CFA results strongly supported a bifactor model of the ASRS-18 items as the best fitting model; except for ASRS-18 item 6, all ASRS-18 items showed significant and non-negligible standardized factor loadings on the ADHD general factor. According to Reise et al. (2013) approach to unidimensionality assessment, the wide majority (i.e., 77.9%) of the overall ASRS-18 reliability ($\omega = 0.78$) was concentrated in its total score, at least as it was operationalized in the ADHD general factor; moreover, both specific factors showed sub-optimal reliability estimates (i.e., ω_s values), suggesting that ASRS-18 subscale scores has very limited reliability when the effect of the general factor was controlled for (Reise et al., 2013).

Consistent with the available evidence on adult subjects (e.g., Kessler et al., 2005, 2007), in our study the ASRS-18 proved to be able to effectively differentiate adolescents who received a MINI ADHD diagnosis from adolescents who did not receive a MINI ADHD diagnosis. According to Mann–Whitney U tests, 83.3% of the ASRS-18 items showed significantly higher median scores among ADHD adolescents than among non-ADHD adolescents. Confirming and extending previous findings (e.g., Kessler et al., 2005, 2007; Sanchez-Garcia et al., 2015; Ustun et al., 2017), our logistic regression analysis results suggested that six ASRS-18 items may be sufficient to summarize the information that is necessary to effectively discriminate ADHD adolescents from non-ADHD adolescents, although the six items that emerged as the best predictors of ADHD in community-dwelling adolescents in our LR analyses were largely different from those that were originally included in the ASRS-6. Our results were at least partially consistent with Sanchez-Garcia et al. (2015) results indicating how in adults with substance use disorder the ASRS-6 should be modified to yield adequate diagnostic accuracy, as well as Ustun et al's (2017) results suggesting the need for a complete re-definition of the ASRS six-item screener.

Consistent with previous studies (Kessler et al., 2005, 2007), our 10-fold CV ROC analysis results suggested adequate diagnostic efficacy (i.e., AUC values ≥ 0.80) for ASRS-18 and ASRS-6-LR total scores. When we relied on ROC-based cut-off scores for ASRS-18, ASRS-6, and ASRS-6-LR total scores in order to identify potential ADHD adolescents, Cohen κ values suggested at least moderate diagnostic agreement with MINI ADHD diagnosis only for ASRS-18 and ASRS-6-LR total scores; this finding, as well as the values of sensitivity, specificity, PPP, and NPP for the three total scores that were considered in our study, suggested care in using the ASRS-6 total score as an ADHD screener in community-dwelling adolescents with problem behavior. In our study, a significantly higher proportion of false positives (FP) than of false negatives (FN) was observed for the ASRS-18, ASRS-6, and ASRS-6-LR cut-off scores, respectively. In our opinion, this represents a desirable property for a fast, self-report screening measure for ADHD in adolescence, particularly considering the relatively limited FP frequency that was observed in our adolescent sample. On the other hand, FN rates ranged from 7.4% (ASRS-18 total score) to 10.3% (ASRS-6 total score), showing that a non-negligible proportion of ADHD adolescents may go undetected if clinicians would rely uncritically only on self-reports (particularly on ASRS-6 self-reports) to identify adolescents at risk for ADHD needing for in-depth ADHD assessment.

Of course, our findings should be considered in the light of several limitations. Our sample was composed of adolescents who volunteered to participate in the study, rather than of adolescents who were randomly selected from the Italian adolescent population. Moreover, only adolescents who were reported by their teachers as manifesting externalizing problem behaviors participated in this study, and this may have introduced a bias in our sampling strategy. Indeed, ADHD is often underrecognized in girls, due to a symptom profile (i.e., more inattentive and less hyperactive/impulsive than males) that is less likely to be disruptive in the class (Quinn and Madhoo, 2014). Thus, our sample was more akin to a convenience study group than to a random sample representative of the adolescents in the Italian general population. The MINI interview has been designed to yield epidemiological ADHD diagnosis, rather than clinically sound ADHD diagnoses.

Table 3

Adult ADHD Self-Report Scale in ADHD (n = 80) and non-ADHD (n = 143) adolescents: Descriptive statistics, bivariate comparisons, and logistic regression analysis results.

Adult ADHD Self-Report Scale Items	ADHD (n = 80)		Non-ADHD (n = 163)		z/t(241)	Logistic Regressions	
	M	SD	M	SD		OR	95% CI
1. Wrapping up final details ^S	1.79	0.92	1.31	0.75	3.90***	1.87 (1.69)	1.19, 2.92 (1.13, 2.55)
2. Difficulty getting things ^S	1.94	1.13	1.13	0.94	5.47***	1.56(1.71)	1.09, 2.23 (1.24, 2.38)
3. Remembering appointments	1.59	1.23	1.10	1.00	2.89**	1.09	0.79, 1.50
4. Avoid or delay	2.30	1.02	1.67	1.01	4.61***	1.22	0.84, 1.75
5. Fidget or squirm	2.33	1.35	1.92	1.27	2.33*	1.04	0.78, 1.37
6. Feel overly active	1.93	1.26	1.72	1.06	1.11	1.19	0.84, 1.69
7. Make careless mistakes ^S	2.71	0.98	1.96	0.88	5.61***	1.59 (1.79)	1.04, 2.44 (1.20, 2.66)
8. Difficulty keeping attention ^S	2.74	0.96	2.10	1.04	4.44***	1.55 (1.61)	1.04, 2.33 (1.12, 2.31)
9. Difficulty concentrating	1.31	1.01	0.85	0.84	3.56***	0.98	0.65, 1.49
10. Difficulty finding things	2.30	1.08	1.60	1.13	4.61***	1.39	1.00, 1.94
11. Distracted by activity	2.36	1.11	1.72	1.09	4.32***	1.19	0.85, 1.67
12. Leave seat in meetings	1.10	1.11	0.73	0.88	2.41*	1.04	0.71, 1.52
13. Feel restless or fidgety ^S	2.30	1.15	1.75	1.00	3.56***	1.26 (1.39)	0.89, 1.78 (1.02, 1.90)
14. Difficulty unwinding	1.73	1.35	1.44	1.28	1.50	0.97	0.73, 1.29
15. Talking too much	1.96	1.36	1.79	1.04	0.94	0.87	0.64, 1.20
16. Finishing the sentences	1.50	1.11	1.20	1.08	1.98*	1.22	0.87, 1.71
17. Difficulty waiting turn ^S	1.78	1.17	1.13	0.96	4.12***	1.79 (1.82)	1.25, 2.58 (1.32, 2.52)
18. Interrupt others	1.55	0.98	1.32	0.87	2.01*	0.82	0.54, 1.24
$R^2_{McFadden}$						0.31***	
Goodness-of-fit $\chi^2_{(224)}$						211.69	
$R^2_{McFadden}$ Forward LR						0.28***	
Goodness-of-fit $\chi^2_{(214)}$						241.05	
Adult ADHD Self-Report Scale Total Scores							
18-item Total Score	35.20	7.76	26.44	7.38	8.55***	1.18	1.12, 1.24
$R^2_{McFadden}$						0.21***	
Goodness-of-fit $\chi^2_{(38)}$						36.41	
6-item Total Score	11.86	3.40	8.86	2.99	7.03***	1.36	1.22, 1.50
$R^2_{McFadden}$						0.15***	
Goodness-of-fit $\chi^2_{(16)}$						15.66	
6-item Total Score (based on Forward LR)	13.25	2.92	9.38	2.88	9.80***	1.66	1.44, 1.91
$R^2_{McFadden}$						0.27***	
Goodness-of-fit $\chi^2_{(17)}$						10.38	

Note. z: Mann–Whitney U z-test; OR: odds ratio; CI: confidence interval; LR: logistic regression; S: item selected in forward LR; odds ratios based on forward LR are listed between brackets;

- * p < 0.05.
- ** p < 0.01.
- *** p < 0.001.

Table 4

Cut-Off Scores, Cohen κ value, Sensitivity, Specificity, Positive Predictive Power and Negative Predictive Power Values for the Adult ADHD Self-Report Scale.

	Cut-off	Cohen κ	Sensitivity	Specificity	Positive predictive power	Negative predictive power	Positive likelihood ratio	Negative likelihood ratio
ASRS-18	≥ 31	0.46***	0.78	0.72	0.58	0.87	2.79	0.31
ASRS-6	≥ 11	0.39***	0.69	0.73	0.56	0.83	2.56	0.43
ASRS-6-LR	≥ 12	0.48***	0.75	0.76	0.61	0.86	3.33	0.33

Note. ASRS: Adult ADHD Self-Report Scale; LR: logistic regression.
*** p < 0.001.

Moreover, clinical assessment of ADHD requires careful consideration of multiple sources of information and indicators. Although we tried to increase the validity of our MINI ADHD diagnoses by testing their associations with objective indicators of poor performance and discipline at school (i.e., school and behavior grades, respectively), our ADHD diagnoses were far from clinically sound ADHD assessment.

The MINI adolescence ADHD module does not allow for assessing ADHD subtypes/presentations (Sheehan et al., 1997); this prevented us to obtain a detailed picture of our ADHD adolescents. Moreover, semi-structured interviews allowing for fine-grained ADHD diagnosis in adolescence may yield different relationships with the ASRS-18 score. It should be observed that diagnostic criteria for adult ADHD were revised in the DSM-5 Section II; regrettably, we relied on a sound epidemiological, structured interview that was explicitly designed to assess only DSM-IV (and ICD-10) disorders.

Finally, diagnostic agreement statistics may be influenced by the disorder base rate estimates; thus, the ASRS-18 may yield different

diagnostic agreement estimates in samples that are characterized by different ADHD base rates. These considerations inherently limit the generalizability of our finding and stress the need for further studies before accepting our conclusions.

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References

APA, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association, Washington, DC text revised-DSM-IV-TR.
 APA, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association, Washington, DC DSM-5.
 Agnew-Blais, J.C., Polanczyk, G., Danese, A., Wertz, J., Moffitt, T.E., Arseneault, L., 2016. Persistence, remission and emergence of ADHD in young adulthood: results from a

- longitudinal, prospective population-based cohort. *JAMA Psychiatry* 73, 713–720.
- Asherson, P., Buitelaar, J., Faraone, S.V., Rohde, L.A., 2016. Adult attention-deficit hyperactivity disorder: key conceptual issues. *Lancet Psychiatry* 3, 568–578.
- Coghill, D., Sonuga-Barke, E.J., 2012. Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders—implications of recent empirical study. *J. Child. Psychol. Psychiatry* 53, 469–489.
- Cohen, J., 1988. *Statistical Power Analysis for the Behavioral Sciences*, second ed. Lawrence Erlbaum Associates, Hillsdale, NJ.
- Faraone, S.V., Biederman, J., Mick, E., 2006. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol. Med.* 36, 159–165.
- Flory, K., Molina, B., Pelham, W., Gnagy, E., Smith, B., 2006. Childhood ADHD predicts risky sexual behavior in young adulthood. *J. Clin. Child. Adolesc. Psychol.* 35, 571–577.
- Grimes, D.A., Schulz, K.F., 2005. Refining clinical diagnosis with likelihood ratios. *Lancet* 365, 1500–1505.
- Haberman, S.J., 2008. When can subscores have value? *J. Educ. Behav. Stat.* 33, 204–229.
- Hu, L.T., Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Model.* 6, 1–55.
- LeDell, E., Petersen, M., van der Laan, M., 2014. *cvAUC: Cross-Validated Area Under the ROC Curve Confidence Intervals*. <https://CRAN.R-project.org/package=cvAUC>.
- Kent, K.M., Pelham, W.E.Jr., Molina, B.S., Sibley, M.H., Waschbusch, D.A., Yu, J., et al., 2011. The academic experience of male high school students with ADHD. *J. Abnorm. Child Psychol.* 39, 451–462.
- Kessler, R.C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., et al., 2005. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol. Med.* 35, 245–256.
- Kessler, R.C., Adler, L.A., Gruber, M.J., Sarawate, C.A., Spencer, T., Van Brunt, D.L., 2007. Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) screener in a representative sample of health plan members. *Int. J. Methods Psychiatr. Res.* 16, 52–65.
- Kumar, G., Faden, J., Steer, R.A., 2011. Screening for attention-deficit/hyperactivity disorder in adult inpatients with psychiatric disorders. *Psychol. Rep.* 108, 815–824.
- Molina, B.S.G., Pelham, W.E., Gnagy, E.M., Thompson, A.L., Marshal, M.P., 2007. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcohol. Clin. Exp. Res.* 0, 643–654.
- National Comorbidity Survey, 2005. *Adult ADHD Self-Report Scale (ASRS) Version 1.1: Background information*. Retrieved from. <http://www.hcp.med.harvard.edu/ncs/asrs.php>.
- Quinn, P.O., Madhoo, M., 2014. A review of attention-deficit/hyperactivity disorder in women and girls: uncovering this hidden diagnosis. *Prim. Care Companion CNS Disord.* 16.
- Reise, S.P., Bonifay, W.E., Haviland, M.G., 2013. Scoring and modeling psychological measures in the presence of multidimensionality. *J. Pers. Assess.* 95, 129–140.
- Rossi, A., Alberio, R., Porta, A., Sandri, M., Tansella, M., Amaddeo, F., 2004. The reliability of the MINI-international neuropsychiatric interview-Italian version. *J. Clin. Psychopharmacol.* 24, 561–563.
- Sanchez-Garcia, M., Fernandez-Calderon, F., Carmona-Marquez, J., Chico-Garcia, M., Velez-Moreno, A., Perez-Gomez, L., 2015. Psychometric properties and adaptation of the ASRS in a Spanish sample of patients with substance use disorders: application of two IRT Rasch models. *Psychol. Assess.* 27, 524–533.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Janavs, J., Weiller, E., Keskiner, A., et al., 1997. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur. Psychiatry* 12, 232–241.
- Sibley, M.H., et al., 2012. Diagnosing ADHD in adolescence. *J. Consult. Clin. Psychol.* 80, 139–150.
- Sibley, M.H., Pelham, W.E., Molina, B.S.G., Gnagy, E.M., Waschbusch, D.A., Biswas, A., et al., 2011. The delinquency outcomes of boys with ADHD with and without comorbidity. *J. Abnorm. Child Psychol.* 39, 21–32.
- Takeda, T., Tsuji, Y., Kurita, H., 2017. Psychometric properties of the Japanese version of the adult attention-deficit hyperactivity disorder (ADHD) Self-Report Scale (ASRS-J) and its short scale in accordance with DSM-5 diagnostic criteria. *Res. Dev. Disabil.* 63, 59–66.
- Thompson, A., Molina, B., Pelham, W., Gnagy, E., 2007. Risky driving in adolescents and young adults with childhood ADHD. *J. Pediatr. Psychol.* 32, 745–759.
- Ustun, B., et al., 2017. The World Health Organization Adult attention-deficit/hyperactivity disorder Self-Report Screening Scale for DSM-5. *JAMA Psychiatry* 74, 520–526.
- Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., Pennington, B.F., 2005. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol. Psychiatry* 57, 1336–1346.

RUBRICHE

DALLA PARTE DEI BAMBINI

a cura di Franca Rusconi

Registri di malattia: strumenti dinamici per la qualità delle cure. Il registro ADHD della Regione Lombardia

Disease registries: a dynamic instrument evaluating quality of care. The ADHD registry of Lombardy Region (Northern Italy)

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Nel 2011 in Regione Lombardia è stato attivato un registro regionale per garantire un'adeguata valutazione del disturbo da deficit di attenzione/ipertattività (*attention deficit hyperactivity disorder*, ADHD) a ogni bambino e adolescente fin dal momento in cui il disturbo è sospettato o segnalato.

L'ADHD

L'ADHD è un disturbo neurobiologico dell'età evolutiva, le cui manifestazioni sono la difficoltà a prestare attenzione, comportamenti impulsivi e un livello di attività motoria accentuato.¹ I sintomi sono solitamente evidenti in età scolare, più frequentemente nei maschi, e possono persistere nell'età adulta. Un disturbo descritto per la prima volta nel 1902 da George Still come lesione organica cerebrale, definito poi "disfunzione cerebrale minima" nel Manuale diagnostico e statistico dei disturbi mentali (DSM) 1 del 1952, "reazione ipercinetica dell'infanzia" nel DSM-2 del 1968, "disturbo da deficit di attenzione con o senza ipertattività" nel DSM-3 del 1980, "distur-

bo da deficit di attenzione/ipertattività» nel DSM-4 del 1996, definizione mantenuta nel DSM-5 del 2013 inserendo l'ADHD come disturbo a sé stante tra i disturbi del neurosviluppo. Percorsi della classificazione dei disturbi mentali che non solo indicano l'acquisizione nel tempo di evidenze cliniche, ma anche la complessità e l'eterogeneità dei singoli disturbi mentali e comportamentali che si manifestano con comorbidità e pattern di sintomi comuni.

La prevalenza mondiale dell'ADHD nei bambini e negli adolescenti è del 5,3%, sebbene le stime varino molto tra aree geografiche, anche all'interno di uno stesso Paese, ma soprattutto in base alla modalità di valutazione diagnostica utilizzata.² Così come eterogenee sono le risposte terapeutiche, che dovrebbero basarsi su un approccio multimodale e

adattato alle caratteristiche del soggetto, combinando interventi psicologici con terapie mediche. In Italia, la prevalenza basata sulla valutazione clinica è dell'1,4% (1,1%-3,1%) nei bambini di 7-14 anni d'età (circa 55.000 individui).³ I trattamenti psicologici includono interventi psicoeducativi rivolti ai genitori e agli insegnanti e di tipo cognitivo-comportamentale per il paziente. L'intervento farmacologico prevede l'uso degli psicostimolanti come farmaci di prima scelta (in particolare il metilfenidato, sintetizzato nel 1937), comunque non come unico intervento terapeutico.

L'USO INAPPROPRIATO DEGLI PSICOFARMACI NEI BAMBINI

Nel mondo, il 10%-20% di bambini e adolescenti soffre di disturbi mentali. La metà di tutte le malattie mentali inizia entro i 14 anni e tre quarti entro i 24 anni di età.⁴ Non deve, quindi, stupire



RUBRICHE

DALLA PARTE DEI BAMBINI

se a partire dagli inizi degli anni Novanta la prescrizione di psicofarmaci a bambini e adolescenti (principalmente per ADHD) ha seguito un trend incrementale in molte nazioni, seppure con tassi differenti.⁵ Un fenomeno più americano che europeo, dove la prevalenza d'uso per l'ADHD interessa il 3,5% di bambini e adolescenti.⁶ In Italia, si incominciò a parlarne nel 1978, quando venne pubblicato il libro *Il mito del bambino iperattivo*⁷ all'interno della collana di Feltrinelli "Medicina e potere". Il testo era il risultato di una vasta indagine giornalistica condotta negli Stati Uniti dagli autori, non medici, e rappresentava la denuncia dell'uso degli psicofarmaci come strumento di controllo del comportamento dei bambini. Un rischio anche italiano, denunciato da Maccacaro nel 1971 dopo la pubblicazione di un articolo⁸ (il primo trial formale in neuropsichiatria!) sull'uso della periciazina somministrata a 150 bambini delle scuole materne di Modena che presentavano "disturbi (turbe) del comportamento". Dopo il trattamento i bambini «sono più adattati, socievoli, tranquilli [...] il farmaco si è dimostrato elettivamente socializzante». Comunque, ci si chiedeva: «vera malattia o mito americano?».⁹ Per impedire che il fenomeno prendesse piede anche in Italia con un uso inappropriato del metilfenidato, nel 2007 presso l'Istituto superiore di sanità venne istituito il Registro nazionale dell'ADHD per monitorare la prescrizione del metilfenidato, quindi un Registro di farmaco. Il protocollo per la prescrizione del farmaco e l'inserimento nel Registro rappresentava l'attuazione del documento nazionale di consenso del 2003.¹⁰ Il metilfenidato veniva immesso nuovamente in commercio in Italia nel 2003, dopo il suo ritiro da parte dei produttori nel 1989, a seguito di una procedura iniziata nel 2000 con una petizione di pediatri di famiglia e neuropsichiatri all'allora Ministro Veronesi... una storia italiana.

IL REGISTRO ADHD DELLA REGIONE LOMBARDIA

Il Registro dell'ADHD è stato, quindi, concepito come registro di malattia, raccogliendo informazioni relative non solo ai pazienti con diagnosi e in trattamento farmacologico, ma a tutti i pazienti che afferiscono ai 18 Centri di riferimento per sospetto ADHD. Il Registro rappresenta lo strumento di un'iniziativa volta a: • stimare la prevalenza del disturbo; • definire e garantire percorsi diagnostico-terapeutici appropriati attraverso l'applicazione di un protocollo condiviso di valutazione e monitoraggio del disturbo; • intensificare la formazione e l'aggiornamento degli operatori; • informare i cittadini.¹¹ Un progetto ambizioso, a tutt'oggi unico non solo nel panorama nazionale che ha sinora valutato i percorsi di cura di 6.000 bambini e adolescenti che presentavano, nel 66% dei casi, altri disturbi psichiatrici (in particolare, disturbi di apprendimento: 56%; disturbi del sonno: 23%; disturbo oppositivo-provocatorio: 20%).¹² I risultati sono positivi e vanno oltre l'ADHD, come è

stato il caso della valutazione dell'inserimento precoce scolastico, associato a un aumento di diagnosi anche di altri disturbi del neurosviluppo;¹³ dell'analisi dei tempi di attesa per i singoli Centri tra la richiesta e la diagnosi e i possibili interventi per ridurre le ampie differenze; della formazione continua, comune e condivisa, degli operatori partecipanti. Oltre a un sito dedicato al progetto (www.adhd.marionegri.it) e una newsletter mensile con l'aggiornamento della letteratura internazionale in tema di ADHD pubblicata nel mese precedente (inviata gratuitamente a chiunque interessato), all'inizio di ogni mese ciascun Centro riceve un *report* sui dati inseriti, le eventuali incongruenze e le successive scadenze per ciascuno dei suoi pazienti.

Risultati importanti per i pazienti, le famiglie, gli insegnanti e gli operatori (neuropsichiatri, psicologi, pediatri di famiglia), ma anche per i decisori istituzionali. Un approccio da implementare e migliorare non solo per la cura dell'ADHD, ma anche per gli altri disturbi neuropsichiatrici dell'età evolutiva.

BIBLIOGRAFIA

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th Edition (DSM-5). Arlington, American Psychiatric Publishing, 2013.
2. Polanczyk GV, Jensen O. Epidemiologic considerations in attention deficit hyperactivity disorder: a review and update. *Child Adolesc Psychiatr Clin N Am* 2008;17(2): 245-60.
3. Reale L, Bonati M. ADHD prevalence estimates in Italian children and adolescents: a methodological issue. *Ital J Pediatr* 2018;44(1):108.
4. World Health Organization. Child and adolescent mental health. Disponibile all'indirizzo: https://www.who.int/mental_health/maternal-child/child_adolescent/en/
5. Kalverdik LJ, Bachmann CJ, Aagaard L et al. A multi-national comparison of antipsychotic drug use in children and adolescents, 2005-2012. *Child Adolesc Psychiatry Ment Health* 2017;11: 55.
6. Hales MC, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents-United States, 1999-2014. *JAMA* 2018;319(19):2009-20.
7. Schrag P, Divoky D. Il mito del bambino iperattivo e altri strumenti di controllo del bambino. Milano, Feltrinelli Editore, 1978.
8. Cavazzuti GB, Amore F, Giacalone M. Sperimentazione terapeutica della periciazina in bambini di 3-6 anni. *Neuropsichiatria infantile* 1969;98:288-302.
9. Diller LH. ADHD, realtà o mito Americano? *Quaderni acp* 2003;10(3):22-23.
10. Consensus Conference di Cagliari. Indicazioni e strategie terapeutiche per i bambini e gli adolescenti con disturbo da deficit attentivo con iperattività. *Quaderni acp* 2003;10(2):33-36.
11. Bonati M, Reale L, Zanetti M et al. A Regional ADHD center-based network project for the diagnosis and treatment of children and adolescents with ADHD. *J Atten Disord* 2018;22(12):1173-84.
12. Reale L, Bartoli B, Cartabia M et al. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur Child Adolesc Psychiatry* 2017;26(12): 1443-57.
13. Bonati M, Cartabia M, Zanetti M et al. Age level vs grade level for the diagnosis of ADHD and neurodevelopmental disorders. *Eur Child Adolesc Psychiatry* 2018;27(9):1171-80.

Per ricevere la newsletter iscriversi al seguente indirizzo:
<http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter>

link per potersi cancellare dalla mailing list:
<http://adhd.marionegri.it/index.php/newsletter/cancellazione-newsletter>

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
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5954 del 05/12/2016 e N. 1077 del 02/02/2017) Capofila Progetto: UONPIA Azienda
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