NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD MARZO 2021

Acad Pediatr. 2021.
TOWARD EQUITABLE HEALTH OUTCOMES FOR DIVERSE CHILDREN WITH ADHD AND THEIR FAMILIES.
Lindly OJ, Nasol E, Tarazi CL, et al.

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Acta Medica Mediterranea. 2021;37:591-97.
CLINICAL ANALYSIS OF OBSTRUCTIVE SLEEP APNEA WITH HYPOPNEA COMBINED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Wu J, Gu M, Chen S, et al.
Introduction: A comparative study of dopamine/norepinephrine in children with pure obstructive sleep apnea hypopnea syndrome (OSAHS) and children OSAHS plus Attention deficit hyperactivity disorder (ADHD).
Materials and methods: A total of 437 children hospitalized for OSAHS from January 2014 to December 2014 were included in this trial. Based on the presence of ADHD and the ADHD classification, the patients were divided into a pure OSAHS group and a OSAHS plus ADHD group. The differences in the patients gender, age, OSA-18 scores, sleep monitoring findings (AHI, lowest oxygen saturation), and serum dopamine and norepinephrine levels between the two groups were examined. SPSS20.0 was used for the statistical analysis.
Results: Men are more likely to suffer from OSAHS than women, and males are the majority of the children with ADHD in the present study. More serious respiratory events occurred among the children with OSAHS plus ADHD than among the pure OSAHS patients (P<0.001), and oxygen deficiency and sleep disorders were also more serious among the former group (P<0.01). The children with attention deficit-type ADHD and mixed-type ADHD had the worse sleep quality (P<0.001), and the OSA-18 scores were more severe among the children with ADHD plus sleep disorders (P<0.001). Among subjects aged 4-5 years, higher dopamine and dopamine/ norepinephrine levels were observed among the children with ADHD (P<0.001). Children with hyperactivity-type ADHD had the highest levels, those with mixed-type ADHD had the second-highest levels, and those with pure OSAHS had the lowest levels. Norepinephrine levels were not significantly different between groups. In the 6 to 11-year-old group, the differences in dopamine, norepinephrine, and dopamine/norepinephrine levels were statistically significant (P<0.05), but dopamine and dopamine/norepinephrine levels were lower in the pure OSAHS group than in the group with OSAHS combined with hyperactivity-type ADHD.
Conclusion: The incidence of ADHD in children with OSAHS is more than 30%, which increases with age since longer durations of OSAHS have a more severe influence on the brain. Sleep disorders are more severe among children with OSAHS plus ADHD. Dopamine/norepinephrine levels are higher in children with hyperkinetic-type ADHD, suggesting that an imbalance between dopamine and norepinephrine is associated with hyperkinetic ADHD

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Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

Acta Paediatr Int J Paediatr. 2021.

FOOD PREFERENCES, FOOD NEOPHOBIA AND CHEMOSENSATION AMONG ADOLESCENTS WITH ADHD.

Stankovic J, Hove Thomsen P, Ovesen T.

Aim: It has been suggested that adolescents diagnosed with ADHD have an unhealthier diet compared to their peers without ADHD. The association between chemosensation (smell and taste) and dietary patterns remains unknown. The aim is to investigate unhealthy food preferences and food neophobic behaviour among adolescents diagnosed with ADHD. Additionally, it is to investigate the relationship between dietary patterns and chemosensory function.
Methods: We enrolled 36 adolescents with and without ADHD to complete a food item and a food neophobia questionnaire and to undergo chemosensory testing.
Results: Adolescents with ADHD performed significantly worse on both chemosensory tests compared to the non-ADHD group. No difference in food preferences nor food neophobia was found between the two groups.
Conclusion: Adolescents with ADHD have a lower score on chemosensory tests compared to their peers, suggesting impaired chemosensory function. No differences in dietary preferences nor food neophobia were seen between the two groups

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Acta Paediatr Int J Paediatr. 2021;110:1380.

LETTER IN RESPONSE: HYPERACTIVITY IS ASSOCIATED WITH HIGHER FAT-FREE MASS AND PHYSICAL ACTIVITY IN SWEDISH PRESCHOOLERS: A CROSS-SECTIONAL STUDY.

Vadgama AN, Kharel E, Singh GV.

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Am J Phys Med Rehabil. 2021 Mar;100:215-28.

BIOPSYCHOSOCIAL FACTORS ASSOCIATED WITH ATTENTION PROBLEMS IN CHILDREN AFTER TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW.

Bolikal PD, Narad M, Raj S, et al.

OBJECTIVE: The aim of this review was to examine biopsychosocial factors associated with an increased risk of attention problems after a traumatic brain injury in children.
DESIGN: A systematic review of the literature was conducted using data sources of MEDLINE, PsycINFO, and CINAHL up to August 30, 2020. Literature primarily examined pediatric patients with traumatic brain injury and attention problems. Risk factors for attention problems posttraumatic brain injury examined in all articles were identified and grouped into broad categories of biological, psychological, and social factors. Methodological quality of each study was assessed using the modified Downs and Black checklist. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines from 2009 were used in completing this review.
RESULTS: Forty articles met inclusion criteria for this study. Overall findings were mixed but suggested that younger age at injury, presence of preinjury attention-deficit/hyperactivity disorder, poorer preinjury adaptive functioning, lower socioeconomic status, and poorer family functioning were associated with increased risk of developing attention problems posttraumatic brain injury.
CONCLUSIONS: Development of attention problems after pediatric traumatic brain injury is complex and influenced by an array of biologic, environmental/social, injury-related, and host factors. Evidence is mixed, and further study is needed to better understand the relationships between these factors and how they influence attention after traumatic brain injury. Nonetheless, screening for attention problems in children with risk factors may allow for earlier identification and intervention, minimizing negative impacts of attention problems after traumatic brain injury in children. Limitations of this study included heterogeneity of studies and overall low to moderate methodological quality of studies included as measured by the modified Downs and Black checklist.
TO CLAIM CME CREDITS: Complete the self-assessment activity and evaluation online at http://www.physiatry.org/JournalCME.

CME OBJECTIVES: Upon completion of this article, the reader should be able to: (1) Describe the importance of recognizing and identifying attention problems after traumatic brain injury in children; (2) Identify risk factors for development of attention problems after pediatric traumatic brain injury; and (3) Recognize gaps in existing literature regarding predictors of attention problems after pediatric traumatic brain injury.
LEVEL: Advanced.
ACCREDITATION: The Association of Academic Physiatrists is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Association of Academic Physiatrists designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)â„¢. Physicians should only claim credit commensurate with the extent of their participation in the activity

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An Pediatr. 2021.

NEUROCOGNITIVE AND BEHAVIORAL PROFILE OF FETAL ALCOHOL SPECTRUM DISORDER.

Maya-Enero S, Ramis-Fern+índez SM, Astals-Vizcaino M, et al.

Prenatal alcohol exposure is the leading preventable cause of cognitive deficit in developed countries and can lead to fetal alcohol spectrum disorder (FASD). This term encompasses a wide range of physical, mental, behavioral, and cognitive effects that result from damage caused by exposure to alcohol during intrauterine life. Alcohol consumption among the general population is common in Eastern European countries and especially among women at risk of social exclusion, who are the ones who lose or give up custody of their children. A high number of these children are adopted in Spain and many of them present neurocognitive and behavioral disorders, causing FASD to be a public health problem in our country. In many occasions this clinical spectrum is delayed or under-diagnosed due to the overlapping of neuropsychological symptoms caused by the abandonment. A neurocognitive and behavioral profile specific for FASD has not been defined and all the symptoms are common to other etiologies. The aim of this work is to review the neuropsychological profile in the diagnosis of TEAF

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Ann Med -Psychol. 2021.

COMORBID DISORDERS INCIDENCE ON THE EFFECT OF A PSYCHOTHERAPY AIMED AT DECREASING EXPLOSIVE OUTBURSTS OF CHILDREN WITH TOURETTE SYNDROME.

Blanchet MM, Leclerc JB.

The present study examines whether the severity of inattention and hyperactivity symptoms as well as the severity of obsessions and compulsions symptoms modulate the response to a specialized psychotherapy that aims to decrease the explosive outburst (EO) in children with Tourette syndrome (TS). Indeed, the impulsivity and lack of self-control usually associated to attention-deficit/hyperactivity disorder (ADHD), paired with the rigidity and perfectionism inherent in obsessiveΓÇôcompulsive disorder (OCD) increases the likelihood of EO manifestation. However, no study has directly examined the interactions between the specific symptoms of ADHD and OCD in the treatment of EO. Nineteen children with TS, aged 8 to 14, were recruited and randomly assigned to one of two intervention groups: 1) a specific therapy to reduce EO; 2) an active control group. To our knowledge, the specific therapy named ΓÇ£Prends ton Tourette par les Cornes !ΓÇØ (PTC) (Leclerc, O'Connor, Forget, & Lavoie, 2012) is the only therapy that addresses specifically EO. Moreover, this therapy conceptualises EO as inherent manifestations of TS and takes into account certain cognitive processes inherent in ADHD and OCD, such as cognitive rigidity and lack of self-control. Data were collected regarding the severity of tics and the severity of comorbid ADHD and OCD symptoms. The severity of ADHD symptoms tends to have a negative impact on the effect of the therapy (r = ΓêÆ0.694; P = 0.056), unlike OCD symptoms (r = 0.039; P = 0.920) and the severity of tics (r = 0.262; P = 0.155). However, the lack of association between the severity of OCD symptoms and the response to treatment can be explained by the low prevalence of these symptoms in the sample prior to the treatment. Regression coefficients analysis shows that the inattention subscale of the ADHD questionnaire is the most negatively associated (r

= 0.642) with the reduction of EO after PTC therapy, without however reaching the threshold of statistical significance (P = 0.086). Data shows that the presence of ADHD accounts for 48.10% of the variance in EO after therapy and that inattention symptoms could affect the effectiveness of treatment. In short, inattention behaviour prior to the therapy could make it more difficult to process information and ultimately interfere with the integration of therapeutic steps or with the adhesion of essential elements of the therapy. Consequently, ADHD symptoms should be taken into account from the start and be directly targeted by the addition of specific exercises for attentional difficulties, while considering the parentsΓÇÖ urgency to address EO quickly in the therapeutic process. Future studies examining the association between EO and comorbid disorders would benefit from being part of a transdiagnostic current in order to clarify the role of symptoms and cognitive or emotional processes present in the broad spectrum of associated symptoms in children with TS

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Ann Neurol. 2020;88:S62-S63.

CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER BENEFIT FROM YOGA TRAINING.

Kiselev S.

Background: It is known that children with attention deficit/ hyperactivity disorder (ADHD) have deficit in executive abilities. It is important to search for effective treatments which aim to improve executive abilities in children with this disorder. The goal of this study was to reveal effect of yoga training on executive abilities in 8-9 years of age children with ADHD. We compared the efficacy of two methods of training (yoga training vs. conventional motor exercises) in a randomized controlled pilot study.

Methods: 18 children with ADHD at the age of 8-9 years (M = 8.74 years, SD = 0.96) were included and randomly assigned to treatment conditions according to a 2+ù2 crossover design. Both groups of children have participated in 12 weeks of training (body-oriented training vs. conventional motor exercises). A total of 36 training sessions lasting 30 minutes were performed. To assess the executive functions we used 3 subtests from NEPSY (Auditory Attention and Response Set, Visual Attention, Statue). Effects of training were analyzed by means of an ANOVA for repeated measurements. We have also performed qualitative neuropsychological assessment based on Luria's syndrome analysis.

Results: The ANOVA has revealed (pΓëñ0,05) that for all subtests (Auditory Attention and Response Set, Visual Attention, Statue) the yoga training was superior to the conventional motor training, with effect sizes in the medium-tohigh range (0.43-0.88). Luria's syndrome analysis has revealed in children from experimental group the improving in third functional unit of the brain which is responsible for voluntary attention and executive abilities according to Luria's approach.

Conclusions: The findings from this pilot study suggest that yoga training has positive effect on executive abilities in children with ADHD. We can propose that yoga training is one of the most effective approaches for helping children with ADHD. However, it is necessary to do further research into the impact of yoga training on children with ADHD. Particularly, we are going to reveal long-term effect of this training on executive abilities using longitudinal design

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Arch Dis Child. 2020;105:A226.

A RETROSPECTIVE STUDY TO UNDERSTAND EMERGING THEMES FROM USING LONG ACTING GUANFACINE-NON STIMULANT MEDICATION IN 70 CHILDREN AND YOUNG PEOPLE WITH ADHD(ATTENTION DEFICIT HYPERACTIVITY DISORDER) IN A SECONDARY CARE SETTING.

Jainer R, Wilkins B, Yemula C.

Aims As most clinicians have limited experience and are still not confident about using Guanfacine since its license in 2016 in UK, this study was undertaken to identify any emerging themes-any gender differences, comorbid factors and side effects which could impact on its usage.

Method Data was collected from clinical notes on all our patients on Guanfacine over the past one year. This study looked at demographics, co morbidity, tolerance and dosage needed. Emerging themes were identified in addition which could inform future studies on use of Guanfacine.

Results Age range 4-15 years (12 girls and 58 boys) received treatment with Guanfacine. Comorbidity was seen in 48 patients (69%): Autism spectrum disorder was commonest (16), Developmental coordination disorder (13), Leaning disability (10) some had other conditions e.g. Conduct disorder, tic disorder, dyslexia. Guanfacine was discontinued in 36 patients (51%), the common set side effect was sedation in 20patients (29%) and other reasons for discontinuation included headaches, aggressive behaviour and in effective control of ADHD symptoms. The success rate was 98.8% in teenage girls. The dose range was 1 mg (19) to 6 mg (1), and most patients (36) needed 2 to 3 mg for effective control of symptoms.
Conclusion It is small observational study and would be useful to have larger studies comparing the side effects and efficacy of low dose Guanfaicne in teenage girls specifically across different regions

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Asian J Psychiatry. 2021;58.

PSYCHOMETRIC PROPERTIES OF THE PERSIAN VERSION OF PRESCHOOL AGE PSYCHIATRIC ASSESSMENT (PAPA) FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: BASED ON DSM-5.

Hassanzadeh M, Malek A, Norouzi S, et al.

Childhood and adolescence psychiatric disorders affect subsequent stages; early diagnosis of these disorders, such as attention-deficit/hyperactivity disorder (ADHD), is necessary. There is no reliable and valid diagnostic interview for ADHD in Asian Persian or Farsi speaking countries. The DSM 5-based version of the interview was sent to the 14 child and adolescent and general psychiatrists to ensure the validity of the ADHD section of the PAPA interview through an online website. Out of 59 health centers, 15 centers were selected via systematic random sampling. Three hundred children participated in the study. ADHD questions of the PAPA had the power to differentiate, with a sensitivity of 0.92, a specificity of 0.01. It had positive diagnostic value = 95.83 %, negative diagnostic value = 98.91 %, negative correlation ratio = 0.12, overall diagnostic accuracy = 98.67 % and diagnostic chance ratio = 2085.35. ADHD questions of the PAPA diagnostic interview can diagnose ADHD in preschool as a reliable tool based on DSM-5

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Assessment. 2021 Mar;28:380-94.

TESTING THE LONGITUDINAL STRUCTURE AND CHANGE IN SLUGGISH COGNITIVE TEMPO AND INATTENTIVE BEHAVIORS FROM EARLY THROUGH MIDDLE CHILDHOOD.

Dvorsky MR, Becker SP, Tamm L, et al.

Previous studies have demonstrated that sluggish cognitive tempo (SCT) behaviors are empirically distinct from inattentive (IN) behaviors that are used to define attention-deficit/hyperactivity disorder. However, most studies used cross-sectional designs during middle childhood. Using parent and teacher ratings from the Family Life Project (N = 1,173), we investigated the factor structure, longitudinal measurement invariance, developmental trajectories, and predictors of developmental change in SCT and IN from age 3 years through Grade 5. SCT and IN were dissociable but correlated constructs that exhibited longitudinal invariance for both informants. Mean levels of SCT increased modestly with age, becoming more prominent between age 5 years and first grade, while IN was more stable. Lower parental education was associated with higher parent- and teacher-reported SCT, male sex was associated with higher teacher-reported IN, and African American race was associated with higher teacher-reported IN but lower teacher-reported SCT. These findings support the validity of SCT starting in early childhood

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Aten Prim. 2021;53.

ASSESSING ADHD SYMPTOMS IN CLINICAL PUBLIC PRACTICE: IS A RELIABLE FINAL DIAGNOSIS POSSIBLE?

Viuda Suírez ME, Alonso Lorenzo JC, et al.

Introduction: Attention deficit and hyperactivity disorder (ADHD) rates vary between 1% and 20% depending on the type of diagnosis guide used, the test used in the assessment, psychosocial factors, and professional in charge of the assessment.

Goal: to describe and compare current clinical ADHD assessment processes in public health system in two cohorts and analyze variables related to final diagnosis.
Design: Descriptive, multicenter, longitudinal (retrospective-prospective).
Location: primary care (PC) centers in Oviedo, Asturias (Spain).
Participants: a Spanish clinical ADHD symptomatic sample (n = 134) from two cohorts (2004 and 2009).
Variables: clinical professional in charge of ADHD assessment (PC, mental health professional [MH], neuropediatrician [NP]), type of test used in the assessment, confirmation/disconfirmation of ADHD diagnosis, and final diagnosis.
Results: the use of symptoms checklists and the assessments in charge of primary care (PC) and neuropediatrician (NP) professionals show an upward trend from 2004 to 2009. ADHD final diagnosis shows low inter-professional (NP-MH) reliability (kappa = 0.39). Final diagnoses for the same symptoms are different depending on the professional (NP or MH).
Discussions: the professional in charge of the assessment appears to be a relevant variable for the final diagnosis. ADHD diagnosis criteria seem not to be clear. This data suggests that ADHD diagnosis must be used with caution to ensure good quality clinical standards when assessing and treating ADHD symptoms. Assessments supported by symptoms checklists and performed by NP or PC could be contributing factors to an ADHD over-diagnosis tendency

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Behav Interv. 2021 Feb;36:315-26.

THE EFFECTS OF INDIVIDUALIZED TEACHING OF SCHOOL READINESS SKILLS TO CHILDREN IN PRESCHOOL WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.

Ísfeld Víðisdóttir SL, Sveinbjörnsdóttir B.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders diagnosed among children and adolescents. ADHD is associated with a wide range of health and developmental risks, emotional and behavioral disorders, lack of social skills, and academic underachievement. The purpose of this study was to evaluate the effectiveness of the preschool life skills (PLS) program in teaching important life skills to a 5-year old girl being assessed for ADHD. The participant was taught eight PLS, divided into three units that focused on instruction following, functional communication, and tolerance skills. Teaching included instructions, modeling, role-play, and feedback/descriptive praise. The PLS program effectively increased PLS, and skill achievement was only evident when teaching targeted each unit of skills

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BMC Pediatr. 2021;21.

EFFECTS OF EQUINE-ASSISTED ACTIVITIES ON ATTENTION AND QUALITY OF LIFE IN CHILDREN WITH CEREBRAL PALSY IN A RANDOMIZED TRIAL: EXAMINING THE COMORBIDITY WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ahn B, Joung YS, Kwon JY, et al.

Background: Attention problems and decreased quality of life are frequently accompanied in Cerebral Palsy (CP), which can negatively affect rehabilitation of physical disability. However, the majority of affected children remain untreated in the aspects of attention or psychosocial factors. Equine-Assisted Activities and Therapies (EAAT) use horse as a therapeutic modality including grooming as well as mounted riding activities in which patients exercise and experience mounted stimulation. It is known to help improve attention in children with ADHD, so that it can be an exercise therapy that is expected to improvement of attention as well as rehabilitating effects in CP patients. EAA may be a promising strategy to address the unmet need for CP patients. This study aims to investigate the efficacy of EAA for children with CP, those with both CP and ADHD and confirm the comorbidity between CP and ADHD.
Methods: Forty-six children with cerebral palsy participated in this study. For the exercise group, they participated in a 40-min session twice a week for a 16-week period, while the control group engaged in daily life without any special treatments. Each children individually were assessed on attention and psychological wellbeing at baseline and post-treatment. Comorbidity were identified based on the Diagnostic and Statistical

Manual of Mental Disorder 5th edition (DSM-5) and confirmed by Korean Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL).
Results: Perseveration rated using the Conner's Performance Test (CPT) showed a significant decrease only in the exercise group (p <.024). However, no significant improvement in children's quality of life was observed after EAA program compared with control group. Among the total participants, fifteen children (31.91%) were diagnosed with ADHD. When conducting an additional analysis with the subsample of CP patients diagnosed with ADHD, the d, commission error and perseveration showed a significant decrease only in the exercise group. Children with CP and ADHD reported an improvement in quality of life both in exercise and control group, but only in the exercise group social functioning exhibited a significant difference.
Conclusion: The positive effects of the EAA on attention and quality of life were confirmed. Children with CP in the exercise group were more capable to sustain their attention longer. Those with CP and ADHD showed an increase in attention and perceived to have better social skills after receiving 16 weeks of EAA compared to those in the control group. Considering high comorbidity of CP and ADHD, it seems that the EAA program could be the better alternative treatment for CP with attentional problem. The results of this study will contribute to growing evidence for the efficacy of EAA in children especially with CP and ADHD.
Trial registration: This trial was registered on ClinicalTrials.gov (NCT03870893). Registered 26 July 2017

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BMC Psychiatry. 2021;21.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH DEVELOPMENTAL COORDINATION DISORDER: 24-YEAR FOLLOW-UP OF A POPULATION-BASED SAMPLE.

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

Background: Although the body of research concerning neurodevelopmental disorders is vast, there is a scarcity of longitudinal studies beyond late adolescence, and of studies taking co-existing disorders into account. The present study aimed to investigate outcome in adulthood for children with attention-deficit/hyperactivity disorder (ADHD) combined with developmental coordination disorder (DCD) diagnosed at 6.6 years of age.
Methods: Out of a screening-based population cohort of 589 individuals, 62 (10 female) diagnosed with ADHD+DCD at mean age 6.6 years naïve to stimulant treatment were followed into adulthood through national registries. Results were compared to a screen- and assessment negative population matched group from the same cohort (PM group, n = 51) and a registry-matched (RM group, n = 410) group of the same county and age.
Results: At 30 to 31 years of age, five deaths had occurred; one in the ADHD+DCD group and two each in the comparison groups. In time to event analyses of the composite outcome of any psychiatric disorder, psychotropic prescription, sick pension or criminal sentence, events occurred at a significantly higher rate in the ADHD+DCD group (p = 0.0032, vs PM group p = 0.0115, vs RM group p = 0.0054). The ADHD+DCD group had significantly higher rates of psychiatric diagnoses, prescriptions of psychoactive medications and occurrence of sick pension than both comparison groups. Further, the ADHD+DCD group had significantly lower educational attainment compared to both comparison groups, more years with unemployment, and overall higher welfare recipiency. Rates of pain diagnoses and analgesic prescriptions did not separate the groups.
Conclusion: ADHD+DCD entailed a less favorable outcome in adulthood compared to a non-clinical comparison group and a registry-matched population. Neurodevelopmental disorder diagnosed upon school entry is of prognostic utility with respect to function in adulthood, and warrants early identification and management

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BMC Psychiatry. 2021 Mar;21.

THE ASSOCIATIONS BETWEEN MATERNAL AND CHILD DIET QUALITY AND CHILD ADHD – FINDINGS FROM A LARGE NORWEGIAN PREGNANCY COHORT STUDY.

Borge TC, Biele G, Papadopoulou E, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder. Effective long-term treatment options are limited, which warrants increased focus on potential modifiable risk factors. The aim of this study was to investigate associations between maternal diet quality during pregnancy and child diet quality and child ADHD symptoms and ADHD diagnosis.

Methods: This study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa). We assessed maternal diet quality with the Prenatal Diet Quality Index (PDQI) and Ultra-Processed Food Index (UPFI) around mid-gestation, and child diet quality using the Diet Quality Index (CDQI) at 3 years. ADHD symptoms were assessed at child age 8 years using the Parent Rating Scale for Disruptive Behaviour Disorders. ADHD diagnoses were retrieved from the Norwegian Patient Registry.

Results: In total, 77,768 mother-child pairs were eligible for studying ADHD diagnoses and 37,787 for ADHD symptoms. Means (SD) for the PDQI, UPFI and CDQI were 83.1 (9.3), 31.8 (9.7) and 60.3 (10.6), respectively. Mean (SD) ADHD symptom score was 8.4 (7.1) and ADHD diagnosis prevalence was 2.9% (male to female ratio 2.6:1). For one SD increase in maternal diet index scores, we saw a change in mean (percent) ADHD symptom score of -0.28 (- 3.3%) (CI: -0.41, -0.14 (-4.8, -1.6%)) for PDQI scores and 0.25 (+ 3.0%) (CI: 0.13, 0.38 (1.5, 4.5%)) for UPFI scores. A one SD increase in PDQI score was associated with a relative risk of ADHD diagnosis of 0.87 (CI: 0.79, 0.97). We found no reliable associations with either outcomes for the CDQI, and no reliable change in risk of ADHD diagnosis for the UPFI.

Conclusions: We provide evidence that overall maternal diet quality during pregnancy is associated with a small decrease in ADHD symptom score at 8 years and lower risk for ADHD diagnosis, with more robust findings for the latter outcome. Consumption of ultra-processed foods was only associated with increased ADHD symptom score of similar magnitude as for overall maternal diet quality, and we found no associations between child diet quality and either outcome. No causal inferences should be made based on these results, due to potential unmeasured confounding

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Brain Sciences. 2021;11:1-36.

EEG DATA QUALITY: DETERMINANTS AND IMPACT IN A MULTICENTER STUDY OF CHILDREN, ADOLESCENTS, AND ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Kaiser A, Aggensteiner PM, Holtmann M, et al.

Electroencephalography (EEG) represents a widely established method for assessing altered and typically developing brain function. However, systematic studies on EEG data quality, its correlates, and consequences are scarce. To address this research gap, the current study focused on the percentage of artifact-free segments after standard EEG pre-processing as a data quality index. We analyzed participant-related and methodological influences, and validity by replicating landmark EEG effects. Further, effects of data quality on spectral power analyses beyond participant-related characteristics were explored. EEG data from a multicenter ADHD-cohort (age range 6 to 45 years), and a non-ADHD school-age control group were analyzed (ntotal = 305). Resting-state data during eyes open, and eyes closed conditions, and task-related data during a cued Continuous Performance Task (CPT) were collected. After pre-processing, general linear models, and stepwise regression models were fitted to the data. We found that EEG data quality was strongly related to demographic characteristics, but not to methodological factors. We were able to replicate maturational, task, and ADHD effects reported in the EEG literature, establishing a link with EEG-landmark effects. Furthermore, we showed that poor data quality significantly increases spectral power beyond effects of maturation and symptom severity. Taken together, the current results indicate that with a careful design and systematic quality control, informative large-scale multicenter trials characterizing neurophysiological mechanisms in neurodevelopmental disorders across the lifespan are feasible. Nevertheless, results are restricted to the limitations reported. Future work will clarify predictive value

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Brain Sciences. 2021;11:1-12.

EYE-TRACKING TRAINING IMPROVES INHIBITORY CONTROL IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lee TL, Yeung MK, Sze SL, et al.

Disinhibition is a common sign among children with attention-deficit/hyperactivity disorder (ADHD). The present study examined the effect of computerized eye-tracking training to improve inhibitory control in ADHD children. Thirty-two ADHD children (mean age = 8.4 years) were recruited. Half of the participants underwent 240 min of eye-tracking training over two weeks (i.e., experimental group), while the other half did not receive any training (i.e., control group). After training, the experimental group exhibited significant improvements in neuropsychological tests of inhibition, such as faster reaction time in the incongruent condition of the Flanker test, more unique designs in the Category Fluency and Five-Point Tests, and a faster completion time in Trail 2 of the ChildrenΓÇÖs Color Trail Test. The control group did not show significant changes in any of these tests. Our findings support the use of eye-tracking training to improve the inhibitory control of ADHD children

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Brain Sciences. 2021;11:1-12.

THE ASSOCIATION BETWEEN EXECUTIVE FUNCTIONS AND BODY WEIGHT/BMI IN CHILDREN AND ADOLESCENTS WITH ADHD.

Racicka-Pawlukiewicz E, Ku-ç K, Bielecki M, et al.

Despite the increasing body of research on Attention Deficit Hyperactivity Disorder (ADHD), the results of the studies assessing the relationship between executive function deficit and the risk of obesity in people with ADHD are incongruent. Our study aimed to assess the relationship between measures of executive functions and body weight and Body Mass Index (BMI) in children and adolescents with ADHD and control subjects. The study group consisted of 58 subjects aged from 8 to 17 years with ADHD. The Control group consisted of 62 healthy age and sex-matched participants from primary and secondary schools. Weight, height, and BMI measurements were standardized. The Sustained Attention to Response Test (SART) and the Attention Network Test (ANT) were used to assess executive functions. Based on the analysis of the correlation and analysis of moderation, we found that subjects with higher weight in the study group presented a lower efficiency of the inhibition processes and gave more impulsive and incorrect answers. The occurrence of impulsive reactions might contribute to the risk of excessive weight in children and adolescents with ADHD

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Brain Sciences. 2021;11.

DISTRIBUTION OF VISUAL AND OCULOMOTOR ALTERATIONS IN A CLINICAL POPULATION OF CHILDREN WITH AND WITHOUT NEURODEVELOPMENTAL DISORDERS.

Bilbao C, Pinero DP.

A prospective, non-randomized comparative study was conducted to compare the distribution of oculomotor and visual alterations in children with neurodevelopmental disorders and healthy children without such disorders. Sixty-nine children (aged 6ΓÇô13 years) were enrolled and divided into three groups: a control group (CG) of 23 healthy children; a group of 18 healthy children with oculomotor abnormalities (OAG); and a group of 28 children with a neurodevelopmental disorder (NDDG), with 15 cases of dyslexia, 7 cases of developmental coordination disorder (DCD) and 6 cases of attention deficit/hyperactivity disorder (ADHD). Significantly worse near stereopsis was found in NDDG compared with CG ($p < 0.001$) and OAG ($p = 0.001$). Likewise, a significantly lower amplitude of accommodation was found in NDDG compared with CG in both the right ($p = 0.001$) and left eyes ($p < 0.001$). No statistically significant differences between groups were found in the measurement of near and distance phoria (p 0.557), near point of convergence ($p = 0.700$) and fusional vergences (p 0.059). Significantly impaired oculomotor test scores were found in NDDG compared with CG ($p < 0.001$), with no significant differences between OAG and NDDG (p 0.063). The comparison between the three types of neurodevelopmental disorders included revealed the presence of a significantly lower amplitude of accommodation in children with DCD compared with dyslexics. Furthermore, less exophoria at near was present in children with dyslexia compared with children with ADHD ($p = 0.018$) and

DCD (p = 0.054). In conclusion, children with dyslexia, ADHD and DCD show an altered oculomotor pattern and a more reduced amplitude of accommodation, not always compatible with the diagnostic criteria of an accommodative insufficiency. Accommodative and binocular vision problems are not always present in these children and cannot be considered an etiologic factor

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Brain Behav Immun. 2021.

SALIVARY CYTOKINE CLUSTER MODERATES THE ASSOCIATION BETWEEN CAREGIVERS PERCEIVED STRESS AND EMOTIONAL FUNCTIONING IN YOUTH.

Parent C, Pokhvisneva I, de Mendon+ºa Filho EJ, et al.

Some individuals exposed to early life stress show evidence of enhanced systemic inflammation and are at greater risk for psychopathology. In the current study, caregivers and their offspring (0ΓÇô17 years) were recruited at a pediatric clinic visit at the University of California, San Francisco (UCSF). Mothers and seven-year-old children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) prospective birth cohort were used as a replication cohort. Caregivers perceived stress was measured to determine potential intergenerational effects on the children's functioning and inflammation levels. Children's emotional functioning in the UCSF cohort was evaluated using the Pediatric Quality of Life (PedsQL) inventory. Child emotional and behavioral functioning was measured using the Child Behavior Checklist (CBCL) in GUSTO. Saliva was collected from the children and salivary levels of IL-6, IL-1+¦, IL-8 and TNF-+¦ were measured using an electrochemiluminescent cytokine multiplex panel. Child IL-6, IL-1+¦, IL-8 cytokine levels were clustered into low, average, and high cytokine cluster groups using hierarchical cluster analysis. We did not find that salivary cytokine clusters were significantly associated with children's emotional or behavioral function. However, cytokine clusters did significantly moderate the association between increased caregiver perceived stress and reduced child emotional functioning (UCSF cohort) and increased Attention-Deficit-Hyperactivity (ADH) problems (GUSTO cohort, uncorrected Cohen's F2 = 0.02). Using a cytokine clustering technique may be useful in identifying those children exposed to increased caregiver perceived stress that are at risk of emotional and attention deficit hyperactivity problems

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British Journal of Educational Psychology. 2021 Mar;91:442-62.

ATTAINMENT, ATTENDANCE, AND SCHOOL DIFFICULTIES IN UK PRIMARY SCHOOLCHILDREN WITH PROBABLE ADHD.

May F, Ford T, Janssens A, et al.

Background: Among children aged 6–16, there is a clear association between attention-deficit/hyperactivity disorder (ADHD) symptoms and academic attainment. We wanted to know whether this association was replicated in younger children.

Aims: To explore the relationship between children aged 4–8 with probable ADHD and their academic attainment and school attendance. Secondly, the study aimed to explore their behaviour within school and their reported attitudes towards school.

Sample: A total of 1,152 children who were taking part in the Supporting Teachers and Children in Schools (STARS) cluster randomized controlled trial.

Methods: ADHD status was established by using the Strengths and Difficulties Questionnaire predictive algorithm to identify children with probable ADHD. Using baseline data, random-effects regression models on ADHD status were fitted to attainment, attendance, special educational needs (SEN) provision, and attitudes towards school and classroom behaviour; models that were also fitted to attainment were evaluated again at 9, 18, and 30 months after baseline.

Results: Children with probable ADHD (n = 47) were more likely than controls (n = 1,105) to have below-expected attainment in literacy (odds ratio (OR) 16.7, 95% CI 6.93-to-40.1), numeracy (OR 11.3, 95% CI 5.34-to-24.1) and to be identified as having SEN (OR-55.2, 95%-CI 22.1-to-137). Their attendance was poorer with more unauthorized absences (rate ratio (RR)-1.91, 95%-CI-1.57-to-2.31). They had more teacher-reported behavioural problems (mean difference (MD) 5.0, 95%-CI 4.6-to-5.4) and less positive

attitudes towards school (MD -1.1, 95% CI -0.56 to -1.85). Poorer attainment in literacy and numeracy persisted at all follow-ups.
Conclusions: Children aged as young as 4 whose behaviour indicates probable ADHD struggle to cope at school in terms of academic attainment, attendance, classroom behaviour, and attitude towards school when compared to other children. Early identification and intervention to help these children manage in school are needed

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Cereb Cortex. 2019;29:3902-11.
THE EFFECTS OF COMT POLYMORPHISM ON CORTICAL THICKNESS AND SURFACE AREA ABNORMALITIES IN CHILDREN WITH ADHD.
Jung M, Mizuno Y, Fujisawa TX, et al.
The catechol-O-methyltransferase (COMT) gene is associated with frontal cortex development and the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, how the COMT gene impacts brain structure and behavior in ADHD remains unknown. In the present study, we identify the effect of COMT on cortical thickness and surface area in children with ADHD and children with typically developing (TD) using a machine learning approach. In a sample of 39 children with ADHD and 34 age- and IQ-matched TD children, we found that cortical thickness and surface area differences were predominantly observed in the frontal cortex. Furthermore, a path analysis revealed that a COMT genotype affected abnormal development of the frontal cortex in terms of both cortical thickness and surface area and was associated with working memory changes in children with ADHD. Our study confirms that the role of COMT in ADHD is not restricted to the development of behavior but may also affect the cortical thickness and surface area. Thus, our findings may help to improve the understanding of the neuroanatomic basis for the relationship between the COMT genotype and ADHD pathogenesis

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Child Care Health Dev. 2021 Mar;47:269-80.
EFFICACY OF A SELF-HELP PARENTING INTERVENTION FOR PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADJUNCT TO USUAL TREATMENT—SMALL-SCALE RANDOMIZED CONTROLLED TRIAL.
Daley D, Tarver J, Sayal K.
Background: Multimodal intervention incorporating psychosocial intervention and medication is recommended for school-aged children with attention deficit hyperactivity disorder (ADHD). This randomized controlled trial (RCT) investigates the adjunctive benefit of the self-help version of the New Forest Parenting Programme (NFPP-SH) when offered in addition to treatment as usual (TAU) compared with TAU alone.
Method: Fifty-two children, receiving medication for ADHD as part of their usual care, were randomized to receive NFPP-SH + TAU or TAU alone.
Results: When used in adjunct to TAU, NFPP-SH may have beneficial effects for parenting efficacy (F = 6.28, p = 0.02), child social performance in school and negative comments made by parents during a recorded speech sample. However, the self-help intervention did not have any additional effect on child behaviour.
Conclusions: This study provides further support for self-help interventions as potentially low-intensity and cost-effective alternatives to therapist-led parenting interventions. The findings require replication in larger samples before any firm conclusions about adjunctive efficacy of NFPP-SH can be drawn but underline the potential for self-help within routine treatment

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Child Health Care. 2021.

INTERNALIZED STIGMA AND SELF ESTEEM OF MOTHERS OF CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ozaslan A, Yildirim M.

Evidence suggests that caregivers of children with attention deficit hyperactivity disorder (ADHD) experience greater internalized stigmatization. However, there is no evidence of how self-esteem influences the levels of internalized stigma among parents of children with ADHD in Turkey. This study investigated for the first time the relationship between internalized stigma and self-esteem of mothers of children with ADHD and examined the relationship between mothersΓÇÖ internalized stigma and ADHD severity of children. The sample included mothers of 86 children (65 boys and 21 girls) diagnosed with ADHD. Age of children was between 6 and 17years old (M=11.05, SD=2.62). Participants completed the Conners Parent Rating Scale-Revised Short Form, the Clinical Global Impression, the Parents' Internalized Stigma of Mental Illness Scale and the Rosenberg Self-Esteem Scale. The results showed that mothers with higher education level reported lower internalized stigma, while ADHD severity of children was positively correlated with mothers internalized stigma level. The results also indicated that children with ADHD severity predicted a significant amount of variance in stigma. Furthermore, self-esteem uniquely predicted mother's internalized stigma over and above the mother's education level and ADHD severity of children. The results suggest the importance of self-esteem on internalized stigma and contribute to development of interventions focusing on the role of self-esteem on parents' internalized stigma

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Clin Neurophysiol. 2021;132:953-66.

SENSORY PROCESSING AND P300 EVENT-RELATED POTENTIAL CORRELATES OF STIMULANT RESPONSE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CRITICAL REVIEW.

Peisch V, Rutter T, Wilkinson CL, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with considerable impairment in psychiatric and functional domains. Although stimulant medication can reduce core symptoms of inattention, hyperactivity, and impulsivity, a subgroup of patients does not respond to this intervention. A precision medicine approach has been proposed, whereby biomarkers are used to identify an effective treatment approach for a given individual. This review synthesizes the existing literature on event-related potential (ERP) correlates of stimulant response in children diagnosed with ADHD, with the goal of evaluating the potential for ERP to inform precision medicine care in this population. Forty-three articles were examined and results tentatively suggest that stimulant medications normalize the amplitude of the P300 component, and this is also associated with behavioral improvement. In contrast, results generally indicate that stimulants do not significantly alter early processing components, although there are some exceptions to this finding. Implications for research, theory, and clinical work are considered and concrete recommendations for future directions are provided. While recognizing limitations of existing literature (e.g., homogenous samples, variable methodologies), we conclude that ERP methods represent a promising approach for precision medicine care of patients with ADHD

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Clin Psychopharmacol Neurosci. 2021;19:145-54.

A DIFFERENT VIEW ON THE ETIOPATHOGENESIS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER FROM AN INFLAMMATION PERSPECTIVE.

Dursun S, Demirci E, Kilic E, et al.

Objective: Attention-deficit hyperactivity disorder (ADHD) has a complex etiology and genetic, environmental and biological factors are considered to play a role in the etiology of ADHD by mutually interacting. Recent studies have emphasized that inflammation may be present in the etiology of ADHD. This study aims to investigate the possible role of visfatin, IL-6, IL-1b and TNF-α molecules in the etiology of ADHD.

Methods: The study included 60 patients and 20 healthy controls between the ages of 6-18. Serum visfatin, IL-6, IL-1b and TNF-α levels were evaluated with enzyme-linked immunosorbent assay (ELISA) kits at a biochemistry laboratory.
Results: The study showed no statistically significant difference between children with ADHD and healthy controls in terms of visfatin, IL-6, IL-1b and TNF-α levels. When ADHD subgroups (combined and predominantly inattentive types) and the control group were compared in terms of visfatin, IL-6, IL-1b and TNF-α levels, no statistically significant difference was recorded.
Conclusion: Data on the relationship between ADHD and IL-6, IL-1b and TNF-α in this study are in compliance with the literature. However, no study was found on visfatin in ADHD. This study is the first one evaluating the ADHD-Visfatin relationship.

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Clin Psychopharmacol Neurosci. 2021;19:26-45.

SECOND-TO-FOURTH DIGIT RATIO (2D:4D) IN PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW OF CASE-CONTROL STUDIES.

Fusar-Poli L, Rodolico A, Sturiale S, et al.

The second-to-fourth digit ratio (2D:4D) is an indirect, retrospective, non-invasive measure that correlates negatively with intrauterine exposure to testosterone. The present meta-analysis aimed to evaluate if 2D:4D differs between patients with psychiatric disorders and controls. In September 2019, we searched in Web of Knowledge, PsycINFO, Embase, and CINHAL, and retrieved 619 papers. We finally included 43 case-control studies which compared the 2D:4D ratio of patients with autism spectrum disorder (ASD) (n = 16), schizophrenia (n = 8), gender non-conformity (n = 7), addictions (n = 5), attention deficit-hyperactivity disorder (ADHD) (n = 4), mood disorders (n = 2), and intellectual disability (n = 1) to non-clinical controls. Meta-analyses showed that, overall, psychiatric patients had lower 2D:4D than healthy controls (n = 43, overall sample = 9,484, mean difference = -0.0056, 95% confidence interval from -0.0093 to -0.002, I2= 74%), with more pronounced differences in the right hand, males, and children. Considering psychiatric disorders individually, significant differences were found in the ASD, ADHD, and addictions groups, in which 2D:4D was significantly lower than healthy controls. Conversely, the right hand of males with schizophrenia showed higher 2D:4D than healthy controls. No other significant differences were detected. Although our results need to be cautiously interpreted and find limited applications in clinical practice, they may suggest that 2D:4D is altered in some psychopathological conditions, underlining the role of prenatal exposure to sex steroids in the etiology of psychiatric disorders

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Clin Ther. 2021.

ONCE-DAILY SPN-812 200 AND 400 MG IN THE TREATMENT OF ADHD IN SCHOOL-AGED CHILDREN: A PHASE III RANDOMIZED, CONTROLLED TRIAL.

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

Purpose: SPN-812 (viloxazine extended-release) is under investigation for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. This Phase III study evaluated the efficacy and tolerability of SPN-812 200 and 400 mg once daily in children 6–11 years of age with ADHD.
Methods: Patients were randomly assigned to receive SPN-812 200 mg, SPN-812 400 mg, or placebo, once daily for 8 weeks (including ≤3 weeks titration period). The primary efficacy endpoint was the change from baseline (CFB) in ADHD Rating Scale (RS)-5 Total score at end of study (EOS). Key secondary endpoints included Clinical Global Impression–Improvement (CGI-I) score at EOS, CFB in Conners 3–Parent Short Form (PS) composite T-score at EOS, and CFB in Weiss Functional Impairment Rating Scale–Parent (WFIRS-P) Total average score at EOS.
Findings: A total of 313 patients were enrolled, with 301 in the intent-to-treat population (194 boys, 107 girls; mean age [SD], 8.4 [1.7] years). At EOS, the CFBs in ADHD-RS-5 Total score and CGI-I score were significantly improved with both 200- and 400-mg/d SPN-812 versus placebo (ADHD-RS-5, P = 0.0038 and 0.0063, respectively; CGI-I, P = 0.0028 and 0.0099). At EOS, the CFB in Conners 3-PS composite T-score

was significantly improved with 200- (P = 0.0064), but not 400-mg/d (P = 0.0917), SPN-812 compared to placebo. No significant difference between the groups was found in WFIRS-P Total average score. The rate of discontinuations due to adverse events in both SPN-812 treatment groups combined was <5%.
Implications: SPN-812 200 and 400 mg once daily was associated with improvements in ADHD symptoms in school-aged children and was generally well tolerated.
ClinicalTrials.gov identifier: NCT03247543. (Clin Ther. 2021; 43:XXX–XXX) © 2021 Elsevier Inc.

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CNS Neurosci Ther. 2021.

A POTENTIAL ASSOCIATION OF RNF219-AS1 WITH ADHD: EVIDENCE FROM CATEGORICAL ANALYSIS OF CLINICAL PHENOTYPES AND FROM QUANTITATIVE EXPLORATION OF EXECUTIVE FUNCTION AND WHITE MATTER MICROSTRUCTURE ENDOPHENOTYPES.

Fu GH, Chen W, Li HM, et al.

Aims: Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder of substantial heritability, yet emerging evidence suggests that key risk variants might reside in the noncoding regions of the genome. Our study explored the association of lncRNAs (long noncoding RNAs) with ADHD as represented at three different phenotypic levels guided by the Research Domain Criteria (RDoC) framework: (i) ADHD caseness and symptom dimension, (ii) executive functions as functional endophenotype, and (iii) potential genetic influence on white matter architecture as brain structural endophenotype.
Methods: Genotype data of 107 tag single nucleotide polymorphisms (SNP) from 10 candidate lncRNAs were analyzed in 1040 children with ADHD and 630 controls of Chinese Han descent. Executive functions including inhibition and set-shifting were assessed by STROOP and trail making tests, respectively. Imaging genetic analyses were performed in a subgroup of 33 children with ADHD and 55 controls using fractional anisotropy (FA).
Results: One SNP rs3908461 polymorphism in RNF219-AS1 was found to be significantly associated with ADHD caseness: with C-allele detected as the risk genotype in the allelic model (P = 8.607E-05) and dominant genotypic model (P = 9.628E-05). Nominal genotypic effects on inhibition (p = 0.020) and set-shifting (p = 0.046) were detected. While no direct effect on ADHD core symptoms was detected, mediation analysis suggested that SNP rs3908461 potentially exerted an indirect effect through inhibition function [B = 0.21 (SE = 0.12), 95% CI = 0.02-0.49]. Imaging genetic analyses detected significant associations between rs3908461 genotypes and FA values in corpus callosum, left superior longitudinal fasciculus, left posterior limb of internal capsule, left posterior thalamic radiate (include optic radiation), and the left anterior corona radiate (P FWE corrected < 0.05).
Conclusion: Our present study examined the potential roles of lncRNA in genetic etiological of ADHD and provided preliminary evidence in support of the potential RNF219-AS1 involvement in the pathophysiology of ADHD in line with the RDoC framework.

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Dyslexia. 2021.

THE CO-OCCURRENCE OF NEURODEVELOPMENTAL PROBLEMS IN DYSLEXIA.

Brimo K, Dinkler L, Gillberg C, et al.

The primary aim of this study was to explore the overlaps between dyslexia and a range of neurodevelopmental disorders and problems (NDPs), specifically symptoms of attention-deficit/hyperactivity disorder, autism spectrum disorder, atypical sensory perception and developmental coordination disorder. Capitalizing on a population-based sample of twins, secondary aims included estimating the heritability of dyslexia and reporting on the measurement characteristics of the scale used to assess dyslexia. A telephone interview regarding symptoms of dyslexia and other NDPs was conducted with parents of 1,688 nine-year-old twins. The prevalence and the heritability of dyslexia were estimated at 8 and 52%, respectively. The boy: girl ratio was 1.5:1. Results revealed that there was more than an eight-fold increase in (diagnostic proxy) NDPs prevalence in the dyslexia group as compared to typical readers. Quantitatively measured symptoms of inattention, oral language problems and atypical sensory perception significantly predicted

dyslexia status in a multivariate analysis. By contrast, ASD-related inflexibility was inversely associated with dyslexia in the multivariate model. In sum, dyslexia often overlaps with other NDPs. The current study provides new knowledge supporting the position to move beyond isolated diagnostic categories into behavioural profiles of co-occurring problems when trying to understand the pattern of strengths and needs in individuals with dyslexia

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Environmental Health: A Global Access Science Source. 2021;20.

PRENATAL EXPOSURE TO BISPHENOL A AND AUTISTIC- AND ADHD-RELATED SYMPTOMS IN CHILDREN AGED 2 AND5 YEARS FROM THE ODENSE CHILD COHORT.

Hansen JB, Bilenberg N, Timmermann CAG, et al.

Background: Bisphenol A (BPA) is a non-persistent chemical with endocrine disrupting abilities used in a variety of consumer products. Fetal exposure to BPA is of concern due to the elevated sensitivity, which particularly relates to the developing brain. Several epidemiological studies have investigated the association between prenatal BPA exposure and neurodevelopment, but the results have been inconclusive.

Objective: To assess the association between in utero exposure to BPA and Attention Deficit/Hyperactivity Disorder (ADHD-) symptoms and symptoms of Autism Spectrum Disorder (ASD) in 2 and 5-year old Danish children.

Method: In the prospective Odense Child Cohort, BPA was measured in urine samples collected in gestational week 28 and adjusted for osmolality. ADHD and ASD symptoms were assessed with the use of the ADHD scale and ASD scale, respectively, derived from the Child Behaviour Checklist preschool version (CBCL/1-¢-5) at ages 2 and 5 years. Negative binomial and multiple logistic regression analyses were performed to investigate the association between maternal BPA exposure (continuous ln-transformed or divided into tertiles) and the relative differences in ADHD and ASD problem scores and the odds (OR) of an ADHD and autism score above the 75th percentile adjusting for maternal educational level, maternal age, pre-pregnancy BMI, parity and child age at evaluation in 658 mother-child pairs at 2 years of age for ASD-score, and 427 mother-child pairs at 5 years of age for ADHD and ASD-score.

Results: BPA was detected in 85.3% of maternal urine samples even though the exposure level was low (median 1.2 ng/mL). No associations between maternal BPA exposure and ASD at age 2 years or ADHD at age 5 years were found. Trends of elevated Odds Ratios (ORs) were seen among 5 year old children within the 3rd tertile of BPA exposure with an ASD-score above the 75th percentile (OR = 1.80, 95% CI 0.97,3.32), being stronger for girls (OR = 3.17, 95% CI 1.85,9.28). A dose-response relationship was observed between BPA exposure and ASD-score at 5 years of age (p-trend 0.06) in both boys and girls, but only significant in girls (p-trend 0.03).

Conclusion: Our findings suggest that prenatal BPA exposure even in low concentrations may increase the risk of ASD symptoms which may predict later social abilities. It is therefore important to follow-up these children at older ages, measure their own BPA exposure, and determine if the observed associations persist

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Environ Res. 2021;196.

GESTATIONAL AND PERIPUBERTAL PHTHALATE EXPOSURE IN RELATION TO ATTENTION PERFORMANCE IN CHILDHOOD AND ADOLESCENCE.

Watkins DJ, Meeker JD, Tamayo-Ortiz M, et al.

The prevalence of Attention Deficit/Hyperactivity Disorder (ADHD) has been increasing. Research suggests that exposure to endocrine disrupting chemicals such as phthalates may play a role, but studies of in utero phthalate exposure and ADHD-related symptoms beyond early childhood are limited. We investigated associations between measures of in utero phthalate exposure and ADHD symptoms, such as inattention and impulsivity, in childhood (age 6-11 years, n = 221) and in adolescence (age 9-18 years, n = 200), as well as cross-sectional relationships between phthalate exposure and ADHD symptoms in adolescence (n = 491) among participants in the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) cohort. Women provided urine samples up to three times during pregnancy and adolescents provided a urine sample

at 9-18 years of age for phthalate metabolite measurement. We administered the Conners Continuous Performance Test (CPT) when children were age 6ΓÇô11 years and again at 9ΓÇô18 years of age. We used multivariable linear regression to examine associations between the geometric mean of phthalate metabolite levels across pregnancy and CPT scores in childhood or adolescence separately, adjusting for age, years schooling (at 9-18 only), maternal education, and specific gravity. Although average in utero phthalate concentrations were not associated with CPT scores in childhood, interquartile range (IQR) increases of in utero MBzP, MCPP, and MBP were associated with 4.2%, 4.7%, and 4.5% ($p < 0.05$) higher Omissions scores in adolescence, respectively, indicating higher inattention. In utero MiBP levels were also associated with higher Inter-Stimulus Interval (ISI) and Variability scores (5.4% and 5.5% per IQR, $p < 0.05$) in adolescence. In addition, urinary DEHP metabolite levels during adolescence were cross-sectionally associated with poorer scores on several CPT indices indicating greater inattention. These findings suggest that in utero phthalate exposure may have adverse effects on attention, but these effects may not appear until adolescence, a period of extensive neurodevelopment. Future research investigating the long-term effects of in utero phthalate exposure on attention and ADHD in adolescence, as well as identification of potential mechanisms involved, is needed

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Environ Res. 2021;195.

PRENATAL EXPOSURE TO PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS) AND NEUROBEHAVIOR IN US CHILDREN THROUGH 8 YEARS OF AGE: THE HOME STUDY.

Vuong AM, Webster GM, Yolton K, et al.

Background: Studies of prenatal per- and polyfluoroalkyl substances (PFAS) and attention deficit hyperactivity disorder (ADHD)-related behaviors in children are inconsistent.

Objectives: To examine associations between maternal serum PFAS concentrations and child behavior in 241 mother-child dyads within the Health Outcomes and Measures of the Environment (HOME) Study.

Methods: We quantified perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) in maternal serum collected during pregnancy or at delivery. We evaluated a total of 17 outcomes of child behavior using the Behavioral Assessment System for Children-2 (BASC-2) at 5 and 8 years (n = 240) and ADHD diagnostic symptoms and criteria with the Diagnostic Interview Schedule for Children-Young Child (DISC-YC) at 5 years (n = 190). We used linear mixed models and logistic regression with generalized estimating equations to assess associations between PFAS and continuous or dichotomous at risk BASC-2 scores; negative binomial regression to calculate incident rate ratios for counts of ADHD symptoms; and Poisson regression with robust standard errors to calculate relative risks of meeting ADHD diagnostic criteria.

Results: Each ln-unit increase in PFOS, PFHxS, and PFNA was associated with higher BASC-2 scores and increased odds of at-risk scores for externalizing behaviors, including hyperactivity (PFOS: odds ratio [OR] 2.7, 95% confidence interval [CI] 1.2, 5.9; PFHxS: OR 2.5, 95% CI 1.5, 4.3; PFNA: OR 3.2, 95% CI 1.3, 8.0). PFHxS was also associated with internalizing problems (OR 2.0, 95% CI 1.1, 3.4) and somatization (OR 2.2, 95% CI 1.2, 4.0). PFOS and PFNA were significantly associated with 50ΓÇô80% more DISC-YC symptoms and diagnostic criteria related to hyperactive-impulsive type ADHD. Prenatal PFNA was associated with increased risk of any-type ADHD.

Conclusions: Prenatal PFOS and PFNA were consistently associated with measures related to hyperactive-impulsive type ADHD across two validated assessment instruments. PFHxS was associated with increased problems with both externalizing and internalizing behaviors. No associations were noted between PFOA and child neurobehavior

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Eur Child Adolesc Psychiatry. 2021.

PREDICTIVE VALIDITY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FROM AGES 3 TO 5 YEARS.

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

We investigated to what extent parent-rated attention-deficit/hyperactivity disorder (ADHD) and impairment at age 3-years predicted elevated ADHD symptoms at age 5-years, and whether teacher-rated ADHD symptoms improved these predictions. This study is part of the longitudinal, population-based Norwegian Mother, Father and Child Cohort Study. Parents of 3-year-old children (n = 1195) were interviewed about ADHD and impairment, and teachers rated child ADHD symptoms by the Strengths and Difficulties Questionnaire or the Early Childhood Inventory-4. At 5-years of age, the children (n = 957) were classified as ADHD-positive or -negative using Conners Parent Rating Scale. Relying solely on parent-rated ADHD or impairment at age 3-áyears did moderately well in identifying children with persistent elevation of ADHD symptoms, but gave many false positives (positive predictive values (PPVs):.40-.57). A small group of children (n = 20, 13 boys) scored above cut-off on both parent-rated ADHD and impairment, and teacher-rated ADHD symptoms, although adding teacher-rated ADHD symptoms slightly weakened the predictive power for girls. For this small group, PPVs were.76 for boys and.64 for girls. Limiting follow-up to these few children will miss many children at risk for ADHD. Therefore, we recommend close monitoring also of children with parent-reported ADHD symptoms and/or impairment to avoid delay in providing interventions. Clinicians should also be aware that teachers may miss ADHD symptoms in preschool girls

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Eur Child Adolesc Psychiatry. 2021.

THE LONGITUDINAL ASSOCIATION OF EATING BEHAVIOUR AND ADHD SYMPTOMS IN SCHOOL AGE CHILDREN: A FOLLOW-UP STUDY IN THE RHEA COHORT.

Leventakou V, Herle M, Kampouri M, et al.

Previous evidence suggests a link between attention deficit hyperactivity disorder (ADHD) symptoms and disordered eating behaviours; however, the direction of the causal association remains unclear. Building on our previous research, we aimed to examine the longitudinal association between eating behaviours at 4-years, ADHD symptoms at 6-years of age, and the role of body mass index (BMI). We included children from the RHEA mother-child cohort in Greece, followed up at 4 and 6-years (n = 926). Parents completed the Children's Eating Behaviour Questionnaire (CEBQ) to assess children's eating behaviour at 4-áyears and the ADHD Test (ADHDT) and Child Behaviour Checklist for ages 6-18 (CBCL/6-18) to evaluate ADHD symptoms at 4 and 6-áyears, respectively, as well as measures of BMI. Longitudinal structural equation modeling (SEM) was carried out to evaluate the associations of all variables between 4 and 6-years. Food responsiveness at 4-years was positively associated with hyperactivity at age 6, whereas emotional overeating was negatively associated with hyperactivity. There was no evidence of an association between eating behaviours of preschoolers and BMI at 6-years, or BMI at 4-years and later ADHD symptoms and vice versa. Findings suggest that food responsiveness is an early marker of ADHD symptoms at 6-years of age. In contrast to our hypothesis there was no significant association between ADHD at age 4 and BMI at age 6

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Eur Child Adolesc Psychiatry. 2021.

WHICH FACTORS DETERMINE CLINICIANS' POLICY AND ATTITUDES TOWARDS MEDICATION AND PARENT TRAINING FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Dekkers TJ, Groenman AP, Wessels L, et al.

Behavioral parent and teacher training and stimulant medication are recommended interventions for children with attention-deficit/hyperactivity disorder (ADHD). However, not all children with ADHD receive this evidence-based care, and the aim of the current study was to find out why. More specifically, we investigated cliniciansΓÇÖ policy, guideline use, and attitudes towards medication and parent training when treating children with ADHD, as well as several factors that could affect this. A total of 219 Dutch clinicians (mainly psychologists, psychiatrists and educationalists) completed a survey. Clinicians were likely to recommend medication more often than parent training, and clinicians policy to recommend medication and parent

training was positively associated with their attitudes towards these interventions. Less experienced clinicians and those with a non-medical background reported lower rates of guideline use, whereas clinicians with a medical background reported less positive attitudes towards parent training. Furthermore, a substantial portion of the clinicians based their decision to recommend parent training on their clinical judgement (e.g., prior estimations of efficacy, perceived low abilities/motivation of parents), and many clinicians reported barriers for referral to parent training, such as waiting lists or a lack of skilled staff. To achieve better implementation of evidence-based care for children with ADHD, guidelines should be communicated better towards clinicians. Researchers and policy-makers should further focus on barriers that prevent implementation of parent training, which are suggested by the discrepancy between clinicians' overall positive attitude towards parent training and the relatively low extent to which clinicians actually advise parent training

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Eur Child Adolesc Psychiatry. 2021.

SYSTEMATIC REVIEW AND META-ANALYSIS: RELATIONSHIPS BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND URINARY SYMPTOMS IN CHILDREN.

Mahjani B, Koskela LR, Mahjani CG, et al.

Lower urinary tract symptoms (LUTS), e.g., urinary frequency, pressure, urgency, and overactive bladder syndrome, are commonly reported in children with attention-deficit/hyperactivity disorder (ADHD). Understanding the co-occurrence of these conditions has implications regarding clinical approaches, treatments, and improved quality of life. We conducted a systematic review and meta-analysis to examine the relationships between LUTS and ADHD in children. We searched for articles published between January 1990 and July 2019, in PubMed, CENTRAL, and PsycNet. Two authors independently screened all articles and extracted data. We performed random-effect meta-analyses for ADHD with pooled outcomes for LUTS. We identified 119 relevant articles in the literature and 18 articles fulfilled the inclusion criteria for the systematic review, of which, 5 articles had sufficient data for meta-analysis. Examining ADHD among individuals with LUTS, the odds ratio was 2.99 (95% CI 1.13, 7.88, $p < 0.001$), compared to controls. In multiple studies, the mean overall score for LUTS, using a standardized measure, was significantly higher in patients with ADHD in comparison to controls, and the severity of ADHD was positively associated with the severity of LUTS. Younger age in children was correlated with a higher LUTS score. Different subtypes of urinary incontinence demonstrated differences in behavioral problems and psychiatric comorbidity. Sex differences in LUTS were not consistent across articles. Our results indicate clinically significant associations between ADHD and LUTS in children. Because LUTS and ADHD are common disorders in children, clinicians should be aware of these associations as they inform optimal assessment and treatment strategies

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Eur Child Adolesc Psychiatry. 2021.

EVALUATION OF A STRUCTURED SKILLS TRAINING GROUP FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMISED CONTROLLED TRIAL.

Meyer J, Ramklint M, Hallerb+ñck MU, et al.

Attention-deficit/hyperactivity disorder (ADHD) in adolescence is associated with behavioural, emotional and interpersonal problems, and non-pharmacological treatments targeting these difficulties have been requested. The objective of this study was to evaluate the effectiveness and acceptance of an age-adapted structured skills training group (SSTG) for adolescents with ADHD. Adolescents (n = 184, ages 15ΓÇô18-áyears) with a diagnosis of ADHD were randomly assigned to either the SSTG, which is based on dialectical behavioural therapy, or an active control group based on psychoeducation. Symptoms of ADHD, behavioural and emotional problems, functional impairment, and health-related outcomes were assessed with self-ratings and parental ratings two weeks before, two weeks after, and six months after treatment. All participants who completed the pre-treatment measurements (n = 164) were included in the main analyses, which were conducted using a linear mixed model. Our results demonstrated no significant group differences in favour of the SSTG for any of the study outcomes. A majority of the participants in both groups reported that they

had increased their knowledge about ADHD, improved their ability to manage problems related to the diagnosis, and would recommend the treatment to others. We conclude that the SSTG seems to be acceptable for adolescents with ADHD in a clinical context. However, the treatment was not proved to be more effective or more acceptable than the psychoeducational control intervention. Trial registration: http://www.isrctn.com/ISRCTN17366720,11/05/2016, retrospectively registered

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Eur Child Adolesc Psychiatry. 2021.

VISUAL SEARCH IN NEURODEVELOPMENTAL DISORDERS: EVIDENCE TOWARDS A CONTINUUM OF IMPAIRMENT.

Canu D, Ioannou C, et al .

Disorders with neurodevelopmental aetiology such as Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and Schizophrenia share commonalities at many levels of investigation despite phenotypic differences. Evidence of genetic overlap has led to the concept of a continuum of neurodevelopmental impairment along which these disorders can be positioned in aetiological, pathophysiological and developmental features. This concept requires their simultaneous comparison at different levels, which has not been accomplished so far. Given that cognitive impairments are core to the pathophysiology of these disorders, we provide for the first time differentiated head-to-head comparisons in a complex cognitive function, visual search, decomposing the task with eye movement-based process analyses. N = 103 late-adolescents with schizophrenia, ADHD, ASD and healthy controls took a serial visual search task, while their eye movements were recorded. Patients with schizophrenia presented the greatest level of impairment across different phases of search, followed by patients with ADHD, who shared with patients with schizophrenia elevated intra-subject variability in the pre-search stage. ASD was the least impaired group, but similar to schizophrenia in post-search processes and to schizophrenia and ADHD in pre-search processes and fixation duration while scanning the items. Importantly, the profiles of deviancy from controls were highly correlated between all three clinical groups, in line with the continuum idea. Findings suggest the existence of one common neurodevelopmental continuum of performance for the three disorders, while quantitative differences appear in the level of impairment. Given the relevance of cognitive impairments in these three disorders, we argue in favour of overlapping pathophysiological mechanisms

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Eur Child Adolesc Psychiatry. 2021.

THE COST-EFFECTIVENESS OF TREATMENTS FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW.

Sampaio F, Feldman I, Lavelle TA, et al.

Economic evaluations can help decision makers identify what services for children with neurodevelopmental disorders provide best value-for-money. The aim of this paper is to review the best available economic evidence to support decision making for attention deficit-hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children and adolescents. We conducted a systematic review of economic evaluations of ADHD and ASD interventions including studies published 2010-2020, identified through Econlit, Medline, PsychINFO, and ERIC databases. Only full economic evaluations comparing two or more options, considering both costs and consequences were included. The quality of the studies was assessed using the Drummond checklist. We identified ten studies of moderate-to-good quality on the cost-effectiveness of treatments for ADHD and two studies of good quality of interventions for ASD. The majority of ADHD studies evaluated pharmacotherapy (n = 8), and two investigated the economic value of psychosocial/behavioral interventions. Both economic evaluations for ASD investigated early and communication interventions. Included studies support the cost-effectiveness of behavioral parenting interventions for younger children with ADHD. Among pharmacotherapies for ADHD, different combinations of stimulant/non-stimulant medications for children were cost-effective at willingness-to-pay thresholds reported in the original papers.

Early intervention for children with suspected ASD was cost-effective, but communication-focused therapy for preschool children with ASD was not. Prioritizing more studies in this area would allow decision makers to promote cost-effective and clinically effective interventions for this target group

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European Journal of Molecular and Clinical Medicine. 2021;8:376-81.

AYURVEDIC INTERVENTION FOR AUTISM - A CASE STUDY.

Shinde RV, Patil S, Jha RK.

Holistic health is looking beyond the physical body and is addressing physical, emotional, social, spiritual and intellectual health. In autism there is social, social, emotional, and sometimes intellectual health impairment is observed in the child. It affects boys more than girls and actually exact number of children living with autism is not known. In autistic child there are 3 core symptom interactions observed; Social interaction difficulties, Communicationdifficulties and, Behavioral problems. Autism can occur as a result of genetic mutation, environmental risk factors during pregnancy, paternal age at higher site. The present study describes the case of childhood autism visited at Datta Meghe Ayurvedic Hospital. Child was diagnosed clinically and has been treated with Ayurvedic interventions, Panchakarma therapies and diet modification. Child has got relief symptomatically within one week of therapy started. Case study briefly explained Ayurvedic concepts regarding childhood autism and Ayurvedic treatment protocols in autistic disorder

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European Journal of Nutrition. 2021.

THE EFFECT OF DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET ON ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) SYMPTOMS: A RANDOMIZED CONTROLLED CLINICAL TRIAL.

Khoshbakht Y, Moghtaderi F, Bidaki R, et al.

Background: The dietary approaches to stop hypertension (DASH) diet have several components like high amounts of fruits, vegetables, low-fat dairy products, and vitamin C and low amounts of simple sugars that might improve attention-deficit hyperactivity disorder (ADHD) symptoms. We aimed to investigate the effect of a DASH diet on children (aged 6–12 years) with ADHD, for the first time.

Methods: Participants were randomized to receive a DASH or a control diet for 12 weeks. The severity of ADHD symptoms [determined by abbreviated 10-item Conner's scale (ACS), 18-item Swanson, Nolan and Pelham (SNAP-IV) scale and strengths and difficulties questionnaire (SDQ)] were assessed every four weeks.

Results: Eighty children completed the study. After adjustment for confounders, parent (− 4.71 for the DASH group vs. − 3 for the control group) and teacher-reported (− 5.35 vs. − 1.87) ACS scores, parent-, teacher-, child-reported hyperactivity (− 1.40 vs. − 0.66, − 1.95 vs. -0.63, − 1.60 vs. − 0.43, respectively), emotional symptoms (− 1.50 vs. − 0.45, − 1.42 vs. − 0.63, and − 1.09 vs. − 0.61, respectively), and total SDQ scores (− 3.81 vs. − 1.65, − 4.11 vs. − 1.23, − 4.44 vs. − 1.26, respectively), teacher-reported of conduct problems (− 1.42 vs. − 0.63), peer relationship problems (− 0.87 vs. − 0.07), and prosocial behaviors (1.36 vs. 0.08) assessed by the SDQ were significantly improved in the DASH group compared with the control group ($P < 0.05$).

Conclusion: Adherence to a DASH-style diet might improve ADHD symptoms. Further RCTs which include participants from both sexes and with longer follow-up periods are needed to warrant current findings (The trial registration code: IRCT20130223012571N6; http://irct.ir/trial/12623). Trial registration Trial registration number: The trial was registered in the Iranian registry of clinical trials (registration code: IRCT20130223012571N6), URL: http://irct.ir/trial/12623

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Eur Neuropsychopharmacol. 2021;44:S30.

P.221 INCREASED COMMON CAROTID ARTERY INTIMA-MEDIA THICKNESS (CIMT) IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Ogutlu H, et al.

Introduction: Attention deficit/hyperactivity disorder (ADHD) is associated with impairment in social, academic and job-related functioning in both children and adults. The purpose of this study is to investigate the susceptibility to cardiovascular risk factors in children with ADHD diagnosis through cIMT measurement. To compare common carotid artery intima-media thickness (cIMT) in children with ADHD and a control group and to evaluate the association between cIMT and ADHD symptom severity as quantified by Conners Parent Rating Scale in children with ADHD.

Methodology: The mean carotid intima-media thicknesses of 42 children with ADHD, diagnosed based on DSM-5 clinical criteria, ADHD symptom scales and a semi-structured psychiatric interview, and 42 age and sex matched healthy controls were measured with B-mode Doppler neck ultrasonography by a radiologist. Parents of children with ADHD completed the Conners Parent Rating Scale to quantify the ADHD symptom severity.

Results: Mean age of participants was 10.9 -¦ 3.1 years, and the age range was 6-16 years. Of 83.3% (n = 70) the cases were male. The median cIMT (mm) was significantly higher for the ADHD group compared to the healthy controls (0.5 mm vs. 0.4 mm; z = -6.642, p < 0.001).). This significance was preserved in both genders, where the median value of cIMT in boys with ADHD was significantly higher than that of boys in the control group (0.5 vs. 0.4; z = -6.170, p < 0.001) and the median value of cIMT in girls with ADHD was significantly higher than that of girls in the control group (0.5 vs. 0.3; z = -2.705, p = 0.007). There was a statistically significant, negative, moderate correlation between cIMT (mm) and Conners ADHD index (Spearman r = -0.328, p = 0.034), Conners hyperactivity score (Spearman r=-0.405, p=0.008), Conners opposition score (Spearman r=0.310, p=0.046) and the presence of ODD comorbidity (Spearman r =-0. 312, p=0.044). No significant correlation was found between age, gender, Conners ADHD scores and presence of CD (p>0.05).

Conclusion: In this study we found significantly higher cIMT in children with ADHD when compared to healthy controls. Considering that increased cIMT is a sign of atherosclerosis and it can be used as a marker of cardiovascular risk factors, our finding may indicate that children with ADHD are at increased risk for cardiovascular diseases. We propose that cIMT measurement should be studied as a potential tool for risk assessment before a child with ADHD is started on psychostimulant medications. We have contrarily shown a decrease in cIMT as severity of ADHD symptoms increased as quantified by the ConnersΓÇÖ parent rating scale. This might indicate that a child with ADHD who has more severe hyperactivity, impulsivity and oppositional defiant symptoms may carry less cardiovascular risk factors

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Eur Neuropsychopharmacol. 2021;46:1-13.

DO EFFECTS OF METHYLPHENIDATE ON COGNITIVE PERFORMANCE LAST BEYOND TREATMENT? A RANDOMIZED PLACEBO-CONTROLLED TRIAL IN BOYS AND MEN WITH ADHD.

Tamminga HGH, Reneman L, Schrantee A, et al.

Methylphenidate (MPH) is the first-choice pharmacological treatment for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) across the lifespan. However, it is unclear whether MPH affects cognitive development, while recent (pre-) clinical studies suggest effects on the developing brain. The present randomized, placebo-controlled trial aims to determine whether MPH has short-term, age-dependent effects on cognitive performance in ADHD after a 1-week washout. Effects of 16 weeks MPH treatment were assessed after a one-week washout on cognitive functioning. Boys (age=10ΓÇô12) and men (age=23ΓÇô40) with ADHD were assigned to MPH treatment (boys n=25, men n=24) or placebo (boys n=25, men n=24). Outcome measures were working memory, response inhibition, response speed, episodic memory, and delay aversion. Differences in task performances over time (pre-, mid-, and post-treatment, following a 1-week wash-out) were compared between age and treatment conditions with mixed ANOVAs. MPH improved working memory and response speed, but only during treatment. No lasting age*treatment effects were observed post intervention. Overall, the results from the present randomized, placebo-controlled trial show that the effects of MPH on cognition do not extend past treatment in children or adults. While treatment with

MPH improves cognition during treatment, these effects appear transient after 16-weeks of treatment. (Title trial: Effects of methylphenidate on the developing brain; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3103)

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Evidence-Based Practice in Child and Adolescent Mental Health. 2021.

PAGING DR. GOOGLE: AVAILABILITY AND RELIABILITY OF ONLINE EVIDENCE-BASED TREATMENT INFORMATION ABOUT ADHD.

King S, Ritchie KC, McGonnell M, et al.

It is becoming increasingly common for caregivers and patients to search for health and mental health information on the Internet. Although there is a sizable scientific literature outlining an evidence-based approach to managing Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents, it is not clear how much of the online information about the disorder and its treatment aligns with evidence-based practice. The goal of this study was to conduct a review of online information about ADHD treatment and to systematically analyze this information with respect to accountability, presentation, content and alignment with evidence-based practice, and readability. Thirty-one ADHD-themed websites identified by three common Internet search engines were coded using a set of standardized criteria. Results indicated that the quality of information about ADHD treatment was generally poor, with websites meeting less than half the standardized criteria. Alignment with evidence-based practice was especially poor; most websites did not discuss psychosocial treatments and very few mentioned the treatment guidelines produced by the American Academy of Pediatrics. Flesch-Kincaid reading level was, on average, much higher than the recommended grade 8 level. Results indicate that, although conducting online searches about ADHD treatment could be beneficial in the context of shared-decision making, it is important for clinicians and caregivers to understand the limitations of this approach and to continue to engage in evidence-based treatment of ADHD to ensure positive outcomes for children and adolescents with the disorder

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Focus (United States). 2021;19:31-38.

NOVEL FORMULATIONS OF ADHD MEDICATIONS: STIMULANT SELECTION AND MANAGEMENT.

Childress AC.

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in children and adolescents in the United States. In 2016, approximately 3.8 million U.S. children ages 2 to 17 years with ADHD were being treated with medication. There are approximately 30 different amphetamine (AMPH) and methylphenidate (MPH) formulations on the market. These include immediate-release and extended-release compounds. The extended-release formulations contain various ratios of immediate-release and extended-release components, which determine the pharmacokinetic (PK) profile. For stimulants, the PK and pharmacodynamic (PD) profiles are tightly linked, and the immediate-release and extended-release percentages influence onset and duration of drug effects. Choosing the right stimulant medication for a patient depends on an understanding of the PK/PD profile, the time of day that symptoms are most impairing, the need for morning and evening symptom control and individual patient preferences

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Frontiers in Genetics. 2021;12.

CASE REPORT: WHOLE EXOME SEQUENCING REVEALED DISEASE-CAUSING VARIANTS IN TWO GENES IN A PATIENT WITH AUTISM SPECTRUM DISORDER, INTELLECTUAL DISABILITY, HYPERACTIVITY, SLEEP AND GASTROINTESTINAL DISTURBANCES.

Cerminara M, Spirito G, Pisciotta L, et al.

Autism Spectrum Disorder (ASD) refers to a broad range of conditions characterized by difficulties in communication, social interaction and behavior, and may be accompanied by other medical or psychiatric conditions. Patients with ASD and comorbidities are often difficult to diagnose because of the tendency to

consider the multiple symptoms as the presentation of a complicated syndromic form. This view influences variant filtering which might ignore causative variants for specific clinical features shown by the patient. Here we report on a male child diagnosed with ASD, showing cognitive and motor impairments, stereotypies, hyperactivity, sleep, and gastrointestinal disturbances. The analysis of whole exome sequencing (WES) data with bioinformatic tools for oligogenic diseases helped us to identify two major previously unreported pathogenetic variants: a maternally inherited missense variant (p.R4122H) in HUWE1, an ubiquitin protein ligase associated to X-linked intellectual disability and ASD; and a de novo stop variant (p.Q259X) in TPH2, encoding the tryptophan hydroxylase 2 enzyme involved in serotonin synthesis and associated with susceptibility to attention deficit-hyperactivity disorder (ADHD). TPH2, expressed in central and peripheral nervous tissues, modulates various physiological functions, including gut motility and sleep. To the best of our knowledge, this is the first case presenting with ASD, cognitive impairment, sleep, and gastrointestinal disturbances linked to both HUWE1 and TPH2 genes. Our findings could contribute to the existing knowledge on clinical and genetic diagnosis of patients with ASD presentation with comorbidities

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Front Human Neurosci. 2021 Feb;15.

EXECUTIVE FUNCTIONS IN NEURODEVELOPMENTAL DISORDERS: COMORBIDITY OVERLAPS BETWEEN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND SPECIFIC LEARNING DISORDERS.

Crisci G, Caviola S, Cardillo R, et al.

The present study examines the comorbidity between specific learning disorders (SLD) and attention deficit and hyperactivity disorder (ADHD) by comparing the neuropsychological profiles of children with and without this comorbidity. Ninety-seven schoolchildren from 8 to 14 years old were tested: a clinical sample of 49 children with ADHD (n = 18), SLD (n = 18) or SLD in comorbidity with ADHD (n = 13), and 48 typically-developing (TD) children matched for age and intelligence. Participants were administered tasks and questionnaires to confirm their initial diagnosis, and a battery of executive function (EF) tasks testing inhibition, shifting, and verbal and visuospatial updating. Using one-way ANOVAs, our results showed that all children in the clinical samples exhibited impairments on EF measures (inhibition and shifting tasks) when compared with TD children. A more specific pattern only emerged for the updating tasks. Only children with SLD had significant impairment in verbal updating, whereas children with ADHD, and those with SLD in comorbidity with ADHD, had the worst performance in visuospatial updating. The clinical and educational implications of these findings are discussed

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Frontiers in Neuroanatomy. 2016;10.

TOWARD DEVELOPMENTAL CONNECTOMICS OF THE HUMAN BRAIN.

Cao M, Huang H, Peng Y, et al.

Imaging connectomics based on graph theory has become an effective and unique methodological framework for studying structural and functional connectivity patterns of the developing brain. Normal brain development is characterized by continuous and significant network evolution throughout infancy, childhood, and adolescence, following specific maturational patterns. Disruption of these normal changes is associated with neuropsychiatric developmental disorders, such as autism spectrum disorders or attention-deficit hyperactivity disorder. In this review, we focused on the recent progresses regarding typical and atypical development of human brain networks from birth to early adulthood, using a connectomic approach. Specifically, by the time of birth, structural networks already exhibit adult-like organization, with global efficient small-world and modular structures, as well as hub regions and rich-clubs acting as communication backbones. During development, the structure networks are fine-tuned, with increased global integration and robustness and decreased local segregation, as well as the strengthening of the hubs. In parallel, functional networks undergo more dramatic changes during maturation, with both increased integration and segregation during development, as brain hubs shift from primary regions to high order functioning regions, and the organization of modules transitions from a local anatomical emphasis to a more distributed architecture. These findings suggest that structural networks develop earlier than functional networks;

meanwhile functional networks demonstrate more dramatic maturational changes with the evolution of structural networks serving as the anatomical backbone. In this review, we also highlighted topologically disorganized characteristics in structural and functional brain networks in several major developmental neuropsychiatric disorders (e.g., autism spectrum disorders, attention-deficit hyperactivity disorder and developmental dyslexia). Collectively, we showed that delineation of the brain network from a connectomics perspective offers a unique and refreshing view of both normal development and neuropsychiatric disorders

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Frontiers in Pediatrics. 2021;9.

VERY-LOW-DOSE LEVODOPA THERAPY FOR PEDIATRIC NEUROLOGICAL DISORDERS: A PRELIMINARY QUESTIONNAIRE IN JAPAN.

Hoshino K, Hayashi M, Ishizaki A, et al.

Introduction: Post-synaptic dopamine receptor supersensitivity (DARSS) has been extensively researched by Dr. Masaya Segawa, who has investigated the efficacy of very-low-dose levodopa therapy (VLDT; 0.5-1 mg/kg/day). Considerable Japanese research supports the possibility that VLDT could be used to treat pediatric neurological disorders. We conducted an on-line survey in 2014 to collect real-world data on the use of VLDT to treat DARSS.

Methods: A two-step survey, including a screening test and questionnaire, was posted on a private internet site that could be accessed via the VLDT Research Group home page, and 1,165 pediatric neurologists across Japan were invited to complete it.

Results: A total of 25 respondents reported prescribing VLDT; 19 used VLDT to treat autism spectrum disorder, 14 for tics, 12 for speech delay, 9 for Rett syndrome, 7 for attention-deficit/hyperactivity disorder, intellectual disability, and 6 for sleep problems. Twelve respondents reported prescribing a dose of 0.5 mg/kg. Twenty-two reported that VLDT was effective for treating behavioral problems, and twenty reported a good efficacy for treating motor symptoms. Adverse events had a low incidence. Notably, respondents chose VLDT for its possible action in DARSS and for its safety. VLDT was commonly used for behavioral problems in patients younger than 5 years, and for motor symptoms in aged 5Γ–9 years.

Conclusion: VLDT could safely treat behavioral and motor symptoms in pediatric neurological disorders. In contrast, dopamine antagonists are associated with potent efficacy, but with adverse effects such as sleepiness and obesity. Further surveys should be conducted with a broader participants

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General Medicine. 2020;22:39-43.

THE INFLUENCE OF EASTERN MARTIAL ARTS ON THE PSYCHO-PHYSICAL DEVELOPMENT OF CHILDREN WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER.

Georgiev J, Ruseva Z.

Aim of the study: A study of the impact of kinesitherapeutical complex combined with karate techniques by children with attention-deficit and hyperactivity disorder (ADHD).

Research Methodology: The study included 60 children aged from 4 to 6 years from the "Snow White" Kindergarten in Veliki Preslav. Kinesitherapy was perfonved combined with karate techniques in the kindergarten under the guidance of an assistant karate trainer (Sempai).

Results: After the performed therapy, statistically significant improvement ($P < 0.5$) was observed in children in tenns of concentration, emotional self-regulation and physical selfcontrol. In the rest of the children, retention of condition is seen. This complex is suitable for dosing physical activity according to the child's particularities. A positive effect of practicing martial arts can be seen in the interpersonal relationships between these children.

Conclusion: The kinesitherapy complex conducted improves the strength, balance reactions and muscle response in children with ADHD. This gives us a reason to believe that karate activities in children with attention-deficit and hyperactivity disorder are appropriate for improving the children psycho-physical development

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Genes. 2021;12:1-14.

RARE RECURRENT VARIANTS IN NONCODING REGIONS IMPACT ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) GENE NETWORKS IN CHILDREN OF BOTH AFRICAN AMERICAN AND EUROPEAN AMERICAN ANCESTRY.

Liu Y, Chang X, Qu HQ, et al.

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with poorly understood molecular mechanisms that results in significant impairment in children. In this study, we sought to assess the role of rare recurrent variants in non-European populations and out-side of coding regions. We generated whole genome sequence (WGS) data on 875 individuals, in-cluding 205 ADHD cases and 670 non-ADHD controls. The cases included 116 African Americans (AA) and 89 European Americans (EA), and the controls included 408 AA and 262 EA. Multiple novel rare recurrent variants were identified in exonic regions, functionally classified as stop-gains and frameshifts for known ADHD genes. Deletion in introns of the protocadherins families and the ncRNA HGB8P were identified in two independent EA ADHD patients. A meta-analysis of the two ethnicities for differential ADHD recurrent variants compared to controls shows a small number of overlaps. These results suggest that rare recurrent variants in noncoding regions may be involved in the pathogenesis of ADHD in children of both AA and EA ancestry; thus, WGS could be a pow-erful discovery tool for studying the molecular mechanisms of ADHD

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Hum Psychopharmacol. 2021.

RESTING STATE FUNCTIONAL CONNECTIVITY IN ADOLESCENT SYNTHETIC CANNABINOID USERS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yuncu Z, Yakmak Celik Z, Colak C, et al.

Objective: Synthetic cannabinoids (SCs) have become increasingly popular in recent years, especially among adolescents. The first aim of the current study was to examine resting-state functional connectivity (rsFC) in SC users compared to controls. Our second aim was to examine the influence of comorbid attention-deficit/hyperactivity disorder (ADHD) symptomatology on rsFC changes in SC users compared to controls.

Methods: Resting-state functional magnetic resonance imaging (fMRI) analysis included 25 SC users (14 without ADHD and 11 with ADHD combined type) and 12 control subjects.

Results: We found (i) higher rsFC between the default mode network (DMN) and salience network, dorsal attention network and cingulo-opercular network, and (ii) lower rsFC within the DMN and between the DMN and visual network in SC users compared to controls. There were no significant differences between SC users with ADHD and controls, nor were there any significant differences between SC users with and without ADHD.

Conclusions: We found the first evidence of abnormalities within and between resting state networks in adolescent SC users without ADHD. In contrast, SC users with ADHD showed no differences compared to controls. These results suggest that comorbidity of ADHD and substance dependence may show different rsFC alterations than substance use alone

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Int J Behav Dev. 2021 Mar;45:133-45.

THE EFFECT OF MINDFULNESS-BASED INTERVENTIONS ON INATTENTIVE AND HYPERACTIVE–IMPULSIVE BEHAVIOR IN CHILDHOOD: A META-ANALYSIS.

Vekety B, Logemann HNA, Takacs ZK.

Current research has reported the beneficial effects of mindfulness-based interventions (MBIs) on general domains of cognition and behavior among children. The present study is the first meta-analysis with controlled studies investigating the pre-post change effects of MBIs on two widely experienced behaviors in childhood education, namely inattentiveness and hyperactivity–impulsivity. With a special developmental focus on the early years, a total of 21 studies with 3- to 12-year-old children were included in the meta-analysis. Results indicated that MBIs decreased children's overall inattentive and hyperactive–impulsive behavior with a small but significant effect size ($k = 21$, $g + = .38$, $p < .001$). However, this overall positive effect was only significant when teachers rated children's behavior and nonsignificant when parents and

children themselves were the informants. Additionally, MBIs showed a moderate effect in reducing inattentiveness and hyperactivity–impulsivity for children at risk for such behavior. In conclusion, results indicate that MBIs, which are relatively easily applied in educational practice, have the potential to decrease inattentive and hyperactive–impulsive behavior and might contribute to children's overall better functioning at school

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Int J Environ Res Public Health. 2021;18:1-11.

ATTACHMENT REPRESENTATION AND EMOTION RECOGNITION ABILITY IN CHILDREN WITH ADHD AND THEIR PARENTS: A STUDY PROTOCOL.

Kissgen R, Franke S, Susewind M, et al.

Background: Few studies in clinical attachment research to date have examined children with an attention-deficit/hyperactivity disorder (ADHD) diagnosis. This is surprising for two reasons: first, there are a number of parallels between the behaviors of children with an insecure and disorganized attachment and the behaviors of children with an ADHD diagnosis. Second, secure attachment has a positive effect on the development of skills in areas in which children with ADHD demonstrate problems (e.g., attention span, impulse control). There are currently no findings on whether or not and how insecure and disorganized attachment and ADHD affect children's emotion recognition ability.

Methods: This is a cross-sectional study, part exploratory and part hypothesis-driven in the context of basic research. A clinical sample of 5-to 10-year-old children with an ADHD diagnosis and their parents is to be compared to a non-clinical unaffected control group. Over a period of 3 years, 80 subjects and their parents are to be recruited in each group for participation in the study.

Discussion: This study is the first to examine links between attachment, emotion recognition ability, and ADHD. It is also the first to include not just children with ADHD but also their mothers and fathers in its design. The findings should help reduce the research gap and generate more knowledge for family interventions in the case of ADHD

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Int J Environ Res Public Health. 2021;18:1-15.

PHYSICAL ACTIVITY IMPROVES MENTAL HEALTH IN CHILDREN AND ADOLESCENTS IRRESPECTIVE OF THE DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) – A MULTI-WAVE ANALYSIS USING DATA FROM THE KIGGS STUDY.

Ganjeh P, Meyer T, Hagmayer Y, et al.

Physical activity (PA) may have positive effects on mental health in children and adolescents. This post hoc study aimed to further investigate the relationship between different frequency levels of PA and general mental health as well as specific hyperactivity/inattention symptoms in children and adolescents.

Methods: The analyses were based on data drawn from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) study, a regularly conducted large-scale, epidemiological investigation of somatic and mental health of children and adolescents in Germany. Parents were asked about their children's attention deficit hyperactivity disorder (ADHD) records and answered questionnaires concerning any mental health problem behavior of the children and adolescents using the Strengths and Difficulties Questionnaire (SDQ). The overall problem score as well as the hyperactivity/inattention symptoms subscale (SDQH/I) were entered as outcomes in a regression model controlling for parental socio-economic status and participants sex, age, and body mass index (BMI). Cross-sectional analyses were conducted at three time points of the KiGGS study (baseline, wave 1, and wave 2) using general linear models (GLM). This was performed for different age groups (4-5, 6-9, 10-17 years).

Results: Significant negative relationships were found between PA and general mental health problems. For the relationship between PA and SDQ-H/I, different patterns emerged at the three time points. There was no interaction between PA frequency levels and diagnosis of ADHD (ADHD vs. non-ADHD controls) regarding the SDQ total score.

Conclusion: This study underlines the importance of a high frequency level of PA for a good mental health status among children and adolescents, irrespective of the diagnosis of ADHD

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Int J Epidemiol. 2021;49:944-53.

ASSOCIATIONS OF EXPOSURE TO GREEN SPACE WITH PROBLEM BEHAVIOURS IN PRESCHOOL-AGED CHILDREN.

Liao J, Yang S, Xia W, et al.

Background: Limited evidence is available regarding the association of green-space exposure with childhood behavioural development. This study aimed to investigate the associations of exposure to green space with multiple syndromes of behavioural development in preschool children.

Methods: This cross-sectional study was conducted in Wuhan, China from April 2016 to June 2018. We recruited a sample of 6039 children aged 5-6 years from 17 kindergartens located in five urban districts of the city. We measured the greenness using average Normalized Difference Vegetation Index (NDVI) within a circular buffer area of 100 metres surrounding the central point of residences and kindergartens. We calculated the residence- kindergarten-weighted greenness by assuming that children spent 16 hours per day at home and 8 hours at kindergarten. The problem behaviours of children were evaluated at kindergarten using the Childhood Behavioral Checklist (CBCL) and standardized into problem behavioural T scores. Linear mixed-effect models and linear-regression models were used to estimate the associations.

Results: We observed decreases in problem behaviours associated with kindergarten and residence-kindergarten-weighted surrounding greenness in preschool children. For example, a one-interquartile range increase in kindergarten and residence-kindergartenweighted NDVI was associated with decreased T scores for total behaviour by -0.61 [95% confidence interval (CI): -1.09, -0.13) and -0.49 (95% CI -0.85, -0.12), anxiety and depression by -0.65 (95% CI: -1.13, -0.17) and -0.46 (95% CI: -0.82, -0.10), aggressive behaviour by -0.53 (95% CI: -1.01, -0.05) and -0.38 (95% CI: -0.75, -0.02) and hyperactivity and attention deficit by -0.54 (95% CI: -1.01, -0.07) and -0.48 (95% CI: -0.83, -0.12), respectively. Stratified analyses indicated that the associations of green-space exposure with problem behaviours were stronger in boys than in girls.

Conclusions: Children attending kindergartens with higher levels of surrounding green space exhibited better behavioural development. The mechanisms underlying these associations should be explored further

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Int J Res Pharm Sci. 2020;11:1961-66.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG SCHOOCHILDREN AT SELECTED SCHOOLS, ELURU, ANDHRA PRADESH.

Swetha Prashanthi BS, Ramya Rathi Devi M.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a significant community health problem worrying a considerable quantity of children and grown per-sons. It is single utmost familiar neurobehavioural problems of juvenile and has the possibility for continuousness into youth and adult. 1) To determine the prevalence of ADHD among school children aged between 6-12 years in schools at Eluru District 2) To co-relate the prevalence of ADHD with parent report and teacher report. 3) To associate the prevalence of Attention Deficit Hyperactive Disorder among school children with their demographic vari-ables. Research approach was quantitative, and design was a cross-sectional research design. The study captivated on parents and teachers of school children in four schools at Eluru District recognized by the Board of Secondary Education, Government of Andhra Pradesh. The samples were chosen using convenient sampling technique and consisted of 509 school children studying in selected schools aged between 6-12 years after getting informed consent from their parents & teachers. The prevalence of ADHD was measured using Conner's Abbreviated Rating Scale for parents & teachers. The data were ana-lyzed using descriptive and inferential statistics. Result shows that 19 (3.7%) school children were categorized as ADHD based on parents report and 10 (2.0%) school children were categorized as ADHD based on teachers report.

The analysis depicts that there was a positive correlation between the parents report and teachers report where r = 0.589. This study concludes that ADHD is found to be prevalent in school children and may be continued in the adolescent period if left uncared

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Ir J Med Sci. 2021.

ASSOCIATION OF WENDER UTAH RATING SCALE (WURS)-61 ITEMS WITH CLINICAL PSYCHIATRIC DIAGNOSIS IN ADULTHOOD.

Hanley C, Saleem F, Graffeo I, et al .

Background: The Wender Utah Rating Scale (WURS) is a widely used retrospective scale in adults presenting for ADHD evaluations which features items relating to childhood symptoms. Aims: The aim of this study is to establish if certain childhood symptoms (including ADHD) as identified by the WURS-61 are associated with specific mental health disorders in adulthood.
Methods: Case-control study of N=630 attending Adult Mental Health Services (AMHS) and a control group without mental disorders (N=96).
Results: The mean age of the participants was 39.81 (SD 12.94) of which 387 (53.3%) were females. There were no significant differences between cases and controls in terms of age (t= 1.829, df 724, p=.068) and gender (x2=1.123, df 1, p=.289). Exploratory factor analysis of WURS-61 reveals 5 factors. Using factor scores and after cross-tabulation, we found that: The presence of childhood impulsivity, emotional lability and distress in addition to inattention/disorganisation were significantly associated with adult ADHD diagnosis (F90). WURS items which suggests childhood conduct problems were associated with a number of adult diagnoses, when present either on its own (psychoactive substance use, or when present in combination with childhood impulsivity, emotional lability and distress (personality disorders).
Conclusion: There is an association between certain childhood behaviours and risk for later development of personality disorders, and psychoactive substance use. There is overlap of childhood symptoms to those who later diagnosed in adulthood with ADHD, personality disorders, and substance abuse

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JAMA Network Open. 2021.

RACIAL DISPARITIES IN DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A US NATIONAL BIRTH COHORT.

Shi Y, Hunter Guevara LR, Dykhoff HJ, et al.

Importance: There are limited data on the racial disparities in the incidence of attention-deficit/hyperactivity disorder (ADHD) diagnosis in children at the national level.
Objective: To explore differences in rates of diagnosis of ADHD and use of treatment among children by race and ethnicity.
Design, Setting, and Participants: This retrospective cohort study assessed insurance claims data of children born in the US between January 1, 2006, and December 31, 2012, who had continuous insurance coverage for at least 4 years. The last date of follow-up included in the cohort was June 30, 2019. Race/ethnicity designations were based on self-report and included non-Hispanic White, Black, Hispanic, and Asian. Data were analyzed between October 2019 and December 2020.
Exposures: Race and ethnicity.
Main Outcomes and Measures: ADHD diagnosis as defined by International Classification of Diseases codes (ninth or tenth editions) and treatment within 1 year of diagnosis, including medication and behavior therapy as defined by billing codes. Data on ADHD diagnosis and treatment were adjusted for sex, region, and household income in a multivariate Cox regression model.
Results: Among 238011 children in the cohort (116093 [48.8%] girls; 15183 [6.7%] Asian, 14792 [6.2%] Black, 23358 [9.8%] Hispanic, and 173082 [72.7%] White children), 11401 (4.8%) were diagnosed with ADHD. The cumulative incidence at age 12 was 13.12% (95% CI, 12.79%-13.46%). In multivariate Cox regression adjusting for sex, region, and household income, the hazard ratio for Asian children was 0.48 (95% CI, 0.43-0.53); Black children, 0.83 (95% CI, 0.77-0.90); and Hispanic children, 0.77 (95% CI, 0.72,

0.82) compared with White children. In the first year after diagnosis, 516 preschool children (19.4%) received behavioral therapy only, 860 (32.4%) had medications only, 505 (19.0%) had both, and 774 (29.2%) had no claims associated with either option. A higher percentage of school-aged children (2904 [65.6%]) were prescribed medications, and fewer had therapy only (639 [14.4%]) or no treatment at all (884 [20.0%]). Compared with other groups, White children were more likely to receive some kind of treatment. Asian children had the highest odds of receiving no treatment (odds ratio compared with White children, 0.54; 95% CI, 0.42-0.70).

Conclusions and Relevance: Racial and ethnic disparities in the diagnosis and treatment of ADHD are evident. Future study is needed to elucidate the mechanism behind these disparities, with special attention to Asian children. Clinicians should provide racially sensitive care in the evaluation and treatment of ADHD.

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JAMA Psychiatry. 2021.

ASSOCIATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD AND ADOLESCENCE WITH THE RISK OF SUBSEQUENT PSYCHOTIC DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS .

Nourredine M, Gering A, Fourneret P, et al.

Importance: Growing evidence supports an association between attention-deficit/hyperactivity disorder (ADHD) in childhood and subsequent psychotic disorders. Both disorders share physiopathological features such as attention deficits, dopaminergic imbalance, and genetic susceptibility. However, the results of epidemiologic studies have been conflicting.

Objective: To provide a quantitative synthesis of studies exploring the association between ADHD and the risk of subsequent psychotic disorder.

Data Sources: A systematic literature search of the MEDLINE, Scopus, PsycInfo, and Web of Science databases was performed from inception until the final analysis on July 7, 2020. No restriction of language was applied.

Study Selection: Cohort and case-control studies examining the relative risk of developing a psychotic disorder in people diagnosed with ADHD at younger than 18 years compared with control individuals without ADHD.

Data Extraction and Synthesis: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed in reporting results. Two independent reviewers extracted the data and assessed the risk of bias of individual studies using the Newcastle-Ottawa Scale. Preferably adjusted odds ratios (aORs) or hazard ratios from the identified studies were extracted, and ORs were computed when they were not adjusted. A random-effects model was used to calculate the pooled relative effect using the meta package in R.

Main Outcomes and Measures: An association between ADHD (exposure) and psychotic disorder (outcomes); both diagnoses were based on international classification.

Results: A total of 15 studies were included in the review. Twelve studies were pooled in the meta-analysis, representing 1.85 million participants. A diagnosis of ADHD in childhood was associated with a significant increase in the risk of subsequent psychotic disorder, with a pooled relative effect of 4.74 (95% CI, 4.11-5.46; I2= 43% [95% CI, 0%-70%]). No significant between-group differences were found for subgroup analyses according to psychotic disorder (odds ratio [OR], 5.04; 95% CI, 4.36-5.83) or schizophrenia (OR, 4.59; 95% CI, 3.83-5.50) outcomes, cohort (OR, 4.64; 95% CI, 4.04-5.34) or case-control (OR, 6.81; 95% CI, 4.21-11.03) study design, and adjusted (OR, 4.72; 95% CI, 4.11-5.46) or unadjusted (OR, 3.81; 95% CI, 1.39-10.49) estimates. Meta-regressions were not significant when sex and bias score were used as covariates. No evidence of publication bias was found.

Conclusions and Relevance: These findings suggest that childhood ADHD is associated with an increased risk of a subsequent psychotic disorder. Further studies are required to determine the mechanisms linking these common conditions and whether early intervention for ADHD might reduce the risk of subsequent psychotic disorder.

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J Adolesc Health. 2021 Feb;68:227-28.

OPPORTUNITIES AND CHALLENGES FOR UNDERSTANDING AND TREATING HETEROGENEITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP.

Comments on an article by M. Sultan et al. (see record [rid]2021-14669-010[/rid]). Sultan et al. used the NCS-A sample to document rates of co-occurring emotional and behavioral mental health disorders in adolescents aged 13-17 years, with and without a lifetime history of ADHD. Sultan et al. found that ADHD was associated with numerous adverse events, assessed using individual adolescent-report items, such as poor emotional control, interpersonal difficulties, negative interactions with the police or court, substance use, and suicidal behaviors. The current author reports that these findings are important, particularly as they are drawn from a large, nationally representative sample of adolescents and further document the mental health, the educational, occupational, and socio-emotional burden associated with ADHD across the life span

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J Affective Disord. 2021;286:220-27.

ASSOCIATION OF SYMPTOMS OF ATTENTION DEFICIT AND HYPERACTIVITY WITH PROBLEMATIC INTERNET USE AMONG UNIVERSITY STUDENTS IN WUHAN, CHINA DURING THE COVID-19 PANDEMIC.

Zhao Y, Jiang Z, Guo S, et al.

Background: COVID-19 is still spreading worldwide and posing a threat to individuals physical and mental health including problematic internet use (PIU). A potentially high-risk group for PIU are those with symptoms of attention deficit and hyperactivity (ADHD symptoms), because of restrictions in their physical activity levels and engagement in computer diversions requiring only short attention spans.

Methods: We used convenience sampling in a cross-sectional survey of university students from 30 universities in Wuhan, Hubei Province, China. We assessed PIU using the Internet Addiction Test and ADHD symptoms using the WHO Adult ADHD Self-Report Screening Scale. Using logistic regression and linear regression analyses we adjusted for demographic, epidemic-related and psychological covariates in models of the association between ADHD symptoms and PIU.

Results: Among 11,254 participants, we found a 28.4% (95% CI, 27.5%-29.2%) prevalence of PIU, relatively higher than before the pandemic. In our final logistic regression model, participants with ADHD symptoms had approximately two times the risk for PIU (OR: 2.31, 95% CI: 1.89-2.83). Similarly, individuals with depression, anxiety, insomnia, PTSD symptoms and feeling stress during the pandemic had a higher risk of PIU, while those exercising regularly during the pandemic had a lower risk.

Limitations: The cross-sectional design and reliance on internet based self-reports for ADHD symptoms and PIU assessments, without direct structured interviews for validation, are limitations.

Conclusions: The prevalence of PIU was high during COVID-19, and those people with ADHD symptoms and other mental illness symptoms appear to be at higher risk of PIU. Regular exercise may reduce that PIU risk and hence should be recommended during the COVID-19 pandemic

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J Affective Disord. 2021;284:149-56.

MATERNAL DEPRESSIVE AND ANXIETY SYMPTOMS AND THE RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN OFFSPRING AGED 17: FINDINGS FROM THE RAINE STUDY.

Ayano G, Betts K, Tait R, et al.

Background: While previous studies have suggested that maternal anxiety and depressive symptoms are associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) in their offspring in early and late childhood, studies exploring the risk in late adolescence are however lacking. This study aims to examine the association between maternal anxiety and depressive symptoms and the risk of ADHD symptoms in late adolescence (at age 17).

Methods: We used data from the Raine Study. Maternal depressive and anxiety symptoms were measured when the child was 10 years of age using the Depression, Anxiety, and Stress Scale (DASS). Offspring

ADHD symptoms at age 17 were assessed using the DSM-oriented scales of the child behavior checklist (CBCL). Log-binomial regression was used to explore the associations.
Results: We found an increased risk of ADHD symptoms in offspring of mothers with comorbid anxiety and depressive symptoms when compared with offspring of mothers with no symptoms [RR 5.60 (95%CI 3.02-10.37)]. There was a nearly three-fold increase in the risk of ADHD symptoms in offspring of mothers with increased anxiety symptoms compared with offspring of mothers who were in the normal range [RR 2.84 (95%CI 1.18-6.83)]. No association was observed with maternal depressive symptoms.
Conclusion: This study found an increased risk of ADHD symptoms in the offspring of mothers with anxiety as well as comorbid anxiety and depressive symptoms but not among the offspring of mothers with depressive symptoms. Early screening and intervention for ADHD symptoms in offspring with maternal anxiety and comorbid anxiety and depressive symptoms are warranted

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J Autism Dev Disord. 2021.
WHAT IS THE EFFECT OF STIMULUS COMPLEXITY ON ATTENTION TO REPEATING AND CHANGING INFORMATION IN AUTISM?
Arora I, Bellato A, Gliga T, et al.
Slower habituation to repeating stimuli characterises Autism, but it is not known whether this is driven by difficulties with information processing or an attentional bias towards sameness. We conducted eye-tracking and presented looming geometrical shapes, clocks with moving arms and smiling faces, as two separate streams of stimuli (one repeating and one changing), to 7-15 years old children and adolescents (n = 103) with Autism, ADHD or co-occurring Autism+ADHD, and neurotypical children (Study-1); and to neurotypical children (n = 64) with varying levels of autistic traits (Study-2). Across both studies, autistic features were associated with longer looks to the repeating stimulus, and shorter looks to the changing stimulus, but only for more complex stimuli, indicating greater difficulty in processing complex or unpredictable information

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J Clin Diagn Res. 2021;15:VE01-VE04.
ROLE OF EARLY CHILDHOOD ADVERSITY, BEHAVIOUR PROBLEMS AND ACADEMIC PERFORMANCE AMONG ADOLESCENTS WITH ADHD: A SYSTEMATIC REVIEW.
Sharma A, Khan W.
Introduction: "Hyperactivity", is characterised by difficulties related to task, oriented behaviour in children particularly hyperactive children also tends to be socially intrusive and immature. Attention Deficit Hyperactivity Disorder (ADHD) children have great difficulty in compatibility with their parents and their peer group. This disorder occurs majorly in boys than girls and some residual effects, such as attention difficulties may persist into adolescence. Aim: Understanding of behavioural concerns among ADHD adolescents with their parents.
Materials and Methods: A comprehensive search in the international databases of academic search complete, Psych articles, J GATE, Psychology and behavioural sciences collection, Proquest, Science Direct, and Google scholar was conducted. Studies included in this review were prospective studies, retrospective study, case-control study, cohort study, descriptive study, and review studies. The study consisted of 15 studies from review journals. Psycho social correlates were investigated in ADHD patients. The studies published from 2000 to 2016 were included in this review.
Results: The present review revealed that there is significant role of early Childhood Adversity (CA), poor scholastic performance and behaviour problems in the formulation of ADHD among adolescents.
Conclusion: It was concluded that there is a problem in ADHD patients related to their poor academic performances which also reflects in their adolescence, and behavioural problems with parents also. Parents with ADHD children faced more stress in comparison to parents of Non-ADHD children. There is a need to develop specific parent's intervention training and early identification of ADHD children

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J Clin Psychol. 2021 Mar;77:732-44.

A LATENT PROFILE ANALYSIS OF BORDERLINE PERSONALITY FEATURES AND EXTERNALIZING PROBLEMS IN YOUTH.

Babinski DE, McQuade JD, Waschbusch DA.

Objective: This study investigated the co-occurrence of borderline personality disorder (BPD), attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) features in elementary-aged youth.

Method: Latent profile analysis characterized subgroups of youth based on the presence of BPD, ADHD, and ODD features, and subgroups were compared on academic, social, and emotional impairment.

Results: Seven subgroups were identified, including subgroups with slight, subclinical, clinical, and severe levels of co-occurring BPD, ADHD, and ODD features, and a subgroup of youth with no elevations in these symptom domains. Subgroups of youth with only clinical elevations in ADHD and only clinical levels in BPD features were also identified. Groups differed on level and type of impairment.

Conclusion: Youth with ADHD and ODD represent a high-risk group likely to also show early prodromal clinical elevations in BPD. Future work is needed to examine the longitudinal outcomes of these subgroups to inform prevention and treatment

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J Fam Psychol. 2021 Mar.

PARENTING GROUP COMPOSITION DOES NOT IMPACT PROGRAM EFFECTS ON CHILDREN'S CONDUCT PROBLEMS.

Leijten P, Wijngaards-de Meij L, Weeland J, et al.

Many established parenting programs for children's conduct problems are delivered in groups. Various, and at times conflicting, beliefs exist about whether families fare better in groups with parents that are more similar to them, or in groups that are more diverse. We set out to test these beliefs empirically. We integrated data from four trials of the Incredible Years parenting program in the Netherlands, including 452 families (children age 2–10 years) participating in 44 parenting groups. We used multilevel regression to test whether families benefit more (or less) when they participate in a group with parents that are more similar to them in terms of ethnic background, educational level, and children's baseline conduct problems, Attention Deficit/Hyperactivity Disorder (ADHD) symptoms, and emotional problems. In addition, we tested whether relative group position effects were stronger for some families than for others (e.g., whether especially ethnic minority families benefit from groups that are more ethnically diverse). Families with more severe conduct problems benefited more, but they did not fare better (or worse) in groups where other families were more similar to them. Regarding the other group characteristics, families' relative group position did not predict parenting program effects on children's conduct problems. Our findings held across families with different sociodemographic backgrounds and different levels of children's ADHD symptoms and emotional problems. We found no evidence that parenting group composition impacts the effectiveness of the Incredible Years parenting program for children's conduct problems

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Journal of Learning Disabilities. 2021 Mar;54:124-38.

THE ASSOCIATION OF EXECUTIVE FUNCTIONING WITH ACADEMIC, BEHAVIOR, AND SOCIAL PERFORMANCE RATINGS IN CHILDREN WITH ADHD.

Tamm L, Loren REA, Peugh J, et al.

This study investigated the association of a performance-based measure of executive functioning (EF) with academic, social, and behavioral performance ratings in a convenience sample of 153 children aged 5 to 12 (78% male, 83% Caucasian) diagnosed with attention-deficit/hyperactivity disorder (ADHD). Multivariate regression showed that above and beyond age and ADHD severity, poorer EF performance was uniquely associated with more impairment in reading, written expression, and math by teacher report, and more impairment in the overall school and reading domains by parent report. ADHD symptoms were more strongly associated with ratings of impairment in social relationships, organized peer activities, and classroom behaviors than EF performance. Age did not moderate the findings, but younger children were rated as having more trouble with participation in organized activities by parents, as more likely to disrupt class by

teachers, and to have problematic relationships with peers by parents and teachers. EF and academic performance appeared worst in the groups seen as highly symptomatic and impaired by both parents and teachers, and by teachers only. EF deficits may be a specific risk factor for academic impairment in children with ADHD

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J Pediatr Urol. 2020;16:S13.

EFFICACY OF UROTHERAPY AND RISK FACTORS FOR TREATMENT RESISTANCE IN CHILDREN WITH BLADDER DYSFUNCTION AND BEHAVIOURAL DISORDERS.

Eliezer D, Samnakay N, Starkey M, et al.

Introduction: Children with behavioural disorders have a higher risk of associated bladder dysfunction. We evaluate the efficacy of urotherapy in children with behavioural disorders and urinary incontinence or lower urinary tract symptoms (LUTS).

Methods: This is a prospective study of a cohort of children aged 6-16 years with bladder dysfunction, and under medical treatment for behavioural disorders. Children with no response to urotherapy alone were offered combination treatment. We reviewed patient characteristics, interventions for incontinence and subjective and objective bladder-related outcomes as per ICCS definitions over a 6 month follow-up. Descriptive analyses were undertaken to identify predictors of treatment resistance.

Results: Twenty-four patients (Male=15, median age=10 years) were recruited. Twenty children had Attention Deficit/Hyperactivity disorder (83%), 9 had Autism Spectrum Disorder (38%), 8 had Oppositional Defiance Disorder (33%) and 7 had an anxiety disorder (29%). Majority of children were on stimulants (n=17) and/or clonidine (n=12). Urological symptoms included: nocturnal enuresis (n=9), diurnal enuresis (n=8), daytime incontinence/LUTS (n=4) or bladder/bowel dysfunction (n=3). Eight children received urotherapy alone. Eleven received combination therapy with alarms (n=4), desmopressin (n=4) or oxybutynin (n=3). Five (21%) children were non-compliant with treatment and were excluded. Overall, partial response was seen in 15/19 (78.9%) and complete response in 2/19 (10.5%). Urotherapy alone was adequate in 8/19 (42.1%) children. Presence of daytime incontinence was associated with a poorer overall response to treatment. Types of medications for behavioural disorders and constipation did not appear to be associated with treatment resistance.

Conclusions: In children with behavioural disorders, daytime incontinence is a predictor for treatment resistance in bladder dysfunction. In this group, urotherapy should be instituted as an effective first line treatment; though combination therapy is required in over 50% of cases

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J Am Acad Child Adolesc Psychiatry. 2021.

SYSTEMATIC REVIEW: ASSESSMENT OF SLUGGISH COGNITIVE TEMPO OVER THE PAST DECADE.

Becker SP.

Objective: To conduct a systematic review of the measures designed to assess sluggish cognitive tempo (SCT) since the first SCT scale using careful test-construction procedures was published in 2009.

Method: MEDLINE (PubMed), Embase, PsychINFO, and Web of Science databases were searched from September 2009 through December 2019. Articles reporting on reliability (internal consistency, test-retest, and interrater reliability), structural validity (an aspect of construct validity focused on items' convergent and discriminant validity), concurrent and longitudinal external validity, invariance, or intervention/experimental findings were included.

Results: Full criteria for data extraction and inclusion were met by 76 studies. Nine measures for assessing SCT were identified (7 assessing parent report, teacher report, and/or self-report in children and 2 assessing self-report and/or collateral informant report in adults). Each measure demonstrated acceptable to excellent reliability. All or at least the majority of SCT items on each measure also had structural validity (high loadings on an SCT factor and low loadings on an attention-deficit/hyperactivity disorder [ADHD] inattention factor). Studies have supported the invariance of SCT across sex and time, and there is initial evidence of invariance across informants, youths with ADHD and youths without ADHD, and ADHD presentations. The Child and

Adolescent Behavior Inventory (CABI), Child Concentration Inventory, Second Edition (CCI-2), and Barkley Adult ADHD Rating Scale-IV (BAARS-IV) have particularly strong support for assessing parent/teacher-reported, youth self-reported, and adult self-reported SCT, respectively.
Conclusion: The SCT measures included in this review share numerous positive properties, have promising psychometric support, and have proven useful for examining the external correlates of SCT across the life span. Although substantial progress has been made over the last decade, work remains to be done to further improve the assessment of SCT and key directions for future research are provided

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J Am Acad Child Adolesc Psychiatry. 2021.
EDITORIAL: TRIALS AND TRIBULATIONS OF DEVELOPING ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER INTERVENTIONS: DIGGING DEEP TO STAY MOTIVATED.
Bussing R.
Attention-deficit/hyperactivity disorder (ADHD) has great public health relevance due to its high prevalence; adverse academic, social, economic, and health impacts on affected individuals and their families; and well established psychosocial and pharmacological treatment options.1 Typically presenting with childhood onset, ADHD remains an impairing disorder through adolescence to adulthood for a majority of those affected. It is well established that adolescents with any chronic health condition are difficult to engage in protracted illness management, with an estimated 50%-80% struggling with nonadherence, prompting significant efforts to identify adherence promotion interventions.2 Transition-age youth with ADHD are no exception, especially as it pertains to medication use.3 Indeed, ADHD intervention development for transition ages represents a high public health priority, as signaled through grant opportunities offered by the NIMH for pilot projects to refine and test interventions to sustain ADHD treatment effects across developmental transitions (see https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-100.html)

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J Am Acad Child Adolesc Psychiatry. 2021.
EFFECTIVENESS OF MOTIVATIONAL INTERVIEWING–ENHANCED BEHAVIOR THERAPY FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED COMMUNITY-BASED TRIAL.
Sibley MH, Graziano PA, Coxe S, et al.
Objective: This study tests the effectiveness of parent-teen psychotherapy for adolescent attention-deficit hyperactivity disorder (ADHD) (Supporting Teens Autonomy Daily [STAND]) versus usual care (UC) in 4 community clinics.
Method: A randomized clinical trial was conducted with double randomization of adolescents and therapists to STAND versus UC. Participants were 278 culturally diverse adolescents diagnosed with DSM-5 ADHD at baseline and 82 community therapists. Seven primary outcomes were assessed at baseline (BL), posttreatment (PT; mean = 5.11 months post-BL, SD = 2.26), and follow-up (FU; mean = 9.81 months post-BL, SD = 2.50): inattention (IN; parent/teacher-rated), academics (parent-rated/official records), family functioning (parent/adolescent-rated), and disciplinary records. Treatment engagement indicated consumer fit (eg, number or sessions received, percentage of sessions attended by parent, satisfaction). The impact of treatment on concurrent medication use was also examined. Service delivery features were examined as moderators of outcome.
Results: Intent-to-treat (N = 278) analyses indicated no significant group +ù time effects. STAND only led to superior outcomes when therapists were licensed (22% of sample) versus unlicensed (parent-rated IN: p <. 001, d = 1.08; parent-rated academic impairment: p =. 010, d = 1.17). Compared to UC, STAND was associated with greater parent participation (p <. 001, d = 0.88) and higher scores on certain indices of parent satisfaction. STAND also was associated with superior medication engagement over time compared to UC (odds ratio = 7.18).
Conclusion: Evidence-based psychosocial treatment for adolescent ADHD did not outperform UC on outcome trajectories despite improving some indices of treatment engagement. STAND requires additional adaptation for community contexts.

Clinical trial registration information: STAND Community Trial (STAND); clinicaltrials.gov; NCT02694939

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J Am Acad Child Adolesc Psychiatry. 2021.

EDITORIAL: PRECISION MEDICINE IN NEUROTHERAPEUTICS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Rubia K.

Noninvasive brain stimulation is a novel treatment avenue for attention-deficit/hyperactivity disorder (ADHD). The advantages over pharmacological treatment are relatively minimal and transient side-effects, which make it a treatment preferred by patients and parents. Neurostimulation can furthermore target key neurobiological abnormalities established over decades of neuroimaging research. Trigeminal nerve stimulation (TNS) is the only neuromodulation and device-based nonpharmacological treatment recently licensed for children with ADHD by the US Food and Drug Administration. This was based on a double-blind sham-controlled proof-of-concept trial of 4 weeks of TNS in 62 children, who showed a reduction of ADHD symptoms with an effect size of 0.5, similar to the results with second-line nonstimulant pharmacological treatment.1 Precision medicine approaches, such as establishing predictors of treatment response using relatively cost-effective cognitive and electrophysiological measures would be clinically very useful to screen children with ADHD for whom TNS is likely to be effective

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Kindheit und Entwicklung: Zeitschrift für Klinische Kinderpsychologie. 2021 Jan;30:51-62.

DIE KORTEXDICKE BEI AUTISMUS-SPEKTRUM-STÖRUNG WIRD MODULIERT DURCH EINE KOMORBIDE AUFMERKSAMKEITSDEFIZIT-/ HYPERAKTIVITÄTSSTÖRUNG = CORTICAL THICKNESS IN AUTISM SPECTRUM DISORDER IS MODULATED BY COMORBID ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Schäfer T, Mann C, Bletsch A, et al.

Theoretical Background: Autism spectrum disorder (ASD) is a common neurodevelopmental condition with a highly heterogeneous phenotype that includes several comorbid conditions, such as attention-deficit hyperactivity disorder (ADHD). Both ASD and ADHD are accompanied by atypical brain development that affects several markers of brain anatomy. For example, measures of cortical thickness (CT) have been found to be atypical in both conditions and in several spatially distributed neural networks. The influence of comorbid symptoms is, however, often ignored in conventional neuroimaging studies that typically examine the neuroanatomy of ASD relative to typically developing (TD) controls. It therefore remains largely unknown to what degree neuroanatomical differences in ASD individuals with an additional diagnosis of ADHD differ from those that only display core ASD symptomatology. Objective: In the present study, we examined to what degree the cortical thickness of ASD is modulated by the existence of a comorbid diagnosis of ADHD in a sample of individuals with ASD (with and without ADHD) and neurotypical controls. Method: Our sample consisted of 101 participants (11–19 years), including (a) 60 individuals with ASD (41 without ADHD, 19 with ADHD) and (b) 41 healthy controls matched for gender, age, and full-scale intelligence quotient (IQ). We examined vertex-wise estimates of CT based on structural T1-weighted magnetic resonance imaging scans. Initially, we examined our scientific question using an ANOVA, with ASD and ADHD as fixed-effect variables based on diagnostic labels, an ASD-by-ADHD interaction term, and gender, age, IQ, and mean CT as covariates. In a subsequent analysis, we explored whether differences in CT between ASD individuals with and without ADHD are parametrically modulated by the severity of ADHD symptoms. Here, we used Pearson's correlation coefficients to establish associations between ADHD symptomatology and neuroanatomical differences in CT. Results: Significant neuroanatomical differences for the main effect of ASD were observed in the left posterior cingulate cortex (PCC), where CT was increased in individuals with ASD. Further, ASD individuals with comorbid ADHD as compared with controls and ASD individuals without ADHD exhibited significantly increased CT in the right PCC and right parieto-occipital regions, while a decreased CT was observed in left fronto-central regions. This fronto-central cluster showed a significant negative correlation with ADHD symptom severity. We further observed significant differences between ASD individuals with and without ADHD in the left PCC, lingual gyrus, and precuneus. Discussion and Conclusion: Our study therefore suggests that the neuroanatomy of ASD is modulated by the co-occurrence of ADHD

symptoms, which should be accounted for in future studies examining the neuroanatomical underpinnings of ASD, and in studies attempting to stratify ASD individuals

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Korean J Pediatr. 2021;64:1-2.

HOW CAN PEDIATRICIANS TREAT NEURODEVELOPMENTAL DISORDERS.

Kim YH.

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Lancet Child Adolesc Health. 2021 Mar;5:201-09.

IDENTIFICATION OF GENETIC LOCI ASSOCIATED WITH NOCTURNAL ENURESIS: A GENOME-WIDE ASSOCIATION STUDY.

Jørgensen CS, Horsdal HT, Rajagopal VM, et al.

Background Nocturnal enuresis (bedwetting) is a common disorder affecting 10–16% of 7-year-old children globally. Nocturnal enuresis is highly heritable, but its genetic determinants remain unknown. We aimed to identify genetic variants associated with nocturnal enuresis and explore its genetic architecture and underlying biology.

Methods We did a genome-wide association study (GWAS) of nocturnal enuresis. Nocturnal enuresis cases were identified in iPSYCH2012, a large Danish population-based case cohort established to investigate mental disorders, on the basis of 10th revision of the International Statistical Classification of Diseases (ICD-10) diagnoses and redeemed desmopressin prescriptions in Danish registers. The GWAS was done in a genetically homogeneous sample of unrelated individuals using logistic regression with relevant covariates. All genome-wide significant variants were analysed for their association with nocturnal enuresis in an independent Icelandic sample from deCODE genetics. Standardised polygenic risk scores for attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder were constructed from summary statistics of large GWASs and analysed for association with nocturnal enuresis.

Findings The GWAS included 3882 nocturnal enuresis cases and 31 073 controls. We found two loci at chromosome 6 and chromosome 13 significantly associated with nocturnal enuresis. Six genetic variants at the two loci (five variants at chromosome 6q16.2 and one variant at chromosome 13q22.3) surpassed the threshold for genome-wide significance ($p<5 \times 10^{-8}$). There were two lead variants: rs9376454 (chromosome 6q16.2), with an odds ratio (OR) of 1·199 (95% CI 1·135–1·267; $p=9{\cdot}91 \times 10^{-11}$), and rs60721117 (chromosome 13q22.3), with an OR of 1·149 (1·095–1·205; $p=1{\cdot}21 \times 10^{-8}$). All associated variants in the chromosome 6 locus were replicated ($p<8 \times 10^{-3}$) in the independent Icelandic cohort of 5475 nocturnal enuresis cases and 303 996 controls, whereas the associated variant in the chromosome 13 locus showed nominal significant association (p=0·031). The percentage of nocturnal enuresis phenotypic variance explained by the common genetic variants was 23·9–30·4%. Polygenic risk for ADHD was associated with nocturnal enuresis (OR 1·06, 95% CI, 1·01–1·10; p=0·011). Among the potential nocturnal enuresis risk genes mapped, PRDM13 and EDNRB have biological functions associated with known pathophysiological mechanisms in nocturnal enuresis, and SIM1 regulates the formation of the hypothalamic neuroendocrine lineage that produces arginine vasopressin, a well known nocturnal enuresis drug target.

Interpretation This study shows that common genetic variants contribute considerably to nocturnal enuresis, and it identifies potential nocturnal enuresis risk genes with roles in sleep, urine production, and bladder function. Given that available treatments target these mechanisms, any of the identified genes and their functional gene networks are potential drug targets.

Funding The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Stanley Foundation

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Medicine (Baltimore). 2021 Mar;100:e25245.

KNOWLEDGE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AMONG THE GENERAL PUBLIC, PARENTS, AND PRIMARY SCHOOL TEACHERS.

See LC, Li HM, Chao KY, et al.

We compared the knowledge of attention-deficit hyperactivity disorder (ADHD) among the general public, parents of children with ADHD, and primary school teachers and identified factors associated with ADHD knowledge in each group, separately. Secondary data analysis was made on the pre-lecture data from those (122 from the general public, 64 parents of children with ADHD, and 515 primary school teachers) attending education lectures by the Department of Public Health, New Taipei City Government, Taiwan, 2014.ADHD onset age was least known in these 3 groups. Knowledge of ADHD was significantly better among teachers (test score, 75.3%) than among parents (65.5%) and the general public (59.2%). Among the general public, the test score significantly decreased with age and was worst in those who did not know their friends or relatives with ADHD. Among parents, service workers, and retired/unemployed knew significantly less about ADHD than housewife did. Among teachers, men knew significantly less than women; those who taught children with ADHD knew significantly more than those who did not. Primary school teachers knew more about ADHD than parents and the general public. Factors associated with ADHD knowledge varied among the 3 groups

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Nat Commun. 2021 Mar;12:1793.

PREDICTION OF STIMULUS-INDEPENDENT AND TASK-UNRELATED THOUGHT FROM FUNCTIONAL BRAIN NETWORKS.

Kucyi A, Esterman M, Capella J, et al.

Neural substrates of "mind wandering" have been widely reported, yet experiments have varied in their contexts and their definitions of this psychological phenomenon, limiting generalizability. We aimed to develop and test the generalizability, specificity, and clinical relevance of a functional brain network-based marker for a well-defined feature of mind wandering-stimulus-independent, task-unrelated thought (SITUT). Combining functional MRI (fMRI) with online experience sampling in healthy adults, we defined a connectome-wide model of inter-regional coupling-dominated by default-frontoparietal control subnetwork interactions-that predicted trial-by-trial SITUT fluctuations within novel individuals. Model predictions generalized in an independent sample ofÂ adults with attention-deficit/hyperactivity disorder (ADHD). In three additional resting-state fMRI studies (total nâ€‰=â€‰1115), including healthy individuals and individuals with ADHD, we demonstrated further prediction of SITUT (at modest effect sizes) defined using multiple trait-level and in-scanner measures. Our findings suggest that SITUT is represented within a common pattern of brain network interactions across time scales and contexts

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Ned Tijdschr Tandheelkd. 2021 Mar;128:150-53.

MENTAL DISORDERS IN A DENTAL PRACTICE. ADHD IN CHILDREN AND ADULTS .

Rodrigues PR.

ADHD is common in children as well as in adults. Dental problems are more common in these individuals as they can often be forgetful and impulsive. They are less careful with their teeth and are more at risk of damage. Medication can also have side effects such as a dry mouth which is not conducive to the teeth. A number of advice are given for easier and better dental care. Timing and dosage of medication is of great importance here. Dentists can have ADHD as well, which can be a handicap in their practice

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Neurocase. 2021.

INTERMEDIATE LENGTHS OF THE C9ORF72 HEXANUCLEOTIDE REPEAT EXPANSION MAY SYNERGISTICALLY CONTRIBUTE TO ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILD AND HIS FATHER: CASE REPORT.

Maj C, Chiarenza GA, Faraone SV, et al.

We have summarized the abstract section as follows: "We report a son and his father affected by Attention Deficit Hyperactivity Disorder (ADHD). They belonged to a larger cohort (116 ADHD children, 20 related parents, 77 controls) wholly genotyped forC9ORF72 expansion. Ten ADHD susceptibility genes were further investigated in the family. We revealed that son and father shared an intermediateC9ORF72 expansion and common variants inCDH23, ITGAE and MTRR. Bioinformatics highlighted aC9ORF72-MTRR interaction. This case-report underlines that in relatives with ADHD, carrying variants in ADHD susceptibility genes, the intermediateC9ORF72 repeats might have a potentially pathogenetic synergistic effect, supporting the multifactorial polygenic aetiopathogenetic profile of disease"

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Neuropsychiatr Dis Treat. 2021;17:379-88.

PREVALENCE OF ADHD AND AUTISM SPECTRUM DISORDER IN CHILDREN WITH HYPERMOBILITY SPECTRUM DISORDERS OR HYPERMOBILE EHLERS-DANLOS SYNDROME: A RETROSPECTIVE STUDY.

Kindgren E, Perez AQ, Knez R.

Introduction: Hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS) are both characterized by generalized hypermobility, in combination with pain, affected proprioception, and pronounced fatigue. Clinical observation indicates that behavioral problems, hyperactivity, and autistic traits are overrepresented in children with those conditions. The purpose of this retrospective study was to establish the prevalence of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) among children with HSD and hEDS treated in our clinic since 2012.

Subjects and Methods: Since Ehlers-Danlos syndrome (EDS) diagnostic criteria and international classification were changed in 2017, we equate the older diagnosis EDS hypermobility type with the newer hEDS and the older hypermobility syndrome with HSD. A registry search from the computerized medical record system found 201 children (88 boys, 113 girls) aged 6-18 years who were treated at our pediatrics department with the diagnoses HSD or EDS. All medical records (113 with HSD, 88 with EDS) were reviewed, and key symptoms such as fatigue and pain, as well as diagnosis of ADHD/ASD, were recorded.

Results: All EDS cases could be classified as hEDS. Of the entire study cohort, 16% had a verified ADHD diagnosis and a further 7% were undergoing ADHD diagnostic investiga-tion. Significantly more children with hEDS had ADHD compared to children with HSD (p=0.02). In the age group 15-16 years, 35% of those with hEDS had ADHD and, among those aged 17ΓÇô18 years, ADHD was present in 46%. Children with coexisting ADHD showed a significantly higher proportion of associated symptoms such as fatigue, sleep-problems, and urinary tract problems. ASD had been verified in 6% of the children. Of those with ASD, 92% had sleep problems.

Conclusion: This study shows a strong association between HSD or hEDS and ADHD or ASD. Therefore, children with HSD or hEDS may need to be routinely screened for neuropsychiatric symptoms

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Neuropsychiatr Dis Treat. 2021;17:493-502.

ASYMMETRY IN CORTICAL AND SUBCORTICAL STRUCTURES OF THE BRAIN IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Chen S, Guan L, Tang J, et al.

Background: Human cognitive and emotional functions are asymmetrical between the left and right hemispheres. In neuroimaging studies of attention-deficit/hyperactivity disorder (ADHD) patients, the absence of aberrant asymmetry might serve as a neuroanatomical marker of ADHD. However, few studies have estimated abnormalities in cortical and subcortical asymmetry in children and adolescents of different ADHD subtypes.

Methods: Data were from the results collected by the Peking University site in the ADHD-200 sample dataset, which comprised 31 eligible ADHD (20 inattentive ADHD (ADHD-I), 11 combined ADHD (ADHD-C)) and 31 matched typically developing (TD) individuals. The Asymmetry Indexes (AIs) in cortical thickness, cortical gray-matter volume and subcortical nucleus (SN) volume were calculated based on an automated surface-based approach. The differences in cortical thickness, cortical gray-matter volume, and SN volume AIs were evaluated among groups. We also analyzed the correlation between AIs and the severity of ADHD symptoms.
Results: Compared with the TD group, SN asymmetry in ADHD group did not reveal significant differences. Altered cortical asymmetry of different subtypes in ADHD groups was located in the orbitofrontal and anterior cingulate circuits, including the medial orbito-frontal, paracentral, pars triangularis, caudal anterior cingulate, isthmus cingulate, and superior frontal regions. In the comparisons, cortical gray-matter volume AIs were significantly different in the caudal anterior cingulate, isthmus cingulate, and superior frontal regions between ADHD-I and ADHD-C groups. There were significant correlations between the severity of ADHD symptoms and asymmetric measurements in medial orbitofrontal, para-central and isthmus cingulate regions.
Conclusion: These findings provide further evidence for the altered cortical morphological asymmetry in children and adolescents with ADHD, and these differences are associated (at least in part) with the severity of ADHD symptoms. Brain asymmetry could be an appro-priate precursor of morphological alterations in neurodevelopmental disorders

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NeuroRegulation. 2020;7:171-72.

NEUROFEEDBACK IN ADHD: RATING THE EVIDENCE, APA GUIDELINES, AND A MULTICENTER REPLICATION STUDY OF QEEG-INFORMED NEUROFEEDBACK.

Brown T.

Introduction. Precision medicine is uncovering ways to stratify treatment; for example, qEEG recently demonstrated the ability to inform the likelihood of Sertraline versus rTMS response in major depressive disorder (MDD; Wu et al., 2020). Within the neurofeedback field, qEEG assessment can uncover previously unknown sleep-related vigilance regulation difficulties impacting executive function in ADHD cases. The patient's EEG informs which standard neurofeedback protocol will be most effective. Thus, qEEG-informed neurofeedback allows personalized intervention, stratifying to the most likely effective protocol. To date, clinical effectiveness data for qEEG-informed neurofeedback have only been published in a small sample of 21 ADHD patients (Arns, Drinkenburg, & Kenemans, 2012). Recent research (Krepel et al., 2020, presented as the principal study) replicated this effectiveness in a new sample of 114 patients treated with qEEG-informed neurofeedback, from a large multicentric dataset and investigated potential predictors of neurofeedback response.
Methods (of principal study). A sample of 114 patients were included as a replication sample. Patients were assessed with ADHD-RS, PSQI, qEEG and ERPs, then assigned to a standard neurofeedback protocol (SMR, TBR, or SCP neurofeedback) in combination with coaching and sleep hygiene advice. The ADHD-RS and PSQI were assessed at baseline, every 10th session, and at outtake. Response was defined as ADHD-RS > 25% reduction (R25), > 50% reduction (R50), and remission. Predictive analyses were focused on predicting remission status.
Results (of principal study). In the current sample, response rates were 85% (R25), 70% (R50), and remission was 55%. Clinical effectiveness was not significantly different from the original 2012 sample. Nonremitters exhibited significantly higher baseline hyperactivity ratings. Women who remitted had significantly shorter P300 latencies and boys who remitted had significantly lower individual Alpha Peak Frequencies (iAPF).
Discussion. In the principal study, clinical effectiveness was replicated, suggesting it is possible to assign patients to a protocol based on their individual baseline qEEG to enhance signal-to-noise ratio. Furthermore, remitters had lower baseline hyperactivity scores. Likewise, female remitters had shorter P300 latencies, whereas boys who remitted have a lower iAPF. This latter finding is intriguing, since low iAPF was earlier found to predict nonresponse to MPH (Arns, Gunkelman, Breteler, & Spronk, 2008), thus offering opportunities to use this biomarker to stratify between treatments. The data suggests initial specificity in treatment allocation, yet further studies are needed to replicate the predictors of neurofeedback remission.

A comparison of clinical effectiveness versus RCT efficacy in neurofeedback will lead to a discussion of proposed APA guidelines for rating future evidence (Arns et al., 2020)

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Neurosci Biobehav Rev. 2021;125:582-91.

ADHD AND ACCIDENTS OVER THE LIFE SPAN – A SYSTEMATIC REVIEW.

Brunkhorst-Kanaan N, Libutzki B, Reif A, et al.

Studies have demonstrated an increased risk of accidents and injuries in children, adolescents and adults with attention-deficit/hyperactivity disorder (ADHD). However, little is known about how accident risk may alter over the lifespan. Additionally, it would be important to know if the most common types of accidents and injuries differ in ADHD patients over different age groups. Furthermore, there is increasing evidence of an ameliorating effect of ADHD medication on accident risk. Lastly, the underlying risk factors and causal mechanisms behind increased accident risk remain unclear. We therefore conducted a systematic review focusing on the above described research questions. Our results suggested that accident/injury type and overall risk changes in ADHD patients over the lifespan. ADHD medication appeared to be similarly effective at reducing accident risk in all age groups. However, studies with direct comparisons of accident/injuries and effects of medication at different age groups or in old age are still missing. Finally, comorbidities associated with ADHD such as substance abuse appear to further increase the accident/injury risk

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Nord J Psychiatry. 2021 Apr;75:214-23.

WHO PREDICT ADHD WITH BETTER DIAGNOSTIC ACCURACY?: PARENTS OR TEACHERS?

Tahillioglu A, Bilaç O, Uysal T, et al.

OBJECTIVE: The objectives of the study were to determine which parents or teachers predict attention-deficit/hyperactivity disorder (ADHD) better in children and adolescents, and to detect both diagnostical and symptomatological agreement levels across informant reports.

METHOD: A total of 417 cases aged 6-14 from a non-referred community sample were assessed by a semi-structured interview, parent- and teacher-rated ADHD Rating Scale-IV. Also, impairment criteria were taken into account to ensure the gold standard diagnosis for ADHD. The measures of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated in each categorical sample. Besides, the agreement between parent and teacher reports of ADHD was investigated.

RESULTS: Parents and teachers had similar diagnostic accuracy for predicting ADHD. Both parents and teachers predicted ADHD in similar accuracy in both boys and girls, separately. However, girls were found to be more predictable by both parents and teachers compared to boys. Parents with lower education levels had worse diagnostic accuracy than both parents with higher education levels and teachers. Low to moderate agreement and correlations between parent and teacher ADHD reports were detected.

CONCLUSION: In general, parents and teachers seem to predict ADHD in similar accuracy. Nevertheless, child gender and parental education level may alter the predictability power for ADHD. The findings can guide for clinicians that how to evaluate observation reports of parents and teachers to make accurate ADHD diagnosis in patients

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Nord J Psychiatry. 2021.

DIVERGENT MENTALIZATION TYPES IN ADOLESCENT BORDERLINE PERSONALITY DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Akca OF, Wall K, Sharp C.

Background: Attention deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) have several similarities and it is difficult to distinguish these disorders in adolescents. We aimed to identify the unique correlates of mentalization abilities that may distinguish these two disorders, and to investigate the

mentalization abilities of adolescents with ADHD, BPD and ADHD + BPD in an inpatient sample to determine the effect of co-morbidity on mentalization abilities.
Methods: We have explored the relationship between Child Eye Test (CET) scores, Movie for the Assessment of Social Cognition (MASC) subscales, and ADHD and BPD symptoms in adolescent inpatients. In addition, we compared ADHD, BPD and ADHD + BPD groups in terms of their mentalization abilities.
Results: Correct MASC scores were negatively associated with both ADHD and BPD symptoms in girls, and negatively associated with ADHD symptoms in boys. In addition, hypermentalization scores were associated with BPD symptoms in girls, and hypomentalization and no mentalization scores were associated with ADHD symptoms in girls. CET scores were negatively associated with ADHD symptoms in girls, but no relations with BPD were found. Group comparisons revealed no significant difference among groups.
Limitations: We included only inpatient sample without considering their medication condition, we did not compare the mentalization scores of the patient groups with healthy controls and we used self-report measures for several assessments.
Conclusion: Mentalization patterns in ADHD and BPD are distinct. ADHD may be related to hypomentalization, instead, BPD may be related to hypermentalization

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Noropsikiyatr Ars. 2020;57:283-89.

PSYCHIATRIC COMORBIDITY IN THE SUBTYPES OF ADHD IN CHILDREN AND ADOLESCENTS WITH ADHD ACCORDING TO DSM-IV.

Ipci M, et al.

Introduction: The prevalence rate of psychiatric comorbidity in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) was 60-80%. The objective of this study was to examine comorbid disorders associated with ADHD and the subtypes of ADHD in children and adolescents with the diagnosis of ADHD.
Method: The study included 326 children and adolescents aged between 8-15 years who were diagnosed with ADHD for the first time as a result of an interview by psychiatry, in a child adolescent psychiatry clinic in -¦zmir. Sociodemographic form, Turgay DSM-IV Disruptive Behavior Disorders Rating Scale and Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version were used to assess psychiatric comorbidity.
Results: The comorbidities accompanied ADHD were disruptive behavior disorder (28.8%), depressive disorder (13.2%), obsessive-compulsive disorder (9.5%) and anxiety disorder (6.1%). When the subtypes of ADHD were assessed according to psychiatric comorbidity, oppositional defiant disorder and conduct disorder were frequently seen with ADHD combined type, whereas anxiety disorder was more frequent with ADHD inattentive type.
Discussion: Comorbidity in ADHD Combined type increases the severity of disease, delays treatment response and exacerbates prognosis. Therefore, it is very important to determine which psychiatric diagnosis accompany with ADHD

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Noropsikiyatr Ars. 2020;57:274-79.

HIGH KEAP1, NRF2 AND LOW HO-1 SERUM LEVELS IN CHILDREN WITH AUTISM.

Ayaydin H, Akaltun, Koyuncu, et al.

Introduction: The purpose of our study was to investigate heme oxygenase-1 (HO-1), nuclear factor erythroid-2-related factor 2 (NRF2), and kelch-like ECH-associated protein 1 (KEAP1) levels in children with autism spectrum disorder (ASD) and to reveal their association with the severity of autism.
Methods: This study measured serum HO-1, KEAP1, and NRF2 levels in 43 patients with ASD (aged 3-12 years) and in 41 age and gender-matched healthy controls. ASD severity was rated using the Childhood Autism Rating Scale (CARS). HO-1, KEAP1, and NRF2 levels were determined in the biochemistry laboratory using the ELISA technique.

Results: HO-1 levels were significantly lower in patients aged 3-12 years compared to controls aged 3-12, while KEAP1 and NRF2 levels were significantly higher (p=0.020, p<0.001, and p=0.017, respectively). No correlation was determined between ASD severity on the basis of total CARS scores and HO-1, KEAP1 or NRF2 (p>0.05).
Conclusion: This study suggests that oxidative stress is higher in children with ASD and that HO-1 levels are insufficient to achieve oxidative balance

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Orphanet Journal of Rare Diseases. 2021;16.

IMPACT OF PEDIATRIC HYPOPHOSPHATASIA ON BEHAVIORAL HEALTH AND QUALITY OF LIFE.

Pierpont EI, Simmons JH, Spurlock KJ, et al.

Background: Hypophosphatasia (HPP) is a rare genetic disorder caused by loss-of-function mutations in the ALPL gene encoding tissue nonspecific alkaline phosphatase. It is characterized by defective bone mineralization associated with low alkaline phosphatase activity. Clinical features of pediatric HPP are highly variable, and can include premature loss of teeth, musculoskeletal problems, and impaired mobility. The effects of pediatric HPP on sleep, mood, regulation of attention and behavior, and other aspects of behavioral health have not been comprehensively studied.
Methods: Parents of 30 children with HPP (14 females, 16 males) between the ages of 3 and 16-áyears (mean age = 8.0 years) enrolled in this cross-sectional survey-based study. Molecular genetic and biochemical testing as well as clinical records were reviewed to verify diagnosis of HPP. The cohort included 15 patients with a more clinically severe presentation of HPP who had received treatment with enzyme replacement therapy (asfotase alfa) and 15 children with less severe HPP who were treatment-naïve. Parents provided information regarding psychopathological comorbidity, emotional and behavioral well-being, and quality of life.
Results: Clinically significant behavioral health challenges were evident in 67% of children with HPP. The most common behavioral findings included sleep disturbance and symptoms of attention deficit hyperactivity disorder (ADHD), each of which were observed 50% of individuals. Sleep disturbance, pain interference, poor behavioral regulation, and mood/anxiety symptoms were associated with reduced physical and psychosocial quality of life. Behavioral concerns were evident among children with HPP receiving asfotase alfa treatment as well as among children with clinically less severe disease who had not initiated therapy. Although most children in the cohort (77%) had age-typical development of adaptive skills, emotional and behavioral challenges were associated with weaker adaptive function.
Conclusions: Children with HPP are at increased risk for ADHD symptoms and other behavioral health challenges. There is likely an under-recognition of these findings in clinical practice

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Pediatr Diabetes. 2021.

DUAL DIAGNOSIS OF TYPE 1 DIABETES MELLITUS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mazor-Aronovitch K, Pinhas-Hamiel O, Pivko-Levy D, et al.

Background: Data regarding glycemic control in children and adolescents with a dual diagnosis of type 1 diabetes mellitus (T1DM) and attention-deficit/hyperactivity disorder (ADHD) are limited.
Objective: To compare various aspects of diabetes control among youth with T1DM, between those with and without ADHD.
Methods: In this cross-sectional study of youth with T1DM, 39 had ADHD (mean age 14.1 -¦ 2.8 years) and 82 did not (control group, mean age 12.6 -¦ 3.3 years). Health-related quality of life was assessed by a Diabetes Quality of Life (DQOL) questionnaire submitted to their parents. Glycemic data were downloaded from glucometers, pumps, and continuous glucose monitoring systems. HbA1c levels, hospitalizations, and severe hypoglycemic and diabetes ketoacidosis events were retrieved from the medical files.
Results: Compared to the control group mean HbA1c level of the ADHD group was higher: 8.3 -¦ 1.1% versus 7.7 -¦ 1.0% (p = 0.005) and the percent of time that glucose level was in the target range (70-180 mg/dl) was lower: 48 -¦ 17% versus 59 -¦ 14% (p = 0.006). Mean glucose and glucose variability were higher in the ADHD

group. Youth with ADHD who were not pharmacologically treated had worse HbA1c and more hospitalizations than those who were treated. DQOL did not differ between the control group, the treated ADHD group, and the untreated ADHD-Group.
Conclusions: Dual diagnosis of T1DM and ADHD during childhood leads to worse diabetes control, which is more pronounced in the context of untreated ADHD. Healthcare providers should be aware of the difficulties facing youth with T1DM and ADHD in coping with the current intensive treatment of diabetes

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Pediatrics. 2021;147.

MENTAL HEALTH DISORDERS IN CHILDREN WITH CONGENITAL HEART DISEASE.

Gonzalez VJ, Kimbro RT, Cutitta KE, et al.

BACKGROUND: Data on anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD) are lacking for youth with congenital heart disease (CHD), particularly those with simple CHD. This study aims to characterize these disorders in youth with CHD compared to those without CHD.
METHODS: A comparative cross-sectional study was conducted by using the electronic medical records of a large tertiary care hospital between 2011 and 2016. Inclusion criteria were youth aged 4 to 17 years with.1 hospitalization or emergency department visits. Exclusion criteria were patients with arrhythmias or treatment with clonidine and/or benzodiazepines. The primary predictor variable was CHD type: simple, complex nonsingle ventricle, and complex single ventricle. The primary outcome variable was a diagnosis and/or medication for anxiety and/or depression or ADHD. Data were analyzed by using logistic regression (Stata v15; Stata Corp, College Station, TX).
RESULTS: We identified 118 785 patients, 1164 with CHD. Overall, 18.2% (n = 212) of patients with CHD had a diagnosis or medication for anxiety or depression, compared with 5.2% (n = 6088) of those without CHD. All youth with CHD had significantly higher odds of anxiety and/ or depression or ADHD. Children aged 4 to 9 years with simple CHD had 5 times higher odds (odds ratio: 5.23; 95% confidence interval: 3.87-7.07) and those with complex single ventricle CHD had 7 times higher odds (odds ratio: 7.46; 95% confidence interval: 3.70-15.07) of diagnosis or treatment for anxiety and/or depression. Minority and uninsured youth were significantly less likely to be diagnosed or treated for anxiety and/or depression or ADHD, regardless of disease severity.
CONCLUSIONS: Youth with CHD of all severities have significantly higher odds of anxiety and/or depression and ADHD compared to those without CHD. Screening for these conditions should be considered in all patients with CHD

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Pilot and Feasibility Studies. 2021;7.

OPTIMISING MEDICATION MANAGEMENT IN CHILDREN AND YOUNG PEOPLE WITH ADHD USING A COMPUTERISED TEST (QBTEST): A FEASIBILITY RANDOMISED CONTROLLED TRIAL.

Williams L, Hall CL, Brown S, et al.

Background: Medication for attention deficit hyperactivity disorder (ADHD) should be closely monitored to ensure optimisation. There is growing interest in using computerised assessments of ADHD symptoms to support medication monitoring. The aim of this study was to assess the feasibility and acceptability of a randomised controlled trial (RCT) to evaluate the efficacy of one such computerised assessment, the Quantified Behavior (Qb) Test, as part of medication management for ADHD.
Methods: This feasibility multi-site RCT conducted in child and adolescent mental health and community paediatric settings recruited participants aged 6-15 years diagnosed with ADHD starting stimulant medication. Participants were randomised into one of two arms: experimental (QbTest protocol) where participants completed a QbTest at baseline and two follow-up QbTests on medication (2-4 weeks and 8-10 weeks later) and control where participants received treatment as usual, including at least two follow-up consultations. Measures of parent, teacher, and clinician-rated symptoms and global functioning were completed at each time point. Clinicians recorded treatment decision-making and health economic measures

were obtained. Data were analysed using multi-level modelling and participants (children and parents) and clinicians were interviewed about their experiences, resulting data were thematically analysed.
Results: Forty-four children and young people were randomised. Completion of study outcome measures by care-givers and teachers ranged from 52 to 78% at baseline to 47-65% at follow-up. Participants reported the questionnaires to be useful to complete. SNAP-IV inattention scores showed greater reduction in the intervention than the control group (5.85, 95% CI 10.33, 1.36,). Engagement with the intervention ranged from 100% at baseline, to 78% follow-up 1 and 57% follow-up 2. However, only 37% of QbTests were conducted in the correct time period. Interview data highlighted that the objectivity of the QbTest was appreciated by clinicians and parents. Clinicians commented that the additional time and resources required meant that it is not feasible to use QbTest for all cases.
Conclusion: The trial design and protocol appear to be feasible and acceptable but could be improved by modifying QbTest time periods and the method of data collection. With these changes, the protocol may be appropriate for a full trial. Adding QbTest may improve symptom outcome as measured by SNAP-IV.
Trial registration: ClinicalTrials.gov, NCT03368573, prospectively registered, 11th December 2017, and ISRCTN, ISRCTN69461593, retrospectively registered, 10th April 2018

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2021;110.
SEX-DEPENDENT COMPLEX ASSOCIATION OF TPH2 WITH MULTIPLE DIMENSIONS OF ADHD.
Fageera W, Sengupta SM, Fortier M+, et al.
Background: Tryptophan hydroxylase 2 (TPH2) is a key enzyme in the biosynthesis of serotonin in the brain. This study aims to investigate the role of a functional variant in TPH2 (rs17110747) in the pathophysiology of ADHD. This variant has been implicated in mood disorders in recent meta-analysis. This study uses a comprehensive approach that combines association testing and pharmaco-dynamic evaluation of behaviour, in a large sample of children with ADHD (n = 570).
Methods: The association between various ADHD relevant traits and rs17110747 was analyzed using family-based association tests (FBAT). Children were assessed by parents, teachers and research staff under three experimental conditions (EC): baseline, placebo, and methylphenidate using a double-blind placebo-controlled crossover trial.
Outcomes: FBAT analysis conducted in a sample stratified based on sex of the proband, showed that there was a highly significant overtransmission of the G allele from parents to affected girls. In addition, significant association with several behavioral and cognitive dimensions of ADHD was observed only when the proband was female. Further, girls with the G/G genotype (rs17110747) had greater response to placebo when evaluated by parents.
Interpretation: These results suggest that there may be a complex association of TPH2 in the etiology of ADHD, with a sex-specific effect

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Psychiatry Res Neuroimaging. 2021;311.
DISCREPANCIES OF POLYGENIC EFFECTS ON SYMPTOM DIMENSIONS BETWEEN ADOLESCENTS AND ADULTS WITH ADHD.
Jiang W, Rootes-Murdy K, Duan K, et al.
A significant proportion of individuals with attention-deficit/hyperactivity disorder (ADHD) show persistence into adulthood. The genetic and neural correlates of ADHD in adolescents versus adults remain poorly characterized. We investigated ADHD polygenic risk score (PRS) in relation to previously identified gray matter (GM) patterns, neurocognitive, and symptom findings in the same ADHD sample (462 adolescents & 422 adults from the NeuroIMAGE and IMpACT cohorts). Significant effects of ADHD PRS were found on hyperactivity and impulsivity symptoms in adolescents, hyperactivity symptom in adults, but not GM volume

components. A distinct PRS effect between adolescents and adults on individual ADHD symptoms is suggested

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Psychiatry Res. 2021;299.

CAN POLYGENIC RISK SCORES HELP IDENTIFY PEDIATRIC BIPOLAR SPECTRUM AND RELATED DISORDERS?: A SYSTEMATIC REVIEW.

Biederman J, Green A, DiSalvo M, et al.

The genetic basis of mood disorders can, theoretically, provide diagnostic information in scenarios of clinical uncertainty. Therefore, we examined the available body of knowledge on the association between polygenic risk scores for bipolar disorder (BP-PRSs) and pediatric bipolar spectrum and related disorders. We performed a literature search through PubMed in March of 2020. The following variables were extracted from relevant studies: population age, study sample size, source of polygenic risk scores, source of data, the primary goal of the study, the assessments used during the course of the study, and the main findings/outcomes of each study. BP-PRSs were associated with deficits in executive functioning and the diagnosis of attention deficit/hyperactivity disorder (ADHD). Three studies included in our analysis directly compared major depressive disorder (MDD)-PRSs to BP-PRSs in youth. Results showed that MDD-PRSs, and not BP-PRSs, were associated with ADHD symptoms, internalizing problems, and social problems. ADHD-PRSs were associated with conduct problems, depressive symptomatology, and externalizing disorders symptoms. Findings revealed that ADHD-PRSs were more clearly associated with emotional reactivity, emotional dysregulation, and irritability-frequent correlates of pediatric BP disorder. These findings suggest that ADHD-PRSs may have an important contribution to the development of mood related problems in youth

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Psychol Assess. 2021 Mar.

MULTIPLE INFORMANT AVERAGE INTEGRATION OF ADHD SYMPTOM RATINGS PREDICTIVE OF CONCURRENT AND LONGITUDINAL IMPAIRMENT.

Martel MM, Eng AG, Bansal PS, et al.

To date, there remains no consensus about the best evidence-based method for integrating multiple informant data in the diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD). Several approaches exist, including the psychometrically sound approach of averaging scores, as well as the use of 'OR' and 'AND' algorithms, which are still commonly used in research. The current study tested these major integration methods in their concurrent and longitudinal prediction of clinician-rated impairment, teacher-rated academic, and parent- and self-rated social skill ratings in children overrecruited for ADHD across a 6-year span from childhood to adolescence. The sample included a total of 800 children, 480 with ADHD, ages 6 to 13, who completed a 'gold standard' assessment of ADHD and associated impairment. Overall, the 'OR,' 'AND,' and average integration approaches showed significantly high interrelations with one another (r range from .78 to .96) and were all significantly and strongly related to impairment measures concurrently and longitudinally. Multivariate regressions demonstrated that the average integration approach concurrently and longitudinally out predicted the other two approaches. Results demonstrated that the average approach slightly outperformed the other two in its prediction of concurrent and longitudinal clinician-rated impairment, teacher-rated academic skills, and parent- and self-rated child social skills across childhood and adolescence. Evidence-based assessment integration of parent and teacher ratings of ADHD in childhood might best utilize an averaging approach, as it is most related to later impairment ratings, particularly if such findings are replicated by other groups. (PsycInfo Database Record (c) 2021 APA, all rights reserved)

Public Significance Statement: An average approach to integrating parent and teacher ratings of ADHD slightly outperforms other, more complicated integration approaches in prediction of later clinician-rated impairment, teacher-rated academic skills, and parent- and self-rated social skills. Therefore, average

integration of ADHD symptom ratings may be the best and easiest integration approach for use in clinical practice

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Psychol Med. 2021 Jan;51:102-11.

THE POSITIVE END OF THE POLYGENIC SCORE DISTRIBUTION FOR ADHD: A LOW RISK OR A PROTECTIVE FACTOR?
Li JJ.

Background: Polygenic scores (PGS) are widely used to characterize genetic liability for heritable mental disorders, including attention-deficit/hyperactivity disorder (ADHD). However, little is known about the effects of a low burden of genetic liability for ADHD, including whether this functions as a low risk or protective factor for ADHD and related functional outcomes in later life. The current study examines the association of low ADHD PGS and functional outcomes in adulthood.
Methods: Participants were from Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health) (N = 7088; mean age = 29, S.D. = 1.74). ADHD PGS was computed from an existing genome-wide association study, and adult functional outcomes, including cognition, educational attainment, mental health, and physical health were assessed during in-home interviews.
Results: Individuals at the lowest end of the ADHD PGS distribution (i.e. lowest 20th percentile) had the lowest probabilities of ADHD, exhibiting a 17–19% reduction in risk for ADHD relative to the observed 8.3% prevalence rate of ADHD in Add Health. Furthermore, individuals with low ADHD PGS had higher cognitive performance, greater levels of educational attainment, and lower BMI relative to individuals representing the rest of the ADHD PGS distribution, including those who were in the medium and high-PGS groups.
Conclusions: Findings indicate that psychiatric PGS likely capture far more than just the risk and the absence of risk for a psychiatric outcome; where one lies along the PGS distribution may predict diverging functional consequences, for better and for worse

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Quality of Life Research. 2019;29:S183.

YOGA TRAINING AS AN EFFECTIVE APPROACH FOR IMPROVING THE EXECUTIVE ABILITIES IN CHILDREN WITH ADHD.
Mirzajonova E, Kiselev S.

Aims: It is known that children with attention deficit/hyperactivity disorder (ADHD) have deficit in executive abilities. It is very important to develop trainings for children with ADHD to improve their executive abilities and attention. The goal of this study was to reveal effect of yoga training on executive abilities in 8-9 years of age children with this disorder. We compared the efficacy of two methods of training (yoga training vs. conventional motor exercises) in a randomized controlled pilot study.
Methods: 18 boys with ADHD at the age of 8-9 years (M = 8.41 years, SD = 0.95) were included and randomly assigned to treatment conditions according to a 2 9 2 crossover design. Both groups of children have participated in 12 weeks of training (body-oriented training vs. conventional motor exercises). A total of 36 training sessions lasting 30 min were performed. Yoga training included body-oriented activity and breathing exercises. To assess the executive functions we used 3 subtests from NEPSY (Auditory Attention and Response Set, Visual Attention, Statue). Effects of training were analyzed by means of an ANOVA for repeated measurements. We have also performed qualitative neuropsychological assessment based on Luria's syndrome analysis.
Results: The ANOVA has revealed (p\.05) that for all subtests (Auditory Attention and Response Set, Visual Attention, Statue) the yoga training was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.42-0.86). Besides, we have found a decrease in distractibility in children from experiment group. In particular, these children showed a decrease in sensitivity to various distracting sounds and environmental events. Luria's syndrome analysis has revealed the improving in third functional unit of the brain which is responsible for voluntary attention and executive abilities according to Luria's approach [Luria, 1973].
Conclusion: The findings from this pilot study suggest that yoga training have positive effect on executive abilities in children with ADHD. It influences predominantly the selective and sustained attention, inhibition,

monitoring, and self-regulation. However, it is necessary to do further research for revealing the impact of yoga exercises on the prevention and treatment of attention deficit/hyperactivity disorder in children

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Res Autism Spectr Disord. 2021;83.

PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER: A META-ANALYSIS.

Rong Y, Yang CJ, Jin Y, et al.

Background: Comorbidity with attention-deficit/hyperactivity disorder (ADHD) is very common in autism spectrum disorder (ASD), worsening the developmental trajectory of ASD. The reported rates of ADHD in ASD vary widely. However, no meta-analysis has been conducted specifically to assess both the current and lifetime prevalence of ADHD in ASD. This study aims to fill in this gap.
Method: We searched the Web of Science, PubMed, PsycINFO, CINAHL, and Embase databases for eligible articles published between January 1, 2000, and September 5, 2020. The risk of bias tool was used to assess the studies quality. Overall pooled estimates of the current and lifetime prevalence of ADHD in ASD were obtained using random-effects models. Study heterogeneity was examined by Q and I2 statistics.
Findings: A total of 63 articles were eventually included, of which 56 studies reported the current prevalence, and 13 studies reported the lifetime prevalence. The results revealed that the pooled current and lifetime prevalence rates of ADHD among ASD were 38.5 % (95 % CI 34.0-43.2) and 40.2 % (95 % CI 34.9-45.7), respectively. Our study also confirmed that age, intellectual disability, recruitment settings, and diagnostic criteria significantly influenced the current prevalence of ADHD in ASD.
Conclusion: ASD has considerable high current or lifetime prevalence rates of co-occurring ADHD. The findings demonstrate that clinicians should consider the high prevalence of ADHD in ASD and especially stay alert to possible ADHD diagnoses in school-age children and adolescents with ASD. Medical institutions should improve the assessment and tracking system of ADHD comorbidity in ASD and maximize the diagnostic accuracy for better treatment

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Res Dev Disabil. 2021;112.

CHARACTERISTICS OF SLEEP SPINDLES IN SCHOOL-AGED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ruiz-Herrera N, Cellini N, Prehn-Kristensen A, et al.

Objective: Attention deficit/hyperactivity disorder (ADHD) is a complex disorder, characterized by different presentations with distinct cognitive and neurobiological characterizations. Here we aimed to investigate whether sleep spindle activity, which has been associated with brain maturation, may be a potential biomarker able to differentiate ADHD presentations in school-aged children (7ΓÇô11 years).
Method: Spindle characteristics were extracted from overnight polysomnography in 74 children (27 ADHD-Inattentive [IQ = 96.04], 25 ADHD-hyperactive/impulsive [IQ = 98.9], and 22 ADHD-combined [IQ = 96.1]). We obtained data of the frontal (Fz) and parietal (Pz) derivations using a validated spindle detection algorithm.
Results: Children with ADHD showed a higher number and density of slow compared to fast spindles which were more frequent in frontal area. No differences were observed among ADHD presentations for any spindle characteristics. Spindle frequency and density increased with age, indicating an age-dependent maturation of different sleep spindles. However, no associations between IQ and spindle characteristics were observed.
Conclusions: In children with ADHD the spindle characteristics evolve with age but sleep spindle activity does not seem to be a valid biomarker of ADHD phenotypes or general cognitive ability

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Res Dev Disabil. 2021;112.

SENSORY MODULATION AND NEGATIVE AFFECT IN CHILDREN AT FAMILIAL RISK OF ADHD.

Keating J, Bramham J, Downes M.

Background/aims: Sensory modulation difficulties are commonly reported in patients with ADHD, however there has been little focus on the development of these difficulties in young children at a higher risk of later ADHD diagnosis. This study investigated whether children with a familial history of ADHD show greater sensory modulation difficulties. We also explored whether sensory modulation was linked to negative affectivity, which has been highlighted as a potential early marker of ADHD.

Methods: Parents of children under 6 years with a family history of ADHD (n = 65) and no family history (n = 122) completed questionnaires on sensory modulation and temperament.

Results: Children from families with ADHD were reported to display extreme patterns of hyperresponsiveness and hyporesponsiveness, relative to controls. No differences emerged for the sensory seeking domain. Some children within the high-risk group reported high scores across all three sensory modulation patterns. Regression analysis revealed that hyperresponsiveness predicted higher levels of negative affect.

Conclusions/implications: This study is the first to report greater sensory modulation difficulties in children at familial risk of ADHD. Future research should establish whether children with sensory modulation and temperament difficulties in early childhood are more vulnerable to developing ADHD

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Res Dev Disabil. 2021;113.

CLINICAL CHARACTERISTICS OF CHILDREN WITH ASD AND COMORBID ADHD: ASSOCIATION WITH SOCIAL IMPAIRMENT AND EXTERNALIZING AND INTERNALIZING BEHAVIOURS.

Dellapiazza F, Audras-Torrent L, Michelon C, et al.

Background: Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are frequently occurring conditions that are often associated (ASD + ADHD). However, there are few comparative studies concerning the clinical presentation in patients formally diagnosed with both ASD and ADHD. Here, we aimed to 1) compare social impairment and externalizing/internalizing behavioural problems across four groups of children: ASD + ADHD, ASD alone, ADHD alone, and typical development and 2) examine their bidirectional relationship with ASD and/or ADHD symptoms.

Methods: This study included 186 participants from 6 to 12 years of age: single ASD (n = 98), ASD + ADHD (n = 29), single ADHD (n = 28), and TD (n = 31).

Results: The results showed that children in the ASD + ADHD and single ASD groups had a higher level of social impairment than those in the single ADHD group. In addition, children in the single ADHD group presented a greater attention deficit than those in the single ASD group. Externalizing /internalizing behaviours were more frequent in all groups with neuro-developmental disorders than in typical development. In addition, externalizing behavioural problems were related to ADHD severity in the ASD + ADHD and single ADHD groups, whereas internalizing behaviours were related to ASD severity.

Conclusions: These findings highlight the specific needs of children who have both ASD and ADHD and underscore the necessity of individualizing their interventions

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Research on Child and Adolescent Psychopathology. 2021 Mar;49:311-23.

EARLY DEVELOPMENT OF COMORBIDITY BETWEEN SYMPTOMS OF ADHD AND ANXIETY.

Gair SL, Brown HR, Kang S, et al.

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that shares a high comorbidity with anxiety disorders. However, the early development of comorbid ADHD and anxiety symptoms is not well-understood. In this study, the bidirectional relation between ADHD and anxiety symptoms was examined by testing two models of the development of ADHD and anxiety comorbidity: an anxiety effects model, which posits that anxiety symptoms contribute to the development of ADHD symptoms, and an ADHD effects model, which posits that ADHD symptoms contribute to the development of anxiety symptoms. Within the ADHD effects model, parenting practices were tested as mediators of this relation.

Participants included children who were 3 years old at baseline (n = 258) and their caregivers who reported on their children's ADHD and anxiety symptoms annually for 3 years. The bidirectional relation of parent-reported anxiety and ADHD symptoms was tested using a series of cross-lagged models. Results indicated that ADHD symptoms predicted later anxiety symptoms, but anxiety symptoms did not predict later ADHD symptoms. Parenting practices did not mediate the relation between ADHD and anxiety symptoms within the ADHD effects model. These findings suggest that ADHD-anxiety comorbidity may develop in part because early symptoms of ADHD contribute to the development of anxiety symptoms; future research should be conducted to elucidate the mechanisms of this relation

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Revue Neurologique. 2021.

THE ROLE OF NEUROPSYCHOLOGICAL ASSESSMENT IN ADULTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDERS.

Planton M, Lemesle B, Cousineau M, et al.

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity and/or impulsivity. While ADHD was initially recognized as a childhood syndrome, scientific evidence accumulated to indicate that a significant proportion of ADHD children continue to experience symptoms of ADHD in adulthood. Moreover, the question of ADHD diagnosis can arise in adult patients who were not diagnosed in childhood. Currently, the diagnosis of ADHD in adulthood is based on the revised criteria described for children. However, their application for adults may be difficult for many reasons including compensation and comorbid disorders. To date, no clinical, neuropsychological, biological or imaging marker is available for the diagnosis of ADHD. Considering that ADHD is based on a neuropsychological model, in this article we will examine the usefulness of neuropsychological testing in the diagnosis in adults. We will first present diagnostic criteria of ADHD and the limits of their application in adults. We will then detail the neuropsychological data available in adult ADHD and the French and international clinical recommendations for neuropsychological assessment. Finally, we will explore the predictive value of neuropsychological scores in the diagnosis of ADHD and discuss key methodological points and perspectives for clinical research

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Spec Care Dentist. 2021 Mar;41:178-86.

ORAL HEALTH STATUS AND ORAL HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND OPPOSITIONAL DEFIANT DISORDER.

Jamali Z, Ghaffari P, Aminabadi NA, et al.

Aims: Oral diseases can affect various aspects of life in patients with attention deficit hyperactivity disorder/oppositional defiant disorder (ADHD/ODD). This study aimed to assess the oral health status and oral health-related quality of life (OHRQOL) in ADHD/ODD children.

Methods: Forty ADHD/ODD and 80 control children aged 3-7 years old were included in the study. Gingival index (GI), dmft score, and the pediatric oral health-related quality of life (POQL) questionnaire were used to determine the oral health status and OHRQOL, respectively.

Results: The mean dmft and GI were significantly higher in the ADHD/ODD group than the control group (P = .002 and P = .001). In the ADHD/ODD children, the total score of OHRQOL and the mean scores of the emotional, physical, role, and social domains were lower than that in the control group (P = .0004, P = .027, P = .002, P = .014, and P = .043, respectively). Poisson's regression showed that there was a significant relationship between OHRQOL and dmft scores (P-value < .001). However, the association between GI and OHRQOL scores was not significant.

Conclusion: Higher dmft and GI scores were found in children with ADHD/ODD than the control children. A lower POQL score was detected in ADHD/ODD patients, which translates to a better level of OHRQOL.

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Spiritual Clin Pract (Wash D C). 2021 Mar;8:51-64.

EFFECTIVENESS OF VEDIC CHANTING ON COGNITIVE IMPAIRMENTS IN AN ADHD CHILD: A CASE STUDY.

VK K, Chaube N.

The present study aimed to find out the effectiveness of Vedic chanting in the cognitive impairments of 6 years old Attention Deficit Hyperactivity Disorder (ADHD) child. Psychometric and neuropsychological measures were used to assess cognitive impairments. Gayatri mantra chanting along with customized computerized training as a controlled condition was used for intervention to see improvements in cognitive functioning. Results showed better effectiveness of Gayatri mantra in cognitive functioning such as sustained and divided attention, concentration, short-term verbal and working memory, overactivity, and aggression as compared to computerized training. It is concluded that the Gayatri mantra as a nonpharmacological intervention may improve cognitive functioning in ADHD children and produce better results

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Transl Psychiatry. 2021;11.

TASK-GENERIC AND TASK-SPECIFIC CONNECTIVITY MODULATIONS IN THE ADHD BRAIN: AN INTEGRATED ANALYSIS ACROSS MULTIPLE TASKS.

Chauvin RJ, Buitelaar JK, Sprooten E, et al.

Attention-deficit/hyperactivity disorder (ADHD) is associated with altered functioning in multiple cognitive domains and neural networks. This paper offers an overarching biological perspective across these. We applied a novel strategy that extracts functional connectivity modulations in the brain across one (Psingle), two (Pmix) or three (Pall) cognitive tasks and compared the pattern of modulations between participants with ADHD (n-89), unaffected siblings (n = 93) and controls (n = 84; total N = 266; age range = 8-27 years). Participants with ADHD had significantly fewer Pall connections (modulated regardless of task), but significantly more task-specific (Psingle) connectivity modulations than the other groups. The amplitude of these Psingle modulations was significantly higher in ADHD. Unaffected siblings showed a similar degree of Pall connectivity modulation as controls but a similar degree of Psingle connectivity modulation as ADHD probands. Pall connections were strongly reproducible at the individual level in controls, but showed marked heterogeneity in both participants with ADHD and unaffected siblings. The pattern of reduced task-generic and increased task-specific connectivity modulations in ADHD may be interpreted as reflecting a less efficient functional brain architecture due to a reduction in the ability to generalise processing pathways across multiple cognitive domains. The higher amplitude of unique task-specific connectivity modulations in ADHD may index a more effortful coping strategy. Unaffected siblings displayed a task connectivity profile in between that of controls and ADHD probands, supporting an endophenotype view. Our approach provides a new perspective on the core neural underpinnings of ADHD

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Transl Psychiatry. 2021;11.

STRUCTURAL BRAIN NETWORK TOPOLOGY UNDERPINNING ADHD AND RESPONSE TO METHYLPHENIDATE TREATMENT.

Griffiths KR, Braund TA, Kohn MR, et al.

Behavioural disturbances in attention deficit hyperactivity disorder (ADHD) are thought to be due to dysfunction of spatially distributed, interconnected neural systems. While there is a fast-growing literature on functional dysconnectivity in ADHD, far less is known about the structural architecture underpinning these disturbances and how it may contribute to ADHD symptomology and treatment prognosis. We applied graph theoretical analyses on diffusion MRI tractography data to produce quantitative measures of global network organisation and local efficiency of network nodes. Support vector machines (SVMs) were used for comparison of multivariate graph measures of 37 children and adolescents with ADHD relative to 26 age and gender matched typically developing children (TDC). We also explored associations between graph measures and functionally-relevant outcomes such as symptom severity and prediction of methylphenidate (MPH) treatment response. We found that multivariate patterns of reduced local efficiency, predominantly in subcortical regions (SC), were able to distinguish between ADHD and TDC groups with 76% accuracy. For

treatment prognosis, higher global efficiency, higher local efficiency of the right supramarginal gyrus and multivariate patterns of increased local efficiency across multiple networks at baseline also predicted greater symptom reduction after 6 weeks of MPH treatment. Our findings demonstrate that graph measures of structural topology provide valuable diagnostic and prognostic markers of ADHD, which may aid in mechanistic understanding of this complex disorder

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Transl Psychiatry. 2021;11.

MULTIMETHOD INVESTIGATION OF THE NEUROBIOLOGICAL BASIS OF ADHD SYMPTOMATOLOGY IN CHILDREN AGED 9-10: BASELINE DATA FROM THE ABCD STUDY.

Owens MM, Allgaier N, Hahn S, et al.

Attention deficit/hyperactivity disorder is associated with numerous neurocognitive deficits, including poor working memory and difficulty inhibiting undesirable behaviors that cause academic and behavioral problems in children. Prior work has attempted to determine how these differences are instantiated in the structure and function of the brain, but much of that work has been done in small samples, focused on older adolescents or adults, and used statistical approaches that were not robust to model overfitting. The current study used cross-validated elastic net regression to predict a continuous measure of ADHD symptomatology using brain morphometry and activation during tasks of working memory, inhibitory control, and reward processing, with separate models for each MRI measure. The best model using activation during the working memory task to predict ADHD symptomatology had an out-of-sample R2 = 2% and was robust to residualizing the effects of age, sex, race, parental income and education, handedness, pubertal status, and internalizing symptoms from ADHD symptomatology. This model used reduced activation in task positive regions and reduced deactivation in task negative regions to predict ADHD symptomatology. The best model with morphometry alone predicted ADHD symptomatology with an R2 = 1% but this effect dissipated when including covariates. The inhibitory control and reward tasks did not yield generalizable models. In summary, these analyses show, with a large and well-characterized sample, that the brain correlates of ADHD symptomatology are modest in effect size and captured best by brain morphometry and activation during a working memory task

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Transp Res Part F Traffic Psychol Behav. 2021 Feb;77:274-92.

BEHIND THE WHEELS WITH AUTISM AND ADHD: BRAIN NETWORKS INVOLVED IN DRIVING HAZARD DETECTION.

Bednarz HM, Stavrinos D, Svancara AM, et al.

Driving is a cognitively challenging task, and many individuals with autism spectrum disorder (ASD) or with attention-deficit/hyperactivity disorder (ADHD) struggle to drive safely and effectively. Previous evidence suggests that core neuropsychological deficits in executive functioning (EF) and theory of mind (ToM) may impact driving in ASD and ADHD. This functional magnetic resonance imaging (fMRI) study compares the brain mechanisms underlying ToM and EF during a hazard perception driving task. Forty-six licensed drivers (14 ASD, 17 ADHD, 15 typically developing (TD)), ages 16–27 years, viewed a driving scenario in the MRI scanner and were instructed to respond to driving hazards that were either 'social' (contained a human component such as a pedestrian) or 'nonsocial' (physical objects such as a barrel). All groups of participants recruited regions part of the 'social brain' (anterior insula, angular gyrus, right middle occipital gyrus, right cuneus/precuneus, and right inferior frontal gyrus) when processing social hazards, and regions associated with motor planning and object recognition (postcentral gyrus, precentral gyrus, and supplementary motor area) when processing nonsocial hazards. While there were no group differences in brain activation during the driving task, years licensed was predictive of greater prefrontal and temporal activation to social hazards in all participants. Findings of the current study suggest that high-functioning ASD and ADHD licensed drivers may be utilizing similar cognitive resources as TD controls for decisions related to driving-related hazard detection

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Yonago Acta Medica. 2021;64:92-97.

PSYCHOLOGICAL PREPARATIONS AFFECTING THE EMOTIONS OF CHILDREN WITH DEVELOPMENTAL DISORDERS TOWARD HOSPITALS.

Inoue N, Okanishi T, Inoue M, et al.

Background The psychological preparation factors associated with positive or negative emotions in pediatric patients with developmental disorders are not well known. We aimed to clarify which psychological preparation factors affect positive (favorable) or negative (fear) emotions toward hospitals in pediatric patients with autism spectrum disorder (ASD) or attention deficit hypertensive disorder (ADHD), using the questionnaires for the patients and guardians.

Methods The questionnaires were sent by mail via prefectural patient-family groups to pediatric patients (6 to 15 years old; diagnosed with ASD or ADHD) and their guardians living in seven prefectures in Japan. Thereafter, we statistically analyzed the associations between the background factors or psychological preparations and the patients positive or negative emotions toward the hospital.

Results The questionnaire results of 68 patients (age: 6ΓÇô15 years; 15 = females; 53 = males) and their guardians indicated the main diagnoses for patients were ASD (n = 54) and ADHD (n = 14). Intellectual disability and hypersensitivity were positively associated with fear experiences in the hospital. In contrast, the staff's explanations during interventions negatively associated with patients fear experiences. The psychological preparations performed by doctors during the medical checks were positively associated with the patient's positive emotions toward the hospital.

Conclusion Regarding the psychological preparations for patients with ASD or ADHD, interpersonal communication with doctors and staff promotes positive emotions and reduces anxiety in the hospital

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Review
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Clinical Psychopharmacology and Neuroscience 2021;19(1):26-45

Second-to-Fourth Digit Ratio (2D:4D) in Psychiatric Disorders: A Systematic Review of Case-control Studies

Laura Fusar-Poli[1,*], Alessandro Rodolico[1,*], Serena Sturiale[1], Bianca Carotenuto[1], Antimo Natale[1], Davide Arillotta[1], Spyridon Siafis[2], Maria Salvina Signorelli[1], Eugenio Aguglia[1]

[1]Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania, Italy, [2]Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany

The second-to-fourth digit ratio (2D:4D) is an indirect, retrospective, non-invasive measure that correlates negatively with intrauterine exposure to testosterone. The present meta-analysis aimed to evaluate if 2D:4D differs between patients with psychiatric disorders and controls. In September 2019, we searched in Web of Knowledge, PsycINFO, Embase, and CINHAL, and retrieved 619 papers. We finally included 43 case-control studies which compared the 2D:4D ratio of patients with autism spectrum disorder (ASD) (n = 16), schizophrenia (n = 8), gender non-conformity (n = 7), addictions (n = 5), attention deficit-hyperactivity disorder (ADHD) (n = 4), mood disorders (n = 2), and intellectual disability (n = 1) to non-clinical controls. Meta-analyses showed that, overall, psychiatric patients had lower 2D:4D than healthy controls (n = 43, overall sample = 9,484, mean difference = −0.0056, 95% confidence interval from −0.0093 to −0.002, I^2 = 74%), with more pronounced differences in the right hand, males, and children. Considering psychiatric disorders individually, significant differences were found in the ASD, ADHD, and addictions groups, in which 2D:4D was significantly lower than healthy controls. Conversely, the right hand of males with schizophrenia showed higher 2D:4D than healthy controls. No other significant differences were detected. Although our results need to be cautiously interpreted and find limited applications in clinical practice, they may suggest that 2D:4D is altered in some psychopathological conditions, underlining the role of prenatal exposure to sex steroids in the etiology of psychiatric disorders.

KEY WORDS: Meta-analysis; Mental disorders; Testosterone; Autism spectrum disorder; Attention deficit disorder with hyperactivity; Substance addiction.

INTRODUCTION

The second-to-fourth digit ratio (2D:4D) is a biological marker, defined as the ratio of the length of the index (second digit) to the length of the ring finger (fourth digit) of the same hand. 2D:4D is constant throughout life [1,2] and represents an indirect, retrospective, and non-invasive measure that correlates negatively with intrauterine exposure to testosterone, i.e., a lower 2D:4D is the result of increased levels of fetal testosterone [3,4]. Many debates exist around the reasons why 2D:4D could be considered an indirect marker of the prenatal, but not the present, testosterone level [5] and even more strongly, a marker of the ratio between prenatal testosterone and estradiol levels. More evidence is provided by molecular genetic association studies, relating a polymorphism of the androgen receptor gene to individual differences in the 2D:4D ratio [6].

In humans, the 2D:4D ratio has been assumed to reflect the exposure to testosterone during the second trimester of gestation, because of the sex difference detectable in childhood, and because of postulated mechanisms regarding digit development [2]. Prenatal hormone exposure is critical for sexual differentiation and masculinization. In fact, males are exposed to higher levels of testosterone than females, particularly from about week 8 to 24 of gestation and week 2 to 26 of postnatal life [7]. This is con-

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firmed by the observation that the 2D:4D ratio is sexually dimorphic: generally, females have a higher 2D:4D than males and this effect is more pronounced in the right hands, although the reasons still need to be clarified [8].

Digit ratio has been reported to correlate with a wide number of traits and conditions, ranging in almost every field of medicine, with particular regard to sex hormones-dependent conditions, i.e., breast cancer [9], prostate cancer [10,11], obesity [12], and osteoarthritis [13]. It has also been associated with physical characteristics, such as facial shape [14], sperm count [15], age of menarche [16], and penis size [17]. Of interest, scholars have also investigated the association between the 2D:4D ratio and behavioral features, such as aggression [18], stuttering [19], visuo-spatial ability [20], handedness [21], schizotypal personality [22], sporting ability [23], successful financial risk-taking [24], and sexual orientation [25].

Given the findings obtained in the field of behavioral sciences, over the last years, many researchers have sought to examine potential links between the 2D:4D ratio and psychiatric disorders, aiming to find a significant correlation between intrauterine exposure to testosterone and those conditions. Since the amount of available literature has been constantly growing, we aimed to perform a systematic review and meta-analysis to examine if the 2D:4D ratio consistently differed between people with psychiatric disorders and non-clinical controls. Second, we aimed to investigate potential mediators of 2D:4D differences, such as gender, age, and hand.

METHODS

Search Strategy

We followed the PRISMA Statement guidelines to perform a systematic search [26]. The protocol was registered on PROSPERO, an international database of prospectively registered systematic reviews in health and social care managed by the Centre for Reviews and Dissemination, University of York (Registration number: CRD42019124184).

In September 2019, we searched the following databases: Web of Knowledge℠ (including Web of Science, MEDLINE®, KCI—Korean Journal Database, Russian Science Citation Index, and SciELO Citation Index), PsycINFO, Embase, and CINAHL. The complete search string can be found in the Supplementary Materials, Appendix 1 (available online) [27]. The search was not restricted to any language, reference type, or year of publication. The electronic search was supplemented by hand-searching of reference lists of the included review articles to identify any additional sources.

Study Selection

We selected all the studies published in English on peer-reviewed journals, which fulfilled the following inclusion criteria:

(1) Participants: Individuals of any age and gender, diagnosed with any psychiatric disorder according to valid international diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders; International Classification of Diseases), or with validated scales (e.g., Hamilton Rating Scale for depression and Positive and Negative Syndrome Scale for schizophrenia), or followed by clinics or mental health services. Studies with patients recruited through web-surveys or subjects divided into groups according to scores obtained at self-reported questionnaires were excluded.

(2) Controls: Individuals with no psychiatric disorders.

(3) Outcome: Measurement of 2D:4D ratio through direct or indirect tools, and availability of data.

(4) Study design: Case-control studies.

Data Extraction

Couples of researchers (SS, BC, AN, DA) independently reviewed and extracted the information from the included articles. Discrepancies were solved after consultation with a third reviewer (LF). We extracted data using a format which included:

(1) Study characteristics: author, year, country.

(2) Participants' characteristics: type of diagnosis, diagnostic tool (only for psychiatric patients), sample size, mean age, age range, proportion of males.

(3) 2D:4D measurement tool.

(4) Mean and standard deviation (SD) of the 2D:4D ratio. If reported in the studies, data were extracted separately for left and right hand, and for males and females.

We contacted study authors via e-mail to request missing data or for clarification, providing an individualized data table for reporting the requested information.

Appraisal of Quality

Quality of the included studies was assessed by two review authors (AR, DA) using the Newcastle-Ottawa qual-

ity assessment scale for case-control studies [28]. Any discrepancy was solved after consultation with a third reviewer (LF). The Newcastle-Ottawa comprises eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars [28].

Statistical Analyses

Meta-analysis calculations

The primary aim of this study was to compare the 2D:4D digit ratio in all psychiatric conditions, regardless of the hand measured and the gender of the included subjects. Most of the studies reported the means of 2D:4D divided by hand and gender. Some studies reported results only for the left or the right hand, while other studies reported aggregated data for left and right hands. Thus, we decided to combine the data to have a common estimate of the digit ratio, regardless of gender and hand. First, in order to combine the measure of right and left hand, we calculated the averaged means for left and right hands digit ratio. To avoid an underestimation of the SD, that might be the case in within-subjects data combination, we used the formula suggested by Borenstein *et al.* [29], setting as a correlation coefficient 0.8, as proposed in previous literature. Then, we computed a weighted mean for each study, in order to combine males and females digit ratios, while we calculated SD according to the Cochrane Handbook formula for grouping independent samples [30]. In case SD was missing [31], we replaced it with the mean of the SD among the same diagnostic category (i.e., autism spectrum disorder, ASD).

Effect size and heterogeneity

We used mean differences (MD) as effect size, being the 2D:4D always measured in the same unit. Studies were pooled using a random-effects model since a consistent heterogeneity among observational studies was expected. Between-study heterogeneity was assessed using the I^2 statistic. According to the Cochrane handbook, an I^2 of 0−40% represents a low heterogeneity, I^2 of 30−60% is moderate heterogeneity, I^2 of 50−90% indicates substantial heterogeneity [30]. Small study effects as a proxy of publication bias were explored with contour-enhanced funnel plots for the visual detection of asymmetries. Egger's regression test was used to detect asymmetry in the funnel plots.

Subgroup analyses

For each psychiatric disorder, we conducted subgroup meta-analyses on males and females and left and right hands, separately. In the main analysis of the overall sample, we conducted a subgroup analysis also on children and adults. Chi-squared (χ^2) was used to test differences between subgroups.

Analyses were conducted using meta package (v.4.9-9) within the open-source software environment R (v3.6). α was set at 0.05.

RESULTS

Characteristics of the Included Studies

Our search yielded a total of 619 articles, while four additional papers were retreived from other sources. After duplicates removal, we screened the titles and abstracts of 399 papers and read the full texts of 96 papers. We finally included 43 articles, evaluating the 2D:4D ratio in patients with the following psychiatric diagnoses:

(1) Neurodevelopmental disorders, specifically attention deficit-hyperactivity disorder (ADHD; n = 4), ASD (n = 16), and intellectual disability (ID; n =1)

(2) Schizophrenia (n = 8)

(3) Addictions, specifically alcohol dependence (n = 3) and heroin dependence (n = 2)

(4) Gender nonconformity, such as gender dysphoria, gender identity disorder, transsexualism, or transgenderism (n = 7)

(5) Mood disorders, specifically bipolar disorder (n = 1) and depression (n = 1).

The study selection process and the reasons for exclusion are reported in the PRISMA Flow Diagram (Fig. 1).

Neurodevelopmental disorders

Twenty-one studies evaluated the 2D:4D ratio in neurodevelopmental disorders, such as ADHD, ASD, and ID. Thirteen studies were conducted in Europe, specifically in the United Kingdom, The Netherlands, Belgium, Germany, Greece, Slovak Republic, Sweden, and Turkey. Six stud-

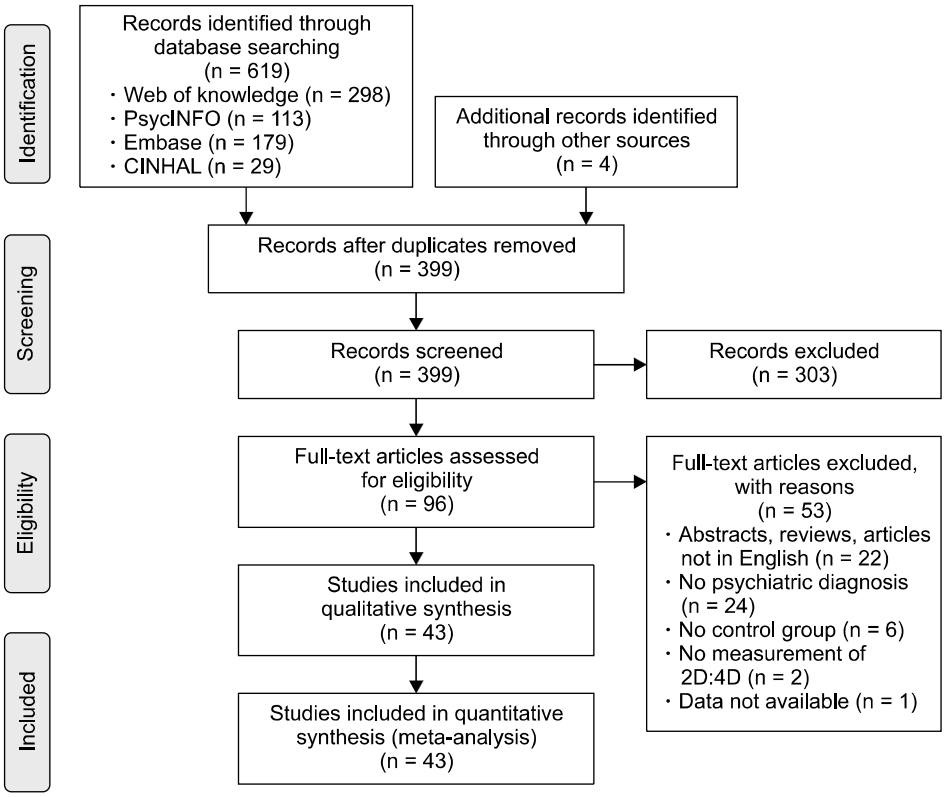


Fig. 1. PRISMA Flow Chart of the study selection process.
2D:4D, Second-to-fourth Digit Ratio.

ies were conducted in Asia, specifically in Japan, Iran, Saudi Arabia, and Thailand. Finally, three studies were conducted in the United States. Participants were children in all the studies involving patients with ADHD and ID. Moreover, five studies evaluated 2D:4D in adults with ASD [32-36], and two studies included mixed samples of children and adults with ASD [37,38]. Four papers included only males [36,39-41], and in two articles [31,42], the proportion of males represented almost the entirety of the sample. Five studies evaluated the 2D:4D only in the right hand, twelve studies in both hands (left and right). In one paper the mean between the 2D:4D of left and right hands was calculated, and in two studies it was unclear which hand was measured. Measurement of 2D:4D was mostly direct (14 studies).

Characteristics of the included studies about 2D:4D ratio in patients with neurodevelopmental disorders are reported in Table 1 [31-51].

Schizophrenia

Eight studies measured 2D:4D in patients with schizophrenia and controls. Half of the studies were conducted in Asia, and particularly two in India [52,53], one in China [54], and one in Singapore [55]. Moreover, two studies were conducted in Turkey [56,57], one in Spain [58], and one in Germany [22]. All participants were adults with mean ages ranging from 22 [57] to 47 [58]. Samples generally included both males and females, apart from Bolu *et al.* [57] that recruited only males. All papers have evaluated 2D:4D in both hands, apart from Collinson *et al.* [55] that has measured the ratio solely of the right hand. Measurements were always direct, except in two cases [22,54]. Characteristics of the included studies about 2D:4D ratio in patients with schizophrenia are reported in Table 2.

Addictions

Two papers recruited individuals with alcohol dependence and were conducted in South Korea [59] and Germany [60]. Moreover, we included three studies involving participants with heroin dependence, which were conducted in Turkey [61,62] and Germany [63]. Participants were all adults, with mean ages ranging from 22.8 [61] to 51.2 [59]. Three studies included only men [59,61,62], while in the remaining two articles samples were mixed. Three papers measured 2D:4D ratio in both hands; one paper

Table 1. Characteristics of studies evaluating 2D:4D in neurodevelopmental disorders, i.e., attention deficit-hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and intellectual disability (ID)

Diagnosis (tool)	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
ADHD (DSM-IV)	Buru	2017	Turkey	104	/ (7−17)	77 (74.03)	436	/ (7−17)	240 (55.04)	L, R	Digital compass (direct)
ADHD (DSM-IV-TR)	Lemiere	2010	Belgium	64	/ (7−12)	47 (73.44)	46	/ (7−12)	25 (54.35)	/	Scanned photocopies (indirect)
ADHD (Clinical)	Martel	2009	USA	168	12.71 (8−17)	106 (63.10)	144	14.01 (8−17)	72 (50)	R	Ruler (direct)
ADHD (DSM-IV-TR)	McFadden	2005	USA	46	9.83 (7−15)	34 (73.91)	33	10.6 (7−15)	17 (51.51)	L, R	Photocopy or digital scanner (indirect)
ASD (DSM-IV)	Al-Zaid	2015	Saudi Arabia	31	5.59 (3−8)	31 (100)	29	5.59 (3−8)	29 (100)	R	Digital Caliper (direct)
ASD (DSM-IV-TR, ADOS)	Baharara	2014	Iran	48	7.38 (7−8)	38 (79.17)	41	7.46 (7−8)	31 (75.61)	L, R	Ruler (direct)
ASD (Clinical, ADOS)	Bejerot	2012	Sweden	50	30 (20−47)	26 (52)	53	30.3 (20−47)	28 (52.83)	L, R	Digital Caliper (direct)
ASD (DSM-IV)	De Bruin	2006	The Netherlands	24	9 (6−14)	24 (100)	96	9 (6−13)	96 (100)	L, R	Digital Caliper (direct)
ASD (DSM-IV-TR)	Falter	2008	UK	28	12.7 (/)	27 (96.43)	28	12.7 (/)	27 (96.43)	L, R	Digital Caliper (direct)
ASD (ADI-R)	Hauth	2014	The Netherlands	216	11.6 (4−21)	178 (82.40)	174	11 (4−21)	79 (45.40)	L, R	Tape (indirect)
ASD (DSM-IV)	Krajmer	2011	Slovak Republic	56	11.2 (/)	56 (100)	32	12.1 (/)	32 (100)	R	Scanner (indirect)
ASD (DSM-IV-TR, ICD-10)	Lai	2013	UK	60	27.5 (18−49)	0	60	27.8 (18−49)	0	L, R	Digital Caliper (direct)
ASD (DSM-5, DISCO)	Masuya	2015	Japan	52	28.5 (/)	35 (67.31)	116	27.74 (/)	59 (42.45)	L, R	Digital Caliper (direct)
ASD (DSM-IV)	Milne	2006	UK	23	10.8 (/)	22 (95.65)	23	10.8 (/)	10 (43.48)	/	Digital Caliper (direct)
ASD (ASQ)	Manning	2001	UK	72	/ (2−15)	62 (86.11)	72	/ (2−15)	62 (86.11)	Mean L, R	Digital Caliper (direct)
ASD (DSM-IV)	Noipayak	2009	Thailand	46	5.25 (1.5−15)	39 (84.78)	46	5.25 (1.5−15)	39 (84.78)	L, R	Digital Caliper (direct)
ASD (Clinical)	Rohde	2018	Germany	26	42.86 (20−55)	14 (53.84)	26	41.44 (20−55)	14 (53.85)	R	Ruler (direct)
ASD (ADOS, ADI-R)	Schieve	2018	USA	599	/ (2−5)	487 (81.30)	811	/ (2−5)	431 (53.14)	L, R	Scanner (indirect)
ASD (DSM-IV)	Sugie	2010	Japan	98	12.7 (5−31)	82 (85.71)	89	/	/	R	Digital Camera (indirect)
ASD (DSM-IV-TR)	Togo	2019	Japan	20	26.75 (/)	20 (100)	14	26 (/)	14 (100)	L, R	Digital Photos (indirect)
Intellectual disability (WISC-III)	Ypsilanti	2008	Greece	100	17.4 (14−18)	47 (47)	85	19.24 (18−23)	37 (43.53)	R	Digital Caliper (direct)

2D:4D, Second-to-fourth Digit Ratio ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASQ, Autism Screening Questionnaire; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; R, right; WISC-III, Wechsler Intelligence Scale for Children-Third Edition; ICD, International Classification of Diseases; DISCO, Diagnostic Interview for Social and Communication Disorders; /, not available.

Table 2. Characteristics of studies evaluating 2D:4D in schizophrenia

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Schizophrenia (DSM-IV)	Akgül	2017	Turkey	48	39.85 (18－55)	25 (52.08)	48	39.73 (18－55)	25 (52.08)	L, R	Digital Caliper (direct)
Schizophrenia (SCID-I)	Bolu	2015	Turkey	103	22.73 (/)	103 (100)	100	21.98 (/)	100 (100)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Collinson	2010	Singapore	64	30.5 (/)	33 (51.56)	64	27.4 (/)	33 (51.56)	R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Divakaran	2012	India	200	31.61 (/)	106 (53)	177	33.82 (/)	92 (51.97)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Paipa	2018	Spain	51	47 (18－65)	33 (64.71)	50	45.5 (18－65)	31 (62)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV-TR)	Qian	2016	China	178	33.8 (15－62)	76 (42.70)	365	33.16 (17－63)	218 (59.73)	L, R	Photography (indirect)
Schizophrenia (DSM-IV)	Venkatasubramanian	2011	India	79	24.4 (/)	41 (51.90)	75	31.1 (/)	37 (49.33)	L, R	Digital Caliper (direct)
Schizophrenia (SCID-I)	Zhu	2014	Germany	51	26.49 (18－45)	24 (47.06)	51	24.98 (18－45)	23 (45.10)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; R, right; SCID-I: Structured Clinical Interview for DSM IV Axis I Disorders; /, not available.

Table 3. Characteristics of studies evaluating 2D:4D in addictions

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Alcohol dependence (DSM-IV)	Han	2016	South Korea	87	51.2 (/)	87 (100)	52	48.32 (/)	52 (100)	L, R	Scanner (indirect)
Alcohol dependence (DSM-5, ICD-10)	Lenz	2017	Germany	200	48 (42－54)	113 (56.50)	240	48 (39－56)	133 (55.42)	Mean L, R	Scanner (indirect)
Alcohol dependence (ICD-10)	Kornhuber	2011	Germany	131	/ (24－77)	87 (66.41)	185	/ (24－77)	83 (44.86)	L, R	Scanner (indirect)
Heroin dependence (DSM-5)	Canan	2018	Turkey	150	22.8 (/)	150 (100)	266	23 (/)	266 (100)	L, R	Digital Caliper (direct)
Heroin dependence (DSM-IV)	Cicek	2017	Turkey	62	24.09 (18－45)	62 (100)	50	24.42 (18－45)	50 (100)	R	Digital Caliper (direct)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; L, left; R, right; /, not available.

Table 4. Characteristics of studies evaluating 2D:4D in individuals with gender non-conforming identities

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	M-to-F, n (%)	Number	Mean age (range)	M-to-F, n (%)		
Gender identity disorder (DSM-IV)	Hisasue	2012	Japan	37	27 (19−45)	0	20	35 (23−60)	0	L, R	Photocopies (indirect)
Gender identity disorder (DSM-IV)	Kraemer	2009	Switzerland	56	37.1 (18−65)	39 (69.64)	366	37.1 (18−65)	176 (48.08)	L, R	Digital Caliper (direct)
Transgender (Clinical)	Leinung	2017	USA	118	Not reported	68 (57.62)	37	Not reported	19 (51.35)	Dominant	Digital Caliper (direct)
Transsexualism (Clinical)	Schneider	2006	Germany	106	37.24 (/)	63 (59.53)	123	39 (/)	58 (47.15)	L, R	Photocopies (indirect)
Gender identity disorder (DSM-IV)	Vujović	2014	Republic of Serbia	80	31.25 (/)	42 (52.50)	93	29 (/)	45 (48.39)	L, R	Digital Caliper (direct)
Gender identity disorder (DSM-IV)	Wallien (study 1)	2008	The Netherlands	147	40.53 (/)	96 (65.30)	202	41.25 (/)	90 (44.55)	L, R	Scanner (indirect)
	Wallien (study 2)	2008	The Netherlands	101	8.29 (/)	67 (66.33)	146	7.8 (/)	74 (50.68)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; M-to-F, male-to-female; R, right; /, not available.

Table 5. Characteristics of studies evaluating 2D:4D in mood disorders

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Bipolar Disorder (MINI)	Tegin	2019	USA	50	52.9 (/)	21 (42)	50	48.6 (/)	21 (42)	L, R	Scanner (indirect)
Depression (DSM-IV)	Sanwald	2019	Germany	139	39.4 (18−65)	49 (35.3)	137	28.74 (18−63)	49 (35.8)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; MINI, Mini-International Neuropsychiatric Interview; L, left; R, right; /, not available.

considered the average between the left and right hand [60] and one measured only right hand [62]. Measurements were indirect in three papers [59,60,63], and direct in two articles [61,62]. See Table 3 for details regarding studies evaluating 2D:4D in addictions.

Gender non-conforming identity

Six papers (including seven studies) measured 2D:4D in people with gender nonconforming identity who had a psychiatric diagnosis or were followed by specialized clinics. Particularly, in four studies participants had a diagnosis of gender identity disorder, in one study a diagnosis of transsexualism, whereas they were defined as transgender in one paper. Studies were conducted mainly in Europe, specifically one in The Netherlands (including two studies) [64], one in Germany [65], one in the Republic of Serbia [66], and one in Switzerland [67]. Moreover, one study was conducted in Japan [68] and one in the United States [69]. One study involved children [64]; all the other studies recruited adults, with the exception of Leinung and Wu [69], where the age of participants was not reported. All studies evaluated 2D:4D in both hands; Leinung and Wu [69] have measured the ratio only in the dominant hand. Measurements were conducted directly in half of the studies, and indirectly in the remaining articles. Study characteristics are reported in Table 4 [66].

Mood disorders

One paper [70] recruited patients with major depression in Germany, and another study recruited individuals affected by bipolar disorder [71] in the United States. All participants were adults and mainly women. In the two studies regarding mood disorders, 2D:4D was measured in both hands and using indirect measurement tools. Details regarding the study characteristics are reported in Table 5.

Meta-analyses of the Included Studies

2D:4D ratio in all psychiatric disorders

To evaluate the global differences of 2D:4D in psychiatric disorders, we conducted four main meta-analyses. In the first one, we pooled the data of all 43 studies, finding that psychiatric patients had significantly lower 2D:4D than healthy controls (n = 43, overall sample = 9,484, MD = −0.0056, 95% confidence interval [CI] from −0.0093 to −0.002, I^2 = 74%). The forest plot is presented in Figure 2 and the funnel plot in Figure 3.

Then, data extracted from included studies were pooled by hand, gender, and age. No differences were found between left and right hand in any psychiatric disorder (χ^2 = 0.85, df = 1, p = 0.36). However, considering each subgroup independently, it could be observed that the 2D:4D in the right hand showed significant lower 2D:4D in psychiatric patients than controls; conversely, no differences between psychiatric patients and controls were detected in the left hand. Moreover, no significant differences were detected between males and females (χ^2 = 0.44, df = 1, p = 0.51), even if both groups showed significantly lower 2D:4D in psychiatric patients than controls. Finally, dividing the studies by age, it could be observed that both adults and children showed significantly lower 2D:4D ratio in psychiatric patients than controls, with no significant differences between the two groups (χ^2 = 0.77, df = 1, p = 0.38). The forest plots are presented in the Supplementary Materials, Appendix 2 (available online) [27].

2D:4D ratio in autism spectrum disorder

The analyses of the 2D:4D ratio in ASD, with data pooled by hand and gender, showed a statistically significant difference between patients and controls (n = 16, overall sample = 2,981, MD = −0.006, 95% CI from −0.0119 to −0.0001). Heterogeneity was moderate (I^2 = 53%). The results of the meta-analysis are presented in Figure 4A.

Subgroup analyses with studies divided by hand and gender did not detect any significant difference between ASD patients and controls. The forest plots of subgroup analyses are presented in the Supplementary Materials, Appendix 3 (available online) [27].

2D:4D ratio in attention deficit-hyperactivity disorder

The meta-analysis of 2D:4D ratio in ADHD showed a statistically significant difference between patients and controls (n = 4, overall sample = 1,128, MD = −0.0124, 95% CI from −0.0188 to −0.0059). Heterogeneity was low (I^2 = 0%). The results of the meta-analysis are presented in Figure 4B.

Subgroup analyses revealed significant differences in the right hand of both males (n = 3, overall sample = 526, MD = −0.0198, 95% CI from −0.036 to −0.0036, I^2 = 65%) and females (n = 3, overall sample = 382, MD = −0.0245,

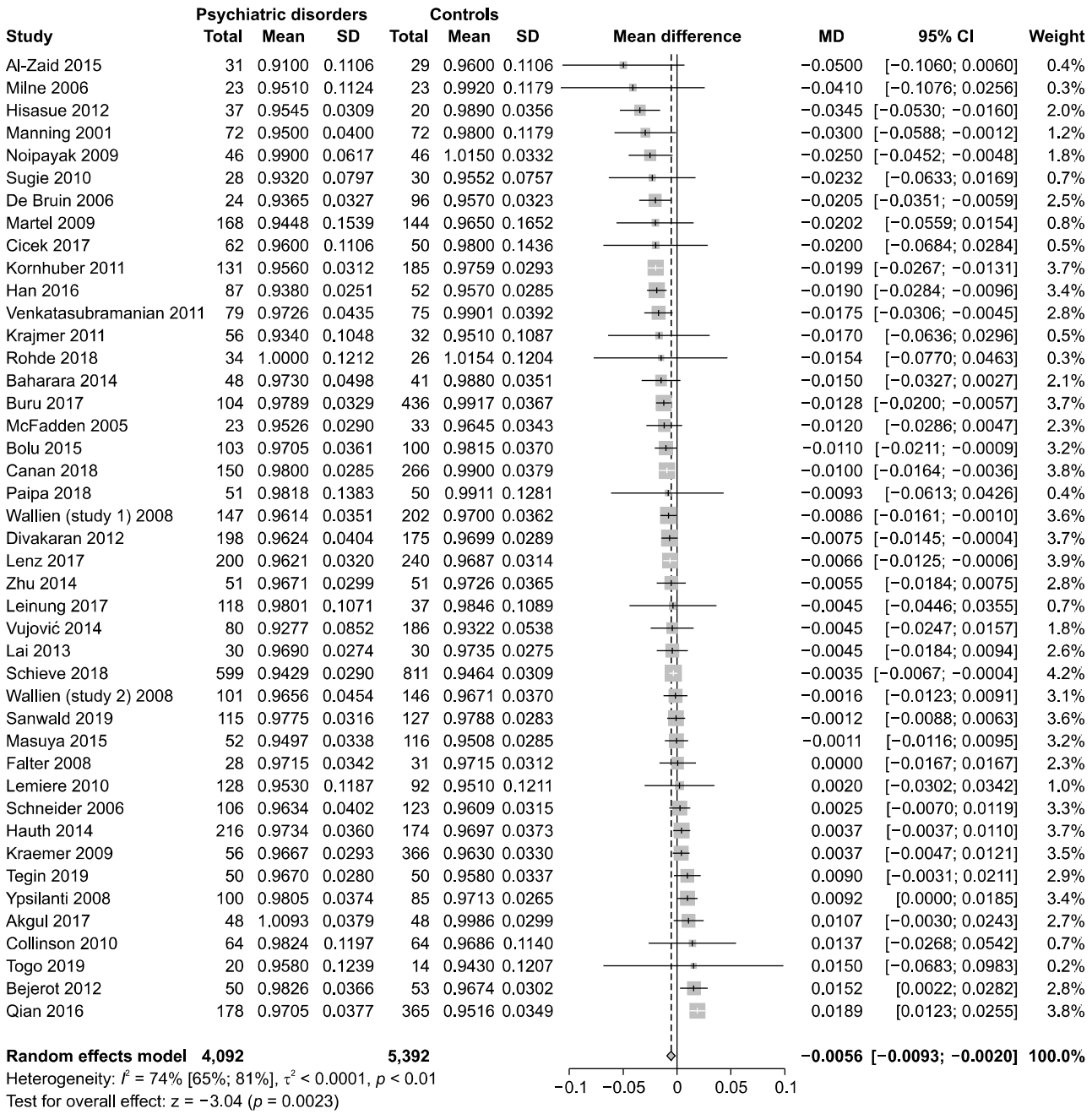


Fig. 2. Meta-analysis of the 2D:4D ratio pooling all psychiatric disorders (n = 43).
2D:4D, Second-to-fourth Digit Ratio; SD, standard deviation; MD, mean difference; CI, confidence interval.

95% CI from −0.0451 to −0.0039, I^2 = 66%). No significant differences were found in the left hand, neither in males nor in females. The forest plots of the subgroup analyses plot are presented in the Supplementary Materials, Appendix 4 (available online) [27].

2D:4D ratio in intellectual disability

Only one study [48] evaluated 2D:4D ratio in ID, without detecting any significant difference. Forest plot is presented in Figure 4C [27].

2D:4D ratio in schizophrenia

The meta-analysis of pooled data did not show any sig-

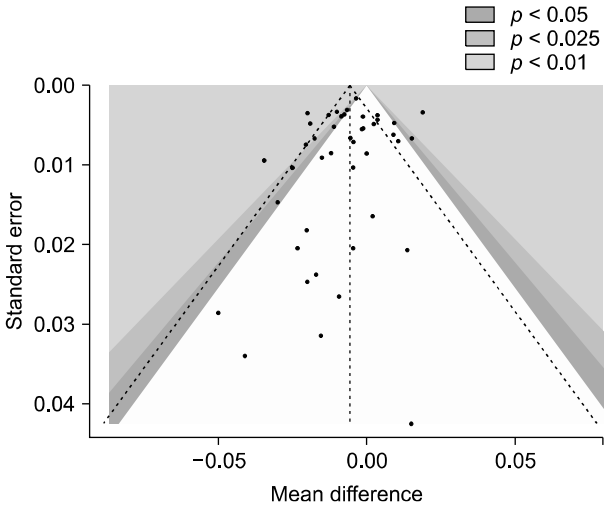


Fig. 3. Funnel plot of the included studies (n = 43).

nificant difference between patients with schizophrenia and other psychotic disorders and non-clinical controls (n = 8, overall sample = 1,700, MD = −0.0012, 95% CI from −0.0129 to 0.0105). Heterogeneity was high (I^2 = 86%). The forest plot is presented in Figure 4D.

Subgroup analyses with data divided by gender and hand did not reveal any significant difference except for the right hand in males: in this group, the 2D:4D ratio was significantly higher in patients than controls (n = 6, overall sample = 882, MD = 0.009, 95% CI from 0.0004 to 0.0177, I^2 = 64%). The subgroup analyses are presented in the Supplementary Materials, Appendix 5 (available online) [27].

2D:4D ratio in addictions

Pooling data of patients affected by addictions, we did find a significant difference, as patients had a significantly lower 2D:4D than controls (n = 5, overall sample = 1,423, MD = −0.014, 95% CI from −0.0199 to −0.0081). Heterogeneity was moderate (I^2 = 50%). The forest plot is presented in Figure 4E.

The subgroup analyses revealed statistically significant differences in both the males right and left hands, while for females the difference between the patients and the control group was limited to the right hand. In all cases, the patients suffering from addictions had a smaller 2D:4D ratio than controls. The analyses are presented in the Supplementary Materials, Appendix 6 (available online) [27].

2D:4D ratio in gender non-conforming people

No significant differences were found between individuals with gender non-conforming identities (n = 7, overall sample = 1,725, MD = −0.0051, 95% CI from −0.0131 to 0.0028). Heterogeneity was substantial (I^2 = 65%). Forest plot is presented in Figure 4F.

Subgroup analyses did not detect any significant differences according to hand or biological sex (see Supplementary Materials, Appendix 7 [available online] [27]).

2D:4D ratio in mood disorders

We found no significant differences between patients with depression or bipolar disorder and healthy controls (n = 2, overall sample = 342, MD = 0.0027, 95% CI from −0.0071 to 0.0125). Heterogeneity was moderate (I^2 = 49%). Forest plot is presented in Figure 4G.

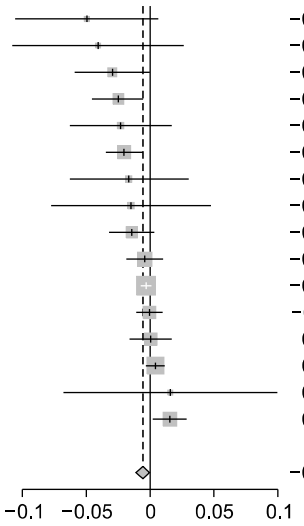
Quality of the Included Studies

The quality of the studies included in the systematic review and meta-analysis has been reported in Table 6. Two studies were judged with a score of 4 out of 9 points [41,42], four studies with 5 out of 9 [49,55,65,66], ten studies with 6 out of 9, four studies with 7 out of 9 and the the remaining papers with 8 or 9 stars. As concerns the study selection, we have found a relatively low risk of bias in diagnostic criteria: in fact, we included only studies in which participants had received a psychiatric diagnosis by a clinician. Only two studies were judged as having high risk: first, participants recruited by Manning *et al.* [50] were members of an autistic society and the diagnoses were confirmed only using the Autism Screening Questionnaire (ASQ), which is not intended as a diagnostic tool [72]; second, in Schneider *et al.* [65], transgenders were followed by a specific clinic for transition, thus we assumed that a clinical diagnosis had been performed, even if not explicitly reported in the paper. As for the remaining items of study selection, the most problematic criterion was the representativeness of cases, as in most studies the authors did not report consecutive recruitment of patients, thus raising concerns regarding potential selection biases. Ten studies did not match patients to controls according to socio-demographic variables, while in seven study only one variable was considered (age or gender). Regarding exposure, we did not find major biases, since the 2D:4D ratio was measured in cases and controls using the same methodology with direct or indirect measures.

A Autism spectrum disorder (ASD)

Study	ASD Total	ASD Mean	ASD SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Al-Zaid 2015	31	0.9100	0.1106	29	0.9600	0.1106	−0.0500	[−0.1060; 0.0060]	1.0%
Milne 2006	23	0.9510	0.1124	23	0.9920	0.1179	−0.0410	[−0.1076; 0.0256]	0.8%
Manning 2001	72	0.9500	0.0400	72	0.9800	0.1179	−0.0300	[−0.0588; −0.0012]	3.4%
Noipayak 2009	46	0.9900	0.0617	46	1.0150	0.0332	−0.0250	[−0.0452; −0.0048]	5.8%
Sugie 2010	28	0.9320	0.0797	30	0.9552	0.0757	−0.0232	[−0.0633; 0.0169]	1.9%
De Bruin 2006	24	0.9365	0.0327	96	0.9570	0.0323	−0.0205	[−0.0351; −0.0059]	8.6%
Krajmer 2011	56	0.9340	0.1048	32	0.9510	0.1087	−0.0170	[−0.0636; 0.0296]	1.5%
Rohde 2018	34	1.0000	0.1217	26	1.0154	0.1215	−0.0154	[−0.0775; 0.0467]	0.9%
Baharara 2014	48	0.9730	0.0498	41	0.9880	0.0351	−0.0150	[−0.0327; 0.0027]	6.9%
Lai 2013	30	0.9690	0.0274	30	0.9735	0.0275	−0.0045	[−0.0184; 0.0094]	9.0%
Schieve 2018	599	0.9429	0.0291	811	0.9464	0.0310	−0.0035	[−0.0067; −0.0004]	17.2%
Masuya 2015	52	0.9497	0.0338	116	0.9508	0.0285	−0.0011	[−0.0116; 0.0095]	11.5%
Falter 2008	28	0.9715	0.0342	31	0.9715	0.0312	0.0000	[−0.0167; 0.0167]	7.4%
Hauth 2014	216	0.9734	0.0360	174	0.9697	0.0374	0.0037	[−0.0037; 0.0110]	14.2%
Togo 2019	20	0.9580	0.1239	14	0.9430	0.1207	0.0150	[−0.0683; 0.0983]	0.5%
Bejerot 2012	50	0.9826	0.0367	53	0.9674	0.0303	0.0152	[0.0022; 0.0283]	9.6%
Random effects model	**1,357**			**1,624**			**−0.0060**	**[−0.0119; −0.0001]**	**100.0%**

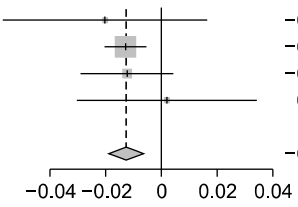
Heterogeneity: I^2 = 53% [17%; 73%], τ^2 < 0.0001, p < 0.01
Test for overall effect: z = −1.99 (p = 0.0461)



B Attention deficit-hyperactivity disorder (ADHD)

Study	ADHD Total	ADHD Mean	ADHD SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Martel 2009	168	0.9448	0.1574	144	0.9650	0.1670	−0.0202	[−0.0564; 0.0160]	3.2%
Buru 2017	104	0.9789	0.0333	436	0.9917	0.0367	−0.0128	[−0.0201; −0.0056]	78.0%
McFadden 2005	23	0.9526	0.0291	33	0.9645	0.0342	−0.0120	[−0.0286; 0.0047]	14.9%
Lemiere 2010	128	0.9530	0.1187	92	0.9510	0.1211	0.0020	[−0.0302; 0.0342]	4.0%
Random effects model	**423**			**705**			**−0.0124**	**[−0.0188; −0.0059]**	**100.0%**

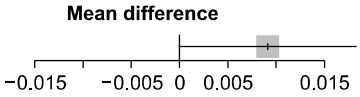
Heterogeneity: I^2 = 0% [0%; 52%], τ^2 = 0, p = 0.81
Test for overall effect: z = −3.77 (p = 0.0002)



C Intellectual disability (ID)

Study	Intellectual disability Total	Intellectual disability Mean	Intellectual disability SD	Controls Total	Controls Mean	Controls SD	MD	95% CI
Ypsilanti 2008	100	0.9805	0.0376	85	0.9713	0.0267	0.0092	[−0.0001; 0.0185]

Heterogeneity: I^2 = NA%



D Schizophrenia

Study	Schizophrenia Total	Schizophrenia Mean	Schizophrenia SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Venkatasubramanian 2011	79	0.9726	0.0436	75	0.9901	0.0394	−0.0175	[−0.0306; −0.0044]	14.2%
Bolu 2015	103	0.9705	0.0361	100	0.9815	0.0370	−0.0110	[−0.0211; −0.0009]	15.4%
Paipa 2018	51	0.9818	0.1388	50	0.9911	0.1282	−0.0093	[−0.0614; 0.0428]	3.9%
Divakaran 2012	198	0.9624	0.0405	175	0.9699	0.0292	−0.0075	[−0.0146; −0.0004]	16.3%
Zhu 2014	51	0.9671	0.0299	51	0.9726	0.0365	−0.0055	[−0.0184; 0.0075]	14.3%
Akgül 2017	48	1.0093	0.0379	48	0.9986	0.0299	0.0107	[−0.0030; 0.0243]	14.0%
Collinson 2010	64	0.9824	0.1202	64	0.9686	0.1174	0.0137	[−0.0274; 0.0549]	5.5%
Qian 2016	178	0.9705	0.0378	365	0.9516	0.0349	0.0189	[0.0123; 0.0255]	16.4%
Random effects model	**772**			**928**			**−0.0012**	**[−0.0129; 0.0105]**	**100.0%**

Heterogeneity: I^2 = 86% [75%; 92%], τ^2 = 0.0002, p < 0.01
Test for overall effect: z = −0.20 (p = 0.8407)

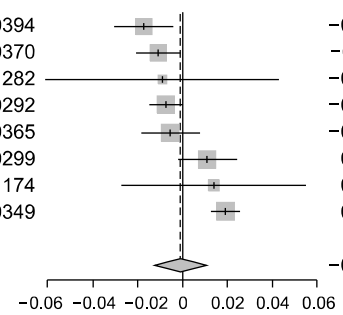


Fig. 4. Meta-analyses of the 2D:4D ratio in individual psychiatric disorders.
2D:4D, Second-to-fourth Digit Ratio; SD, standard deviation; MD, mean difference; CI, confidence interval.

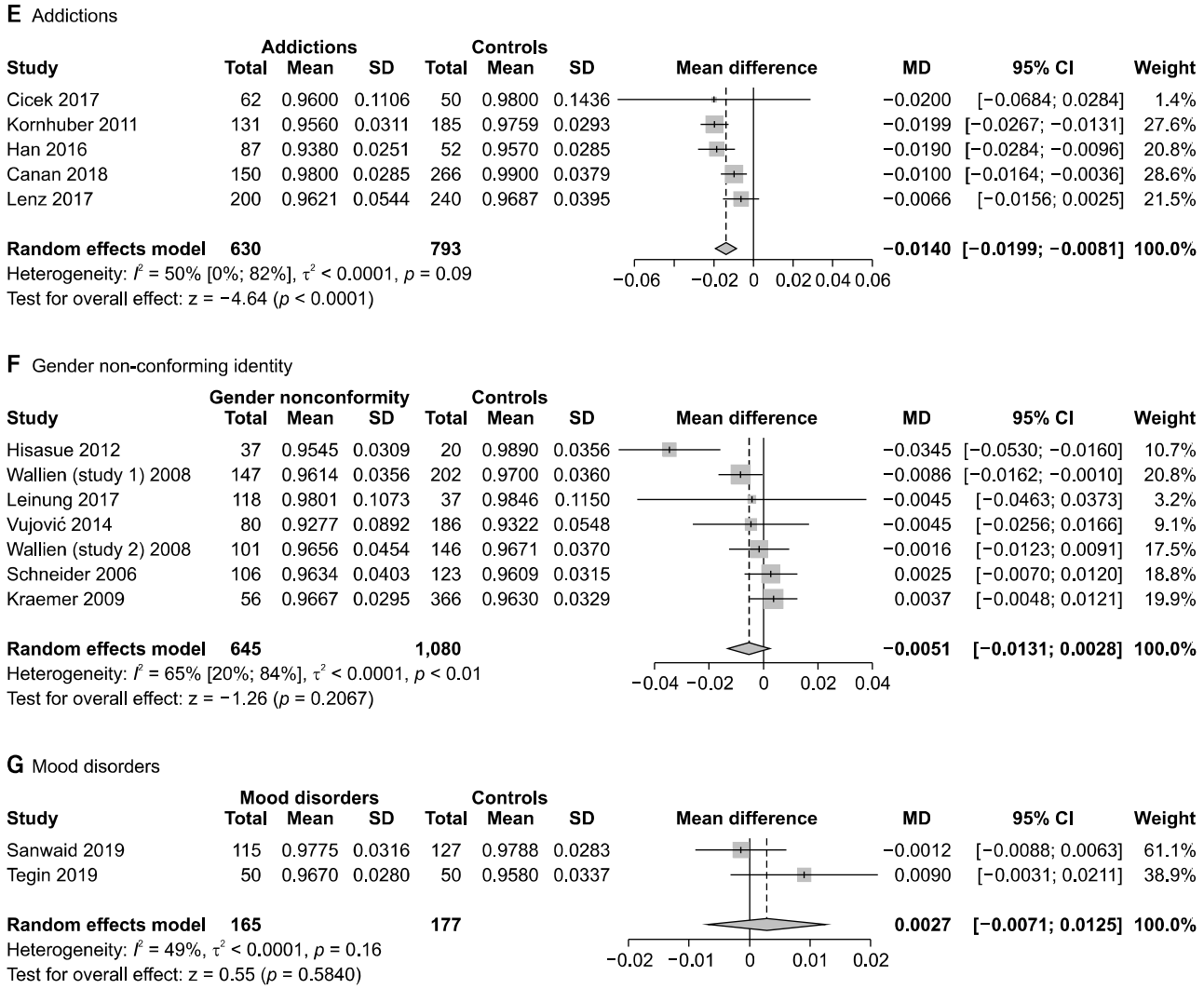


Fig. 4. Continued.

However, in five studies [35,41,42,51,65] concerns were raised because of missing data.

DISCUSSION

The present meta-analysis aimed to evaluate the differences in 2D:4D ratio between psychiatric patients and controls, and thus to explore its potential usefulness as a clinical biomarker for psychiatric disorders. The first and main finding of our meta-analysis is that the 2D:4D ratio is significantly lower in patients than controls, indicating exposure to higher levels of prenatal testosterone in individuals with psychiatric disorder. The effect seemed more pronounced in males than females, in the right than the left hand, and in children than adults, even if between-groups differences were not statistically significant. Our finding is important because, on one hand, it may propose 2D:4D as a potential biomarker for psychiatric disorders in general; on the other hand, it highlights the role of prenatal exposure to hormones, specifically testosterone, in the etiopathogenesis of psychiatric disorders. Interestingly, prenatal exposure to androgens may explain the different sex ratios encountered in several conditions (e.g., schizophrenia, ASD, addictions).

As shown by the number of studies included in our meta-analysis, the literature has extensively evaluated the 2D:4D in ASD for which we have included 16 case-control studies. Nevertheless, the effective measurement of sex steroid levels in the amniotic fluid with a prospective follow-up has been performed by a few researchers.

Table 6. Quality assessment of the included studies using the Newcastle-Ottawa Scale

Diagnosis	Study characteristics			Selection					Comparability		Exposure				Total (n)
	First author	Year	Country	Diagnostic adequacy	Representativeness of the cases	Selection of controls	Definition of controls	Total (n)	Comparability	Total (n)	Ascertainment of 2D:4D	Same method of ascertainment for cases and controls	Missing data rate	Total (n)	
Attention deficit-hyperactivity disorder															
	Buru	2017	Turkey	*	*	/	/	2	/	0	*	*	*	3	5
	Lemiere	2010	Belgium	*	/	*	*	3	/	0	*	*	*	3	6
	Martel	2009	USA	*	*	*	*	4	* (age)	1	*	*	*	3	8
	McFadden	2005	USA	*	*	*	*	4	** (age, gender, CEOAEs)	2	*	*	*	3	9
Autism spectrum disorder															
	Al-Zaid	2015	Saudi Arabia	*	/	/	*	2	** (age, gender)	2	*	*	*	3	7
	Baharara	2014	Iran	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Bejerot	2012	Sweden	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	De Bruin	2006	The Netherlands	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Falter	2008	UK	*	/	*	*	3	** (age, sex, non-verbal reasoning ability)	2	*	*	*	3	8
	Hauth	2014	The Netherlands	*	*	/	*	3	/	0	*	*	*	3	6
	Krajmer	2011	Slovak Republic	*	/	/	*	2	/	0	*	*	/	2	4
	Lai	2013	UK	*	/	/	*	2	** (age, gender)	2	*	*	*	3	7
	Masuya	2015	Japan	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Milne	2006	UK	*	/	/	/	1	* (age)	1	*	*	/	2	4
	Manning	2001	UK	/	/	*	*	2	* (age)	1	*	*	*	3	6
	Nojpayak	2009	Thailand	*	/	/	/	1	** (age, gender)	2	*	*	*	3	6
	Rohde	2018	Germany	*	*	/	*	3	** (age, gender)	2	*	*	/	2	7
	Schieve	2018	USA	*	*	*	/	3	* (age)	1	*	*	/	2	6
	Sugie	2010	Japan	*	/	/	/	1	** (age, gender, IQ)	2	*	*	*	3	6
	Togo	2019	Japan	*	*	*	/	3	** (age, handedness, full scale IQ)	2	*	*	*	3	8
Intellectual disability															
	Ypsilanti	2008	Greece	*	*	*	*	4	/	0	*	*	*	3	7

Table 6. Continued

Diagnosis	Study characteristics			Selection					Comparability		Exposure				Total (n)
	First author	Year	Country	Diagnostic adequacy	Representativeness of the cases	Selection of controls	Definition of controls	Total (n)	Comparability	Total (n)	Ascertainment of 2D:4D	Same method of ascertainment for cases and controls	Missing data rate	Total (n)	
Schizophrenia															
	Akgul	2017	Turkey	*	/	*	*	3	** (age, gender, education)	2	*	*	*	3	8
	Bolu	2015	Turkey	*	/	*	*	3	* (age)	1	*	*	*	3	7
	Collinson	2010	Singapore	*	/	*	/	2	/	0	*	*	*	3	5
	Divakaran	2012	India	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Paipa	2018	Spain	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Qian	2016	China	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Venkatasubramanian	2011	India	*	*	/	*	3	** (age, sex)	2	*	*	*	3	8
	Zhu	2014	China	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
Alcohol dependence															
	Han	2016	South Korea	*	/	*	*	3	/	0	*	*	*	3	6
	Lenz	2017	Germany	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Kornhuber	2011	Germany	*	*	*	/	3	/	0	*	*	*	3	6
Heroin dependence															
	Canan	2018	Turkey	*	*	*	*	4	* (age)	1	*	*	*	3	8
	Cicek	2017	Turkey	*	*	/	/	2	* (age, education)	1	*	*	*	3	6
Gender nonconformity															
	Hisasue	2012	Japan	*	/	/	/	1	** (age, gender)	2	*	*	*	3	6
	Kraemer	2009	Switzerland	*	*	*	*	4	** (age, gender, sexual orientation)	2	*	*	*	3	9
	Leinung	2017	USA	*	/	*	*	3	/	0	*	*	*	3	6
	Schneider	2006	Germany	/	*	/	/	1	** (age, gender)	2	*	*	/	2	5
	Vujović	2014	Serbia	*	*	/	/	2	/	0	*	*	*	3	5
	Wallien (study 1, 2)	2008	The Netherlands	*	*	*	*		** (age, gender, sexual orientation)		*	*	*	3	9
Mood disorders															
	Sanwald	2019	Germany	*	/	*	*	3	** (age, gender, handedness)	2	*	*	*	3	8
	Tegin	2019	USA	*	*	*	*	4	** (age, gender, race, dominant hand)	2	*	*	*	3	9

One star (*) indicates that the item is satisfied, while a slash (/) is assigned when the item is not fulfilled by the study. Comparability can be judged with up to two stars according to the number of control parameters reported by the researchers. One star (*) indicates that the control group has been matched with the patients' group according to one parameter; two stars (**) indicate two or more control parameters. The total score for each study is given by the sum of the stars.
2D:4D, Second-to-fourth Digit Ratio; CEOAEs, click-evoked otoacoustic emissions; IQ, intelligence quotient.

Auyeung *et al.* [73] positively correlated fetal testosterone levels with autism-related behaviors at 18−24 months and at 6−9 years [74]. Elevated fetal steroidogenic activity during the prenatal masculinization window in the amniotic fluid of autistic boys was confirmed by subsequent research [75]. On the contrary, Kung *et al.* [76] recently found no relationship between prenatal androgen exposure and autistic traits in typically developed children nor in young children with congenital adrenal hyperplasia. Of note, 2D:4D has been negatively associated with empathy [77], which is typically lower in people with ASD [78]; conversely, it seems positively correlated with systemizing traits [79], which are more pronounced in autistic individuals [80]. In 2002, Baron-Cohen developed the so-called theory of the "extreme male brain". This theory assumes that women tend to have more social intelligence (i.e., empathizing ability), whereas men tend to excel at following rules and recognizing patterns (i.e., systemizing ability). The "male brain" is typical of individuals in whom systemizing is significantly better than empathizing, while the "female brain" defines the opposite cognitive profile. Using these definitions, ASD could be considered as an expression of the "extreme male brain" [81]. The potential role of fetal testosterone in the onset of ASD is further supported by the link found between autism and maternal polycystic ovarian syndrome, a condition associated with androgenic excess [82]. Moreover, both autistic women and their mothers have elevated rates of steroid-related cancers, such as breast and ovarian cancer [83]. In summary, our findings reflect previous literature: subjects with ASD have significantly lower 2D:4D than controls, suggesting higher levels of fetal testosterone exposure.

Contrary to previous studies [84], our results did not support the notion that patients with schizophrenia would be exposed to lower levels of prenatal testosterone. In fact, it has been hypothesized that schizophrenia, in opposition with ASD, could reflect the "extreme female brain", with higher empathizing and lower systemizing abilities [81]. However, as underlined by other researchers, this theory might be erroneously based on the presumption that "*hyperdeveloped theory-of-mind skills*" in psychotic patients "*would be accurate and adaptive, rather than pathological*" [85]. Indeed, our findings did not confirm the theory of the "extreme female brain", as 2D:4D did not significantly differ between patients with schizophrenia and controls, thus suggesting no differences in empathizing and/or systemizing traits, neither in prenatal exposure to sex hormones. In fact, a significant difference was found only in the right hand of males with schizophrenia (MD = 0.009).

The evidence on addictions was quite robust, as 2D:4D resulted significantly lower in patients than healthy controls (MD = −0.014), indicating exposure to higher levels of prenatal testosterone. Even if no specific studies have evaluated the levels of sex steroids in the amniotic fluid in people with addictions—due to the obvious difficulties in following up the subjects for many years—some studies have linked several typical features of individuals with substance misuse to the digit ratio. For instance, it has been shown that 2D:4D is negatively correlated with risk-taking [18,86] and sensation-seeking [87,88]. Such features have been in turn linked to a higher vulnerability to addictions [89]. 2D:4D appears also negatively correlated with aggression [90] and impulsivity [91], which are in turn connected to the use of illicit substances, particularly alcohol and heroin [92], such as those used by the groups of patients included in our meta-analysis. Other authors [93] have argued an association between 2D:4D and externalizing behavioral symptoms in young boys: it is well-known that conduct disturbances confer an increased risk for substance abuse later in life [94]. Notably, this negative association between 2D:4D and externalizing behaviors may partially explain also the significant difference found between children with ADHD and non-clinical controls (MD = −0.0124).

Our meta-analyses did not retrieve any significant differences between people with non-conforming gender identities, mood disorders and ID, and non-clinical controls. The case of gender identity might seem surprising since in the imagination sex hormones are strictly connected to gender expression. However, it has been reported that gender identity is not exclusively related to prenatal exposure of androgens [95,96], but appears to be strongly influenced by genetic and social factors, with adolescence being a key period for the development of non-conforming identities [97,98]. As far as concern ID and mood disorders, it is worth noting that we have retrieved only one and two studies, respectively, and thus it is too premature to drive to any conclusion.

To our knowledge, this is the most up-to-date and comprehensive meta-analysis examining the 2D:4D ratio in

psychiatry. However, some limitations should be discussed. First, we have included only papers in which psychiatric diagnoses were confirmed by clinicians or valid international diagnostic criteria. Therefore, we have excluded papers reporting analyses about 2D:4D in self-diagnosed individuals, or individuals which were classified as having a disorder only according to self-reported questionnaires [99,100]. Also, we excluded papers about new addictions, such as videogames or computer addiction, which have been instead considered in a previous meta-analysis [101]. A second major limitation is related to the different types of measurement used by the authors included in the studies. In fact, some authors have suggested that indirect 2D:4D measurements (such as in many of the studies included in the present review) may overestimate the length of the ring finger thereby distorting the 2D:4D ratio [16]. Another limitation, directly related to the meta-analytic approach, is the presence of clinical heterogeneity which could not be controlled as for statistical heterogeneity. Even if we tried to reduce clinical heterogeneity by selecting patients with standardized diagnoses, we could not account for the presence of individual or genetic differences, as well as for the influence of environmental factors. Finally, the number of studies included in the meta-analyses were generally small.

In conclusion, our results are promising and highlight the importance of prenatal hormonal factors in the etiopathogenesis of some psychiatric disorders. However, they need to be cautiously interpreted as the measurement of 2D:4D ratio cannot prescind from a complex and exhaustive assessment process. It is important to consider, in fact, that a number of other physiological and pathological conditions linked to the prenatal exposure to sex hormones may influence the length of digit ratio, thus representing potential confounders. The absence of a definite cut-off also represents a limitation for the clinical application of 2D:4D. Future research should investigate more in-depth the relationships between 2D:4D and psychiatric disorders, focusing on other conditions characterized by traits that seem to be linked to lower or higher digit ratio, such as borderline and antisocial personality disorders, eating disorders, or disruptive mood dysregulation disorder.

SUPPLEMENTARY MATERIALS

Supplementary data is available online (https://doi.org/10.6084/m9.figshare.12220493.v1).

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Laura Fusar-Poli conceptualized the study, supervised data extraction, and wrote the original draft of the manuscript. Alessandro Rodolico performed statistical analyses and participated to write the first draft of the manuscript. Serena Sturiale, Bianca Carotenuto, Antimo Natale, and Davide Arillotta performed data extraction and edited the manuscript. Spyridon Siafis helped in statistical analyses and contributed to write the manuscript. Maria Salvina Signorelli and Eugenio Aguglia supervised the project and edited the draft of the manuscript. All authors have read and approved the final version of the manuscript.

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CASE REPORT
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Case Report: Whole Exome Sequencing Revealed Disease-Causing Variants in Two Genes in a Patient With Autism Spectrum Disorder, Intellectual Disability, Hyperactivity, Sleep and Gastrointestinal Disturbances

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Autism Spectrum Disorder (ASD) refers to a broad range of conditions characterized by difficulties in communication, social interaction and behavior, and may be accompanied by other medical or psychiatric conditions. Patients with ASD and comorbidities are often difficult to diagnose because of the tendency to consider the multiple symptoms as the presentation of a complicated syndromic form. This view influences variant filtering which might ignore causative variants for specific clinical features shown by the patient. Here we report on a male child diagnosed with ASD, showing cognitive and motor impairments, stereotypies, hyperactivity, sleep, and gastrointestinal disturbances. The analysis of whole exome sequencing (WES) data with bioinformatic tools for oligogenic diseases helped us to identify two major previously unreported pathogenetic variants: a maternally inherited missense variant (p.R4122H) in *HUWE1,* an ubiquitin protein ligase associated to X-linked intellectual disability and ASD; and a *de novo* stop variant (p.Q259X) in *TPH2*, encoding the tryptophan hydroxylase 2 enzyme involved in serotonin synthesis and associated with susceptibility to attention deficit-hyperactivity disorder (ADHD). *TPH2*, expressed in central and peripheral nervous tissues, modulates various physiological functions, including gut motility and sleep. To the best of our knowledge, this is the first case presenting with ASD, cognitive impairment, sleep, and gastrointestinal disturbances linked to both *HUWE1* and *TPH2* genes. Our findings could contribute to the existing knowledge on clinical and genetic diagnosis of patients with ASD presentation with comorbidities.

Keywords: autism spectrum disorder, attention deficit disorder and hyperactivity, whole exome sequencing, sleep disturbance, oligenic disease, ORVAL, gut motility disorders

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by etiological and clinical heterogeneity, with a frequency around 1% in the general population (Nevison et al., 2018). In the wide picture of ASD, the major clinical manifestations are communicative impairments, difficulties in social interaction, behavior abnormalities. Indeed, ASD patients frequently present with comorbidities, such as intellectual disability (ID) (Postorino et al., 2016), epilepsy (Besag, 2018), sleep or gastrointestinal disturbances (Devnani and Hegde, 2015; Bjorklund et al., 2020; Brooks et al., 2020).

The genetic basis of ASD is deeply heterogeneous implicating different genes, in turn involved in different pathways and biological processes, as those regulating synaptic plasticity, chromatin remodeling, gene transcription, and protein degradation (Bourgeron, 2015). Single nucleotide changes or larger genomic alterations, as copy number variations (CNVs), can be found in ASD cases (Sanders et al., 2015), and recent studies proved that the use of Whole Exome Sequencing (WES) together with CNVs analysis can identify a pathogenetic variant in about 30% of patients (Munnich et al., 2019).

We here report on a male child with ASD and a complex phenotype, who was analyzed by WES with a bioinformatic tool for investigating variants in oligogenic diseases. The results suggest a hypothetical scenario in which two genes (*HUWE1* and *TPH2*) plus 4 possible modifiers could play a role in the patient's phenotype.

METHODS

Clinical Assessment

The clinical assessment of the patient comprised a neurological-behavior examination and evaluation of his sleep and gastrointestinal disturbances as detailed in **Supplementary Material**.

Whole Exome Sequencing

Genomic DNA extraction and subsequent WES and data analysis for affected individual and his parents were carried out by Italian Institute of Technologies (IIT) in Genoa, Italy. Briefly, the exomes were captured using the xGen® Exome Research Panel v1.0 – IDT KIT. Sequences were enriched using the Illumina Nextera Flex For Enrichment KIT. Sequencing was performed on an Illumina NovaSeq 6000 platform (Illumina Inc., CA, USA). The library preparation and its sequencing were performed simultaneously for the parents and the proband using barcode adapters. Alignment of raw paired-end reads to the reference genome (version hg19) was performed with bwa (version 0.7.17) (Li and Durbin, 2010). Duplicated reads were marked with picard (version 2.18.20). Variant discovery was then performed with the GATK4 utility HaplotypeCaller, using the appropriate file containing the coordinates of the sequences targeted by the exome sequencing. Finally all variants were annotated using annovar (databases updated to 27/05/2019) (Wang et al., 2010). The resulting file was used for a manual evaluation of the variants. The sequencing provided a 60x medium coverage.

Variant Prioritization

For the interpretation of variants pathogenicity, we integrated several tools. To unveil the contribution of multiple genes to the patient's phenotype, we used a new platform for the prediction and exploration of candidate disease-causing oligogenic variant combinations (ORVAL, Oligogenic Resource for Variant AnaLysis) following authors recommendations (Renaux et al., 2019). Briefly, we prepared two files: (i) an input file with a list of selected candidate variants and (ii) one file with genes related or possibly related to ASD to be used as "gene panel" file for variant filtering.

The list of candidate variants was obtained by considering the following filtering steps: variants with a frequency below 3% in ExAC/GnomAD v2.11/1000g2015; only exonic, splicing, non-synonymous and stopgain variants with a good coverage were considered; we discarded those variants predicted to be benign or tolerated in PolyPhen and SIFT and retained those with CADD score $\geq$ 20; we also discarded those variants found in more than 1% of in-house controls (i.e., not diagnosed with ASD or any neuropsychiatric disease). Filtering was also based on annotation in public databases as Mouse Genome Database (MGD), OMIM, PubMed, ClinVar. Following this procedure we obtained a list of 71 candidate variants, including both *de novo* and inherited, to be used as input in ORVAL.

The "gene panel" file consisted of genes selected based on three criteria: those related to ASD and present in the SFARI (Simons Foundation Autism Research Initiative) database (August 2020 release); genes with high brain expression, defined as those genes with average log2 RPKM >4.5 in the BrainSpan database (http://www.brainspan.org) (the top 18%) (Miller et al., 2014; Addis et al., 2018) and genes of the KEGG pathways (https://www.genome.jp/kegg) selected for their possible relevance with ASD.

From the output file, a list of possible 23 variants, we kept only those genes/variants characterized by pathogenicity confidence score higher than 99%. These selected genes underwent through a manual revision considering literature and available databases. Briefly, we analyzed all the selected output variants for deleterious prediction through Varsome (Kopanos et al., 2019), we considered the intolerance to loss-of-function variants (pLI) and the deviation of the observed number of missense variants from the expected number (Mis Z-score), as computed by the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/) (genes with pLI scores of 0.9 or higher are extremely intolerant to heterozygous LoF variation, and thus haploinsufficient; Z-scores of 3.09 or higher indicate intolerance to missense variation) (Lek et al., 2016), we also considered haploinsufficiency on the base of an HIPred_score above 0.5 (Shihab et al., 2017). Finally, a list of 6 variants in 6 genes was obtained.

Selected variants in the candidate genes were all validated by co-segregation analysis using polymerase chain reaction (PCR), and bi-directional Sanger sequencing using the ABI 3730 automated sequencer (Applied Biosystems, Forster City, CA, USA).

Network Analysis of Candidate Genes

To unveil enrichment of annotations of identified genes and known ASD genes, we used GeneCodis4 tool (Tabas-Madrid et al., 2012), as already described (Vaccari et al., 2016). Briefly, a list enclosing all 6 candidate genes, obtained from the ORVAL analysis and that passed our manual inspection, together with all genes present in the SFARI database (August 2020 release) were used as input in GeneCodis4 (total genes = 934). Among the databases of biological knowledge available in GeneCodis4, we focused on the GO Biological Process (BP) domain. In the analysis, the hypergeometric test was applied followed by the false discovery rate correction (FDR) with a cut-off of 5% to determine which annotations were significantly enriched. All genes of the top gene ontology terms, including candidate and SFARI genes, were then projected onto the STRING network (v11) (Szklarczyk et al., 2019). Edges within the STRING network were thresholded at 0.4, according to the authors' recommendation. A graphical representation of the GeneCodis4 and STRING results was obtained by using Cytoscape tool (Shannon et al., 2003).

CASE PRESENTATION

We report on a 5-years old male patient born to non-consanguineous Italian parents. The child came to our attention at the age of 3 years for third level investigations, when he had already performed several clinical assessments and tests at the territorial structures (see the timeline, **Figure 1**). After a thorough medical history and after having viewed and analyzed the clinical documentation, he was diagnosed with ASD even by the help of Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). He had developmental delay, absent language, motor impairment, auto and hetero-direct aggressivity, hyperactivity, attentional lability, stereotypes.

In the past, metabolic defects and the main syndromes in differential diagnosis were excluded, Fragile X Syndrome and Prader-Willi/Angelman Syndromes (see timeline, **Figure 1**).

More in details, the clinical assessment of the patient through specific tests showed a low adaptive level for chronological age, prevailing on communication and socialization domains, a deficit on ability of inhibit and self-control inhibition, metacognition, working memory, and ability of organization/planning, problems in the area of withdrawal and isolation, anxiety and depression, somatic complaints, and attentional disturbances, marked impairments on language understanding and production.

By using specific tests (Sleep-CGI-S, Sleep-CGI-I, SDSC) the patient was diagnosed with a moderate sleep disorder. Sleep-CGI-S showed a moderate sleep disorder with marked bedtime resistance, moderate sleep onset delay, moderate difficult to fall asleep, multiple night wakings and family functioning moderately affected. Instead Sleep-CGI-I reported minimal improving in ability to fall asleep, a major improving in bedtime resistance, sleep onset delay, night wakings, and family functioning. At SDSC the results confirmed the mentioned sleep disorders. In particular, the patient has been treated with clonazepam for 2 months and then, until now, with melatonin, that slightly improved his condition (see timeline, **Figure 1**).

Using the Criteria of Rome IV, functional constipation (3 criteria) and functional aerophagia (4 criteria) were diagnosed.

Results obtained from neurological-behavior tests and of sleep evaluation are reported in **Supplementary Table 1**.

RESULTS

Identification of Candidate Genetic Variants

Given the complexity of the patient's phenotype, we suspected a possible genetic basis involving multiple genes. Accordingly, for the identification of candidate variants, we used a bioinformatic tool for the study of oligogenic diseases.

After the bioinformatic analysis of WES data an unreported maternally inherited missense variant affecting the E3 ubiquitin ligase (HECT) domain of *HUWE1* (NM_031407:exon79: c.12 365G>A:p.R4122H), and a *de novo* unreported stop variant in *TPH2* (NM_173353:exon6: c.775C>T:p.Q259X) (see **Figure 2A**, **Table 1**) were identified.

HUWE1 encodes an ubiquitin protein ligase involved in various cellular processes, including synaptogenesis, associated to the Turner type X-linked syndromic cognitive disability (OMIM:309590) and ASD (Moortgat et al., 2018). The *TPH2* gene encodes the tryptophan hydroxylase 2 enzyme involved in serotonin synthesis in central and peripheral nervous tissues. Serotonin modulates various physiological functions, including regulation of gut motility and sleep (Jones et al., 2020). *TPH2* variants are associated to susceptibility to attention deficit-hyperactivity disorder (OMIM:613003) and unipolar depression (OMIM:608516).

The analysis unveiled the presence of additional variants in the following genes, *ALDH5A1, ATG7*, *ITPR3,* and *DIP2C*.

The *ALDH5A1* variant is a rare, maternally inherited stop variant (NM_170740:exon4: c.612G>A:p.Trp204X). *ALDH5A1* encodes the succinic semialdehyde dehydrogenase, implicated in the neurotransmitter GABA catabolism (Chambliss et al., 1995). Homozygous or compound heterozygous mutations in *ALDH5A1* cause the succinic semialdehyde dehydrogenase deficiency (OMIM:271980), a rare complex neurologic disorder mainly characterized by mental retardation and sleep disturbances. By further investigating WES data, we unveiled an additional, paternally inherited, variant in *ALDH5A1* (NM_170740:exon3:c.538C>T:p.His180Tyr). This last variant, present in the general population with a frequency of 0.3154, was considered a hypomorphic variant, leading to a reduction of *ALDH5A1* enzymatic activity of about 20% (Blasi et al., 2002).

The *ITPR3* variant is a paternally inherited, rare missense variant (NM_002224:exon36: c.4862T>C:p.Leu1621Pro). *ITPR3* encodes for the inositol 1,4,5-trisphosphate receptor that transduces many hormonal signals regulating Ca(2+)-dependent processes. To note, the mouse carrying the *tf* spontaneous mutation of the *Itpr3* gene (BTBR T+ Itpr3tf /J strain) has been used as a model of ASD (McFarlane et al., 2008).

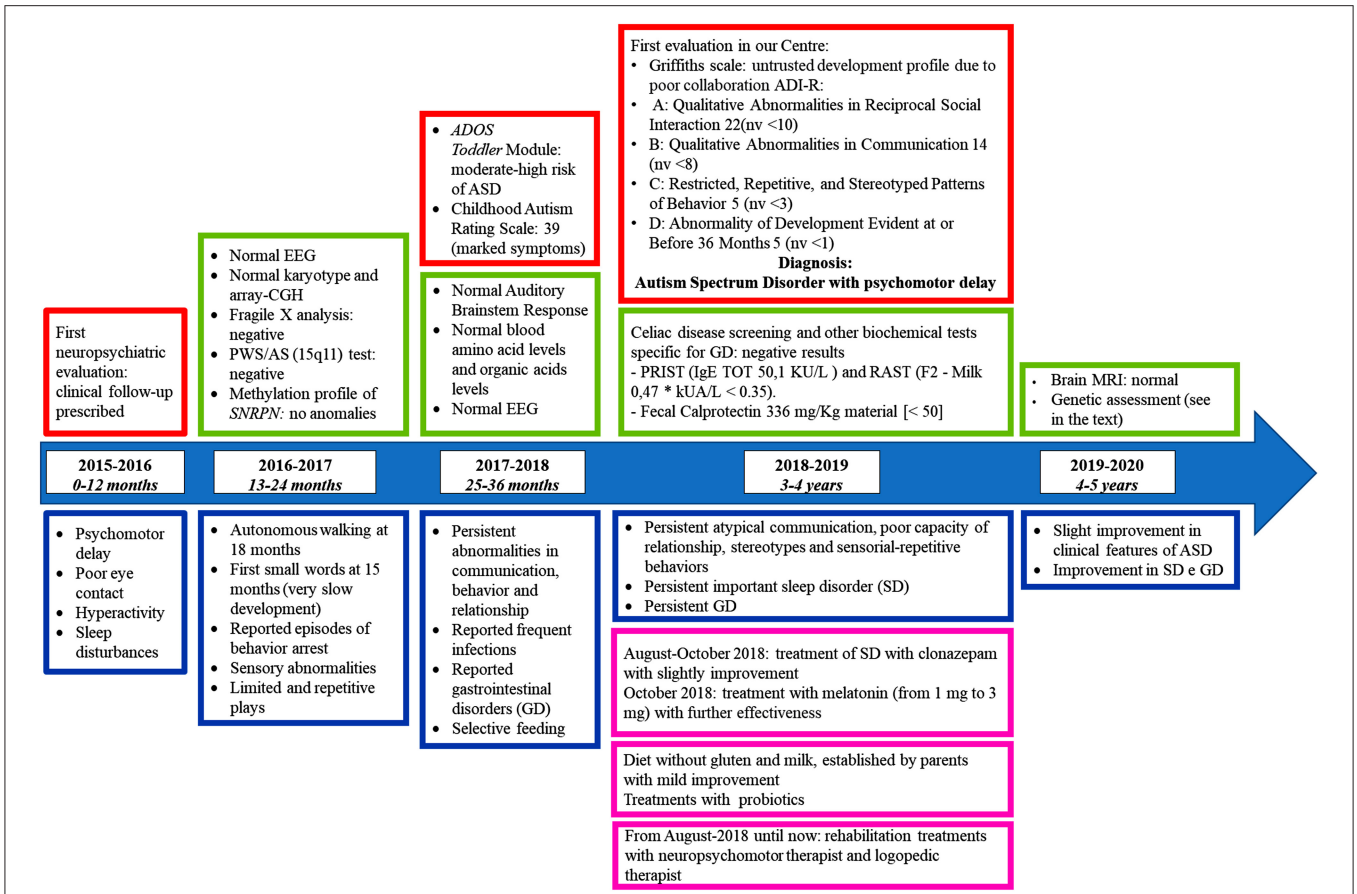

FIGURE 1 | Timeline with patient's relevant clinical data. In this figure main signs and symptoms (blue) shown by the patient, data from his clinical evaluations (red), results of laboratory tests (pink), and treatments (green) are reported. PWS/AS, Prader-Willi Syndrome/Angelman Syndrome; GD, gastro-intestinal disorders; SD, sleep disorders; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview-Revised; ASD, Autism Spectrum Disorder; PRIST, Paper Radio Immuno Sorbent Test; RAST, Radio Allergo Sorbent Test; MRI, Magnetic Resonance Imaging; nv, normal value.

The patient showed a maternally inherited unreported missense variant of *DIP2C* (NM_014974:exon7: c.757C>T:p.Arg253Trp). *DIP2C* encodes a member of the disco-interacting protein homolog 2 family, known to regulate several genes and pathways important in neurological functions (Oo et al., 2020). To note, in ASD cases *de novo* loss of function variants were found in *DIP2C*, which is reported in SFARI database as candidate ASD gene (Yuen et al., 2017).

The maternally inherited *ATG7* variant is a rare missense variant (NM_006395:exon12: c.1277C>T:pPro426Leu). *ATG7* encodes an ubiquitin-activating enzyme E1-like protein that mediates membrane fusion in autophagy (Tanida et al., 2001). Autophagy deficiency induced by conditional Atg7 deletion leads to a similar autistic-like behavioral abnormalities in mice (Hui and Tanaka, 2019). *ATG7* plays a role in modulation of dendritic arborization, and synapses elimination during development, mechanisms relevant to the etiology of neurodevelopmental disorders as ASD (Kim et al., 2017).

We investigated the role of the 6 candidate genes in already known ASD-associated biological processes and their possible connection among each other and with other ASD-associated genes reported in SFARI database.

The results indicated that each of the analyzed genes, except *DIP2C*, takes part to at least one process in which other SFARI genes are involved, namely "long term synaptic potentiation," "neurotransmitter catabolic process," "circadian rhythm," "regulation of circadian rhythm," "cell differentiation" (**Figure 2B, Table 2**).

DISCUSSION AND CONCLUSION

ASD is a complex and heterogeneous condition characterized by impaired communication and social interaction, repetitive behaviors, and restricted interests and associated with a range of comorbid conditions. Intellectual disabilities can affect around 50% of ASD cases (Postorino et al., 2016), ADHD is present in about 11% of children and even higher in adult ASD patients (Lugo et al., 2020), and sleep and gastrointestinal disturbances have elevated prevalence in ASD cases compared to controls (Devnani and Hegde, 2015; Bjorklund

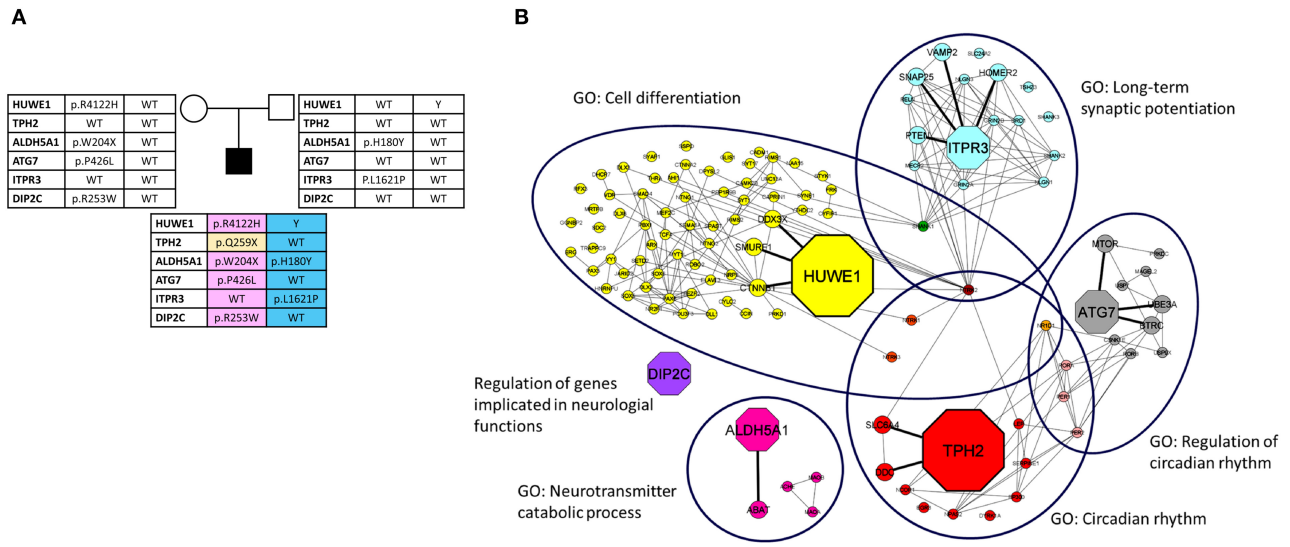

FIGURE 2 | (A) Family's pedigree. Implicated genes and their variants, indicated as amino acid changes, are shown. **(B)** Network analysis. The network depicts the protein-protein interactions (gray lines) revealed by STRING analysis (visualized by Cytoscape tool) on the basis of the enrichment obtained with GeneCodis4 tool. The Figure shows the enriched BP terms clustering the six candidate genes (octagon shape) and the SFARI genes (circle shape). Three candidate genes are also in the SFARI database (*HUWE1, ALDH5A1, DIP2C*). The network has a clear distinction into 6 clusters representing the top six GO-BPs (large ovals).

TABLE 1 | Overview of the variants found in the patient.

Gene	Position	Fnc	RefSeq ID	Variation	GnomAD	1000G	SIFT	Poly-phen2	CADD	dbSNP ID	Var	pLI	Z score	Hapl-insuf
*HUWE1**	X: 53563401	M	NM_031407	c.12365G>A:p.R4122H	NA	NA	D	D	27.7	NA	LP	1	8.87	0.831
TPH2	12: 72366465	Sg	NM_173353	c.775C>T:p.Q259X	NA	NA	–	–	40	NA	VUS	0	1	0.653
ALDH5A1#	6: 24505099	Sg	NM_170740	c.612G>A:p.W204X	0.00004	NA	–	–	41	rs118203982	P	0	0.73	0.505
ALDH5A1#	6:24503590	M	NM_170740	c.538C>T: p.H180Y	0.3105	0.3147	T	B	7.5	rs2760118	B	0	0.73	0.505
ITPR3	6: 33651870	M	NM_002224	c.4862T>C:p.L1621P	0.00001	NA	D	D	29.3	rs1217162248	VUS	0	4.55	0.603
DIP2C°	10: 461811	M	NM_014974	c.757C>T:p.R253W	NA	NA	D	D	34	NA	VUS	1	4.67	0.563
ATG7	3: 11389502	M	NM_006395	c.1277C>T:p.P426L	0.00120	0.0004	D	D	34	rs143545741	VUS	0	1.37	0.652

*Fnc, Function; M, Missense; Sg, Stopgain; NA, not available; D, deleterious; T, tolerated; CADD score, amino acid substitution is predicted damaging if the score is >15; Var, Varsome; VUS, Variant of Uncertain Significance; B, Benign; LP, Likely Pathogenic; P, Pathogenic; GnomAD is referred to GnomAD Exome ALL. *, SFARI gene, syndromic "S"; #, SFARI gene, score 1; °, SFARI gene, score 2.*

et al., 2020). The genetic base of ASD is also heterogeneous, involving at least 102 risk genes (Satterstrom et al., 2020). ASD-associated variants can be rare or more common in the general population. Finally, compensatory mechanisms can tune the major or the minor effect of the variations determining the phenotype present in each subject (Bourgeron, 2015).

In our case, the patient presented ASD associated with intellectual disability, ADHD, sleep, and gastrointestinal disorder. By a deep bioinformatic analysis of WES data we identified *de novo* and inherited variants in six different genes that globally could explain the complex phenotype shown by this patient.

The *HUWE1* p.R4122H variant lies in the HECT domain, known to present an overrepresentation of deleterious variants in patients with X-linked ID (Moortgat et al., 2018). *In vitro* experiments demonstrated that mutations in the HECT domain are likely to impair the gene function (Giles and Grill, 2020). Indeed, certain *HUWE1* variants are present in patients with autism in addition to ID, suggesting *HUWE1* variants could be risk factors for ASD (Giles and Grill, 2020). In the present case, the *HUWE1* variant could account for ID and contribute to ASD together with the other gene candidates. *TPH2* is involved in the synthesis of serotonin, a neurotransmitter with a role in the control of mood, anxiety, sleep-wake regulation and, peripherally, in the modulation of gastrointestinal motility. It has been reported that behavioral symptoms can be associated with gastrointestinal abnormalities in ASD patients, and, in particular, that ASD patients with sleep problems are more likely to have gastrointestinal abnormalities (Maenner et al., 2012; Bjorklund et al., 2020). In this line, we suggest that the *TPH2 de novo* stop variant could account for the hyperactivity, attentional lability, sleep and gastrointestinal disturbances present in this patient.

TABLE 2 | Biological processes associated with genes implicated in the present case and genes reported in the SFARI database.

Annotation	Term	Term genes found	Input size	Term genes	Genes universe	Hyp pval	Hyp pval_adj	Genes
GO:0060291	Long-term synaptic potentiation	17	934	45	18,883	0.0000	0.0000	SLC24A2, SHANK2, NLGN1, VAMP2, SNAP25, PTEN, RELN, NTRK2, MECP2, **ITPR3**, GRIN2B, GRIN2A, SHANK3, DRD1, TSHZ3, NLGN3, SHANK1
GO:0060999	Positive regulation of dendritic spine development	10	934	23	18,883	0.0000	0.0000	ZMYND8, SHANK2, NLGN1, **DLG5**, CDKL5, ITSN1, MTOR, FMR1, SHANK3, SHANK1
GO:0007623	Circadian rhythm	17	934	91	18,883	0.0000	0.0001	NCOR1, NR1D1, PER2, SLC6A4, RORA, PER1, SERPINE1, NTRK3, NTRK2, NTRK1, NPAS2, LEP, **TPH2**, EP300, EGR3, DYRK1A, DDC
GO:0042752	Regulation of circadian rhythm	14	934	66	18,883	0.0000	0.0002	**ATG7**, NR1D1, BTRC, PER2, USP9X, USP7, UBE3A, RORB, RORA, PRKDC, PER1, MTOR, MAGEL2, CSNK1E
GO:0042135	Neurotransmitter catabolic process	5	934	10	18,883	0.0001	0.0021	**ALDH5A1**, ACHE, MAOB, MAOA, ABAT
GO:0030154	Cell differentiation	70	934	1,019	18,883	0.0036	0.0423	CADM1, SYNE1, CYFIP1, SSPO, MYT1L, UNC13A, RIMS1, NTNG1, **HUWE1**, RIMS2, NR1D1, CCIN, SEMA5A, NRP2, CAMK2B, YY1, VDR, THRA, NR2F1, TCF4, SYT1, SPAST, SOX5, SDC2, ROBO2, RFX3, PRKD1, POU3F3, PBX1, PAX6, PAX5, NTRK3, NTRK2, NTRK1, MEF2C, SMAD4, CAPRIN1, JARID2, HNRNPU, FRK, ARX, GLIS1, SYAP1, ERG, PPP1R9B, NTNG2, ELAVL3, TRAPPC9, NAA15, GGNBP2, DPYSL2, YTHDC2, DLX6, DLX3, DLX2, DHCR7, MRTFB, SMURF1, DDX3X, SOX6, STYK1, FEZF2, CYLC2, AHI1, CTNNB1, CTNNA2, SYT17, SHANK1, SETD2, DLL1

Term genes found, number of annotated genes in the reference list; Input size, total number of genes in the input list, including the genes implicated in the present case and the SFARI list genes; Term genes, number of annotated genes in the reference list; Genes universe, total number of human reference genes; Hyp pval, hypergeometric test pValue; Hyp pval_adj, corrected hypergeometric pValue using FDR procedure.

For function and pattern of inheritance, *HUWE1* and *TPH2* could play a major role in the patient's phenotype.

Variants were also identified in *ALDH5A1*, whose absence of activity has been associated to a recessive severe phenotype. In the present case, we could speculate that the stop and the hypomorphic variants leave a quantity of expressed enzyme lower than that expressed by a heterozygous carrier, in this way contributing to the patient's phenotype (Oikonomou et al., 2019; Jones et al., 2020).

Three additional deleterious variants were found, inherited from either patient's healthy mother (*ATG7*, *DIP2C*) or his healthy father (*ITPR3*) suggesting that taken individually, in heterozygosis, these variants do not lead to altered neurodevelopment. Since gene enrichment analysis highlighted they take part to functions notably impaired in ASD, we are unable to exclude they play a role in the patient's phenotype. Rather, they could contribute to the patient's complex phenotype as modifier genes.

To note, increasing findings support an oligogenic model of inheritance for ASD, and combination of inherited and/or *de novo* variants were predicted to range from 2 to 10 (Pickles et al., 1995). However, genetic variants, their connections and how they can act in every single patient, are aspects still largely to be elucidated.

In conclusion, by using an oligogenic approach to the analysis of WES data, we identified a *de novo* stop variant in *TPH2* and one deleterious missense variant in *HUWE1* that could act in a permissive genetic background characterized by deleterious variants in additional four genes. All variants collectively could have a role in the biological processes involved in the pathogenesis of ASD thus contributing to the different features of the patient's phenotype. As this hypothesis is based on the study of a single patient and on variants predicted to be deleterious by bioinformatic analyses, future functional studies are needed to elucidate specific roles of identified genes and variants in the patient's complex phenotype.

DATA AVAILABILITY STATEMENT

Clinical and genetic variant details have been deposited in the Decipher database. Accession number: Patient 421248.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Italian Regione Liguria (P.R. 399REG2017). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s) legal guardian/next of kin, for the publication of data included in this article.

AUTHOR CONTRIBUTIONS

GS, DV, RS, and SG were responsible for whole exome sequencing. MC, MSq, MSe, and AP were responsible for the variant prioritization, oligogenic and network analyses. LP, BB, SB, and LN were in charge of the clinical diagnosis. MD, ML, and AP were in charge of genetic counseling, family recruitment, and ethical procedures. LP and AP wrote the manuscript. All authors gave advises when doing the gene analysis, reviewed the manuscript, and agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2021.625564/full#supplementary-material

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Executive Functions in Neurodevelopmental Disorders: Comorbidity Overlaps Between Attention Deficit and Hyperactivity Disorder and Specific Learning Disorders

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The present study examines the comorbidity between specific learning disorders (SLD) and attention deficit and hyperactivity disorder (ADHD) by comparing the neuropsychological profiles of children with and without this comorbidity. Ninety-seven schoolchildren from 8 to 14 years old were tested: a clinical sample of 49 children with ADHD (n = 18), SLD (n = 18) or SLD in comorbidity with ADHD (n = 13), and 48 typically-developing (TD) children matched for age and intelligence. Participants were administered tasks and questionnaires to confirm their initial diagnosis, and a battery of executive function (EF) tasks testing inhibition, shifting, and verbal and visuospatial updating. Using one-way ANOVAs, our results showed that all children in the clinical samples exhibited impairments on EF measures (inhibition and shifting tasks) when compared with TD children. A more specific pattern only emerged for the updating tasks. Only children with SLD had significant impairment in verbal updating, whereas children with ADHD, and those with SLD in comorbidity with ADHD, had the worst performance in visuospatial updating. The clinical and educational implications of these findings are discussed.

Keywords: ADHD, SLD, comorbidity, neurodevelopmental disorders, executive functions

INTRODUCTION

Neurodevelopmental disorders are mainly explained by a multiple cognitive deficit hypothesis (Willcutt et al., 2010), which emphasizes how clinical profiles are the outcome of complex interactions between several cognitive deficits and shared risk factors (that Pennington called the liabilities hypothesis; Pennington, 2006). These disorders are often characterized by the concomitant presence of more than one clinical condition, leading to the phenomenon of *comorbidity*. The extant research has clearly shown that various developmental problems tend to co-occur (Fawcett and Nicolson, 1995; Dewey and Wall, 1997; Piek et al., 1999), and that their symptoms may lie along a continuum of severity

(Jensen et al., 2001; Kadesjö and Gillberg, 2001; Crawford et al., 2006). What is not clear, however, is whether children with these concomitant problems have two or more separate disorders or several symptoms associated with a single underlying condition. Comorbidity often means that developmental trajectories intersect for different disorders. Understanding these trajectories and how they intersect can shed light on their etiology and mutual interdependence (Pennington et al., 2005).

In particular, the comorbidity between attention deficit and hyperactivity disorder (ADHD) and specific learning disorders (SLD) has been widely studied, mainly because of their high prevalence (Lonergan et al., 2019; Astle and Fletcher-Watson, 2020), but also because they share several problems and symptoms. For example, when children have learning difficulties together with behavioral and attentional deficits, they exhibit symptoms that could indicate a learning disability and/or ADHD, raising issues in their diagnosis and treatment. The main challenge in this research field is to understand why these two disorders occur together, how they interact, and whether this comorbidity coincides with particular neuropsychological profiles.

ADHD and SLD

ADHD is characterized by persistent inattention and/or hyperactivity traits interfering with normal development (DSM-5, American Psychiatric Association, 2013). The clinical picture of ADHD varies considerably, making it difficult to establish whether, in addition to inattention and hyperactivity, other traits should be considered as a part of the syndrome (Wåhlstedt et al., 2009). ADHD is one of the most often diagnosed disorders in childhood (Döpfner et al., 2015), although the prevalence estimates range from 0.2% to 34.5%, depending on the clinical and methodological approach used (Thomas et al., 2015; Reale and Bonati, 2018). Generally speaking, its prevalence is estimated worldwide at 5% in children under 18 years old (Polanczyk et al., 2007). Many children diagnosed with ADHD also have at least one other associated disorder (Tarver et al., 2014). Gillberg et al. (2004) report that the proportion ranges between 60% and 100%, depending on the studies considered (Ianes et al., 2009).

Although the neuropsychological profile of ADHD is heterogeneous, numerous studies indicate that it involves impairments in various executive function (EF) domains (Barkley et al., 1992; Pennington and Ozonoff, 1996; Sergeant et al., 2002). Reported findings are hardly conclusive, however, since the mean effect sizes range from small to moderate for EF measures, and not all children with ADHD show EF deficits (Willcutt et al., 2005), which can also be seen in typically-developing (TD) children (Vaidya et al., 2020), suggesting that none of these EF deficits is a necessary or sufficient explanation for the ADHD profile (Willcutt et al., 2003).

Another complex set of neurodevelopmental disorders are described by the umbrella term *specific learning disorders/disabilities* (SLD). According to the DSM-5, SLD is characterized by problems in academic skills, such as reading, writing, or arithmetic, which provide the foundations for other, more advanced academic learning (DSM-5, American Psychiatric Association, 2013). SLD mainly involve reading-related (dyslexia) and math-related (dyscalculia) disorders. The academic indicators of dyslexia include difficulties in word recognition and reading fluency (decoding skills). Children with dyscalculia may show problems in basic number processing, arithmetic facts, and calculation skills. SLD may also include deficits in reading comprehension, grammar, written expression, math reasoning, and problem-solving skills (Somale et al., 2016).

Like ADHD, so too for SLD, the prevalence estimates vary, mainly depending on the assessment procedures employed. The overall prevalence of SLD is thought to range from 5% to 15%, with 4% to 9% for dyslexia, and 3% to 7% for dyscalculia (Devine et al., 2013; Görker et al., 2017). On the one hand, considering domain-specific processes, dyslexia and dyscalculia seem to exhibit distinct cognitive profiles, with a phonological deficit in dyslexia (Coltheart, 2015), and a deficit in numerosity processing in dyscalculia (Landerl et al., 2009; Moll et al., 2015). On the other hand, when we consider domain-general cognitive processes, the two disorders share cognitive deficits—in working memory (WM), for instance (Schuchardt et al., 2008; Wilson et al., 2015; Moll et al., 2016; Peng and Fuchs, 2016; Toffalini et al., 2017; Mammarella et al., 2018b). These WM impairments might help to explain the co-occurrence of math and reading disorders in 30–70% of individuals diagnosed with SLD (Willcutt et al., 2013).

Moreover, also the comorbidity rate for SLD and ADHD ranges from 31% to 45% (DuPaul et al., 2013), but the incidence varies when specific academic domains are considered. The rate of comorbidity between reading-related deficits and ADHD ranges between 25% and 48% (Sadek, 2018), while it is estimated at between 11% and 30% for math-related deficits and ADHD (Capano et al., 2008). As comorbidity between ADHD and SLD is so common, the two different neuropsychological profiles sometimes seem to overlap (de Jong et al., 2009), but in other cases, a unique new problem seems to emerge (Bental and Tirosh, 2007).

ADHD, SLD, and Executive Functions

In ADHD research, studies on the cognitive factors involved in SLD have generated mixed evidence, suggesting that although some deficits might be specifically related to SLD or ADHD, several factors might be shared (Pennington et al., 1984; Willcutt et al., 2010). Previous studies often showed that ADHD and SLD involve similar deficits in inhibition or planning (Marzocchi et al., 2002). Inhibition and planning are considered two of the most important EFs, which generally include several psychological processes, such as organizing, WM, attention, problem solving, verbal reasoning, cognitive flexibility, and monitoring (Diamond, 2013; Goldstein et al., 2014).

In the present study, we refer to Miyake's model (Miyake et al., 2000), which identifies three basic EFs: (a) inhibition, or the ability to deliberately inhibit dominant, automatic, or imperious responses when required; (b) shifting (also called cognitive flexibility or switching), which is the ability to switch between tasks, operations or mental sets to adjust to changed priorities; and (c) updating, or the

ability to update and monitor information in the WM, replacing old and no longer relevant information with more recent and relevant input, and translating instructions into action plans.

A huge amount of studies revealed the presence of inhibitory processes impairments in children with ADHD (Sonuga-Barke et al., 2002; Willcutt et al., 2005; Toll et al., 2011; Shimoni et al., 2012; Crosbie et al., 2013; Rajendran et al., 2013; Schreiber et al., 2014). Martinussen and Tannock (2006) also indicated WM as having an essential role in ADHD deficits. According to Alderson et al. (2010), major deficits can be seen in the central executive system, followed by visuospatial WM, and then verbal WM. Anomalies in visuospatial WM are thought to be among the most important deficits in the neuropsychological profile of children with ADHD (Prins et al., 2011). Finally, a few studies focused on shifting abilities in children with ADHD, with mixed results. Some studies found no shifting deficit (Biederman et al., 2007); some reported impaired shifting functions in terms of both accuracy and response times (O'Brien et al., 2010); and some only identified a lower accuracy (Holmes et al., 2010) or slower response times (Oades and Christiansen, 2008). These conflicting findings are probably due to the tasks chosen, which usually involve other EFs (Irwin et al., 2019).

On the other hand, the relationship between EFs and poor academic achievement is well documented (Mulder and Cragg, 2014). Children with SLD show deficits in central executive functioning (Landerl et al., 2004; Pickering, 2006), and particularly in WM (Mammarella et al., 2013; Moll et al., 2016; Peng and Fuchs, 2016). Verbal and visuospatial WM both seem to be related to the early acquisition of reading and math abilities (Passolunghi et al., 2008; Peng et al., 2018b). Later on, verbal WM is more implicated in reading performance and comprehension (Peng et al., 2018a), while visuospatial WM seems to be linked to more complex math achievement (Giofrè et al., 2014; Caviola et al., 2020). Moreover, mixed results have been reported for inhibition deficits in children with both reading and math disabilities, probably depending on the type of paradigm used (De Weerdt et al., 2013). Finally, meta-analyses by Yeniad et al. (2013) showed a substantial and significant association between shifting and math, as well as reading performance.

Despite an apparent overlap between the two disorders, few studies have directly compared the different neuropsychological profiles of children with ADHD, SLD, and comorbid ADHD + SLD. Willcutt et al. (2010) found individuals with reading disabilities more impaired than those with ADHD on measures of WM and rapid automated naming. Korkman and Pesonen (1994) reported that children with ADHD showed impairment in inhibition processes, while children with SLD tended to exhibit deficits in verbal aspects (e.g., verbal WM). Other researchers (Marzocchi et al., 2008; Faedda et al., 2019) found that their SLD group scored significantly higher than children with ADHD in all EFs.

As for the comorbidity issue, some researchers emphasized comorbidity as a qualitatively distinct condition (Pennington et al., 1993), showing that impairments relating to the two single disorders co-occurred in some cases (Willcutt et al., 2005; Kibby and Cohen, 2008; de Jong et al., 2009), while new deficits with a distinct cognitive deficit profile (called interactive effect) emerged in others (Bental and Tirosh, 2007). Moreover, further studies underscored the additive effect (i.e., the sum of the single cognitive deficit profiles) of two comorbid disorders (Seidman et al., 1995, 2001; Willcutt et al., 2013; Horowitz-Kraus, 2015). For instance, participants with comorbidity involving ADHD and SLD revealed worse EF deficits than those with ADHD alone (Seidman et al., 2001; Mattison and Mayes, 2012). To the best of our knowledge, however, only a few studies have compared two single deficits with the same two deficits in comorbidity, and such studies mainly considered comorbidity for ADHD and dyslexia. Some authors (Van De Voorde et al., 2010) found no differences in inhibition and WM tasks between cases with single deficits and those with a comorbid condition. Others (Bental and Tirosh, 2007) found more severe impairments in WM in comorbid than in single-deficit groups. As regards the WM task presentation format (verbal or visuospatial), Martinussen and Tannock (2006) found verbal WM performance to be worse in their groups with dyslexia (with or without ADHD), than in their group with ADHD alone. Kibby and Cohen (2008) found that the comorbid group performed worse in both verbal and visuospatial WM tasks than ADHD or dyslexia alone. In short, a definite conclusion has yet to be reached on this matter.

Taking into account the extant literature, to the best of our knowledge, previous studies rarely compared EF profile in children with a clinical diagnosis of ADHD and SLD in comorbidity, with children who had either ADHD or SLD (with both reading and math impairments), despite some studies highlighted the importance of EF as potential shared risk factor between SLD and ADHD (Pennington et al., 2005; Pennington, 2006). This reveals a potential methodological bias in our understanding of the role of specific deficits in EF domains in these disorders. Astle and Fletcher-Watson (2020) suggested that this was because studies often used strict exclusion criteria that excluded children with co-occurring difficulties (Willcutt et al., 2001; Toplak et al., 2005). Since comorbidity is common in neurodevelopmental disorders, rather than an exception (Gillberg, 2010), we need to include a comorbid group (ADHD + SLD) in our efforts to understand the neuropsychological differences between the two disorders.

The Present Study

As previous studies showed that children with ADHD and SLD may both have specific EF deficits (Willcutt et al., 2010; Schreiber et al., 2014; Peng and Fuchs, 2016; Faedda et al., 2019), we analyzed EF profile to reveal potential differences in the profiles associated with ADHD and SLD considered separately, but also in comorbidity (ADHD + SLD). As mentioned earlier, no systematic studies in EF have directly compared children with a clinical diagnosis of ADHD, SLD, and ADHD + SLD.

We, therefore, assessed different EF components in four groups of children: children with ADHD; children with SLD; children with ADHD + SLD; and a control group of TD children. In our study measures of inhibition, shifting, and updating

(verbal and visuospatial) were administered. Samples of children with a clinical diagnosis were matched with TD children for chronological age and intelligence level. Our main aims were to investigate specific impairments in EF domains in the clinical groups and to test the potential additive effect of the comorbidity between ADHD + SLD.

Based on previous studies, we expected all children in the clinical groups (ADHD, SLD, and ADHD + SLD) to show EF impairments (Hari and Renvall, 2001; Sergeant et al., 2002; Martel et al., 2007; Bull et al., 2008; Barkley, 2011) compared to TD children. We expected children with ADHD to have significant impairments in all EF measures compared with TD children, except for updating tasks, where we expected the ADHD group's performance to differ depending on the presentation format (verbal vs. visuospatial): the ADHD group was expected to perform less well than the TD group in the visuospatial task, but not in verbal one (Prins et al., 2011). Based on previous studies, the SLD group was expected to perform less well than the TD group in terms of inhibition (De Weerdt et al., 2013), shifting (Yeniad et al., 2013), and both verbal and visuospatial updating (Peng et al., 2018a; Caviola et al., 2020).

We expected that children with ADHD and SLD had difficulties in both inhibition and shifting, with specific WM differences, according to the presentation format (Willcutt et al., 2001; de Jong et al., 2009). Children with ADHD were expected to perform worse than children with SLD in visuospatial updating (de Jong et al., 2009). In contrast, children with SLD were expected to show more impairments in verbal updating (Kibby and Cohen, 2008).

Considering the few, inconsistent studies in the literature, we might expect several cognitive profiles in children with comorbid ADHD and SLD compared with those with either ADHD or SLD. Children with comorbid ADHD + SLD could have a more significantly impaired neuropsychological profile than those with a single disorder (Seidman et al., 2001; Mattison and Mayes, 2012), in line with an additive effect of the two disorders together (Willcutt et al., 2013). We might also expect children with comorbid ADHD + SLD to have a worse EF performance than those with a single neurodevelopmental disorder (either ADHD or SLD; Fernández-Andrés et al., 2019), pointing to the co-occurrence of the symptoms of the two clinical conditions rather than a third, separate disorder with a qualitatively different cognitive subtype.

MATERIALS AND METHODS

Participants

The total sample consisted of 97 children, 66 males, and 31 females, aged between 8 and 14 years (M = 11, SD = 1.73). Children with a clinical diagnosis of ADHD, SLD, or ADHD + SLD were recruited at the child and adolescent neuropsychiatry services. TD children were enrolled at primary and secondary schools. The children in the clinical groups had already been independently diagnosed according to the DSM-5 (American Psychiatric Association, 2013), based on comprehensive assessments reported in their medical records. All children in the SLD group had been clinically diagnosed as cases of SLD, with major impairments in both math and reading abilities. **Table 1** summarizes the general characteristics of the four groups.

All participants were native Italian speakers, and none had any diagnosed neurological conditions. Exclusion criteria for all participants were: a history or concurrent diagnosis of other neurodevelopmental disorders; a history of neurological problems; current use of medication; medical illness requiring immediate treatment; psychological treatments in progress; or a certified intelligence quotient (IQ) below 80 (**Table 1**). The clinical groups consisted of: 18 children with ADHD (M = 123.11 months, SD = 20.48); 18 with SLD (M = 136.83 months, SD = 17.67); and 13 with ADHD + SLD (M = 134.15 months, SD = 24.7). They were matched with 48 TD children (M = 133.08 months, SD = 20.15) for chronological age ($F_{(3,93)} = 1.56$, $p = 0.20$, $AdjustedR^2 = 0.02$), gender ($\chi^2_{(df=3)} = 5.16$, $p = 0.16$, $Cramer\text{-}V = 0.231$), and FSIQ[1] ($F_{(3,93)} = 0.39$, $p = 0.76$, $AdjustedR^2 = 0.02$).

For the study, all diagnoses were confirmed by assessing ADHD symptoms and learning difficulties as explained below in the "Group Selection Measures" section.

The Research Ethics Committee of the University of Padua approved the study.

Materials

Group Selection Measures

Conners Rating Scale-Revised

CPRS R:S (Conners, 1997). This parent-report was used in the clinical evaluation of ADHD to identify and measure the intensity of inattention, hyperactivity, and impulsivity traits. It covers the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders [4th Edition text revision (DSM-IV-TR); American Psychiatric Association, 2000] and oppositional traits that are often seen in children with ADHD. It took under 10 min to complete. The parent's form, consisting of 27 items, was used in this study to confirm the presence of ADHD symptoms. A parent-rated how much the symptoms described had been typical of their child's behavior during the previous month using a 4-point Likert scale from 0 (not true at all) to 3 (very true). Cronbach's alpha ranged from 0.86 to 0.94 (Maruish, 2004).

Reading Tasks

DDE-2 (Sartori et al., 2007). Children's reading skills were measured with two different tasks that involved reading lists of words and pseudo-words. The first consisted of four lists of 28 words each, including high-frequency words (i.e., man, morning) and low-frequency words (i.e., prowess, globule) of two to four syllables. In the pseudo-words task, there were three lists of 16 made-up words each. Participants were asked to read each word out loud as quickly and accurately as possible. The experimenter recorded the time spent on each list, and scored the reading errors (letter substitutions,

[1]All children in the clinical sample had already been diagnosed after a comprehensive clinical assessment that included the whole WISC IV battery (Wechsler, 2003), but only their full-scale IQ was made available to us by the clinical centers involved.

TABLE 1 | Characteristics of the groups: means (M) and standard deviations (SD) for group selection measures.

		ADHD (*n* = 18) *M* (SD)	SLD (*n* = 18) *M* (SD)	ADHD + SLD (*n* = 13) *M* (SD)	TD (*n* = 48) *M* (SD)	ANOVAs $F_{(3,93)}$	*p*	*Adjusted* R^2	*Post-hoc*
Age (in months)		123.11 (20.48)	136.83 (17.67)	134.15 (24.70)	133.08 (20.15)	1.56	0.20	0.02	
IQ		108.50 (8.95)	109.39 (8.86)	107.92 (13.27)	110.56 (8.66)	0.39	0.76	0.02	
CPRS-R:S (*T*-score)	Oppositive	66.00 (14.75)	52.17 (11.09)	58.62 (12.72)	50.40 (10.26)	8.56	<0.001	0.19	ADHD, ADHD + SLD > TD; ADHD > SLD
	Inattention	75.06 (12.99)	57.39 (8.3)	64.46 (10.03)	48.27 (8.74)	35.97	<0.001	0.52	ADHD > ADHD + SLD > SLD > TD
	Hyperactivity	62.78 (13.86)	45.17 (3.37)	59.92 (13.91)	46.69 (7.08)	19.18	<0.001	0.36	ADHD, ADHD + SLD > SLD, TD
	ADHD index	76.11 (12.14)	56.94 (8.43)	66.23 (12.20)	48.48 (8.25)	39.69	<0.001	0.55	ADHD > ADHD + SLD > SLD > TD
DDE-2 (*z*-score)	Words, syll/s	−0.28 (0.95)	−1.79 (1.07)	−1.41 (1.35)	−0.10 (1.23)	11.69	<0.001	0.25	TD, ADHD > SLD, ADHD + SLD
	Words, errors	0.39 (1.32)	1.23 (1.23)	2.83 (3.76)	−0.11 (0.97)	11.12	<0.001	0.24	ADHD + SLD > SLD > TD; ADHD + SLD > ADHD
	Pseudo-words syll/s	−0.27 (0.69)	−1.39 (0.92)	−1.22 (1.17)	−0.18 (1.08)	8.72	<0.001	0.19	TD, ADHD > SLD, ADHD + SLD
	Pseudo-words, errors	−0.17 (0.72)	1.17 (1.54)	0.75 (1.53)	−0.44 (0.86)	11.47	<0.001	0.25	SLD, ADHD + SLD > TD, ADHD
DDE-2 (*z*-score)	Homophones not homographs	0.96 (1.20)	1.92 (1.27)	2.94 (1.56)	0.82 (0.95)	13.69	<0.001	0.28	ADHD + SLD > SLD > TD, ADHD
AC-MT (*z*-score)	Mental C–errors	0.14 (1.25)	0.41 (1.11)	0.73 (1.59)	−0.53 (0.81)	6.77	<0.001	0.15	ADHD, SLD, ADHD + SLD > TD
	Mental C–time	0.25 (0.95)	1.13 (1.07)	0.47 (1.25)	−0.15 (1.00)	6.86	<0.001	0.15	ADHD + SLD, SLD > TD
	Written C–errors	−0.24 (0.53)	1.06 (1.10)	1.37 (1.28)	−0.14 (0.88)	15.15	<0.001	0.31	SLD, ADHD + SLD > TD, ADHD
	Written C–time	0.18 (1.12)	1.61 (1.31)	1.45 (2.14)	0.46 (1.30)	4.95	0.003	0.11	TD, ADHD > SLD, ADHD + SLD
	Transcoding	−0.05 (1.24)	1.52 (2.28)	1.38 (2.08)	−0.24 (0.78)	9.26	<0.001	0.21	SLD, ADHD + SLD > TD, ADHD
	Fact retrieval	0.19 (1.7)	1.52 (1.03)	0.64 (1.50)	−0.71 (0.84)	17.28	<0.001	0.34	SLD > ADHD + SLD, ADHD > TD
AC-FL (raw score)		25.56 (13.3)	22.64 (9.02)	20.15 (11.39)	34.71 (12.48)	7.98	<0.001	0.18	TD > ADHD, SLD, ADHD + SLD

Note: ADHD, attention deficit and hyperactivity disorder; SLD, specific learning disabilities; ADHD + SLD, ADHD and SLD in comorbidity; TD, typical development; IQ, intelligence quotient; CPRS-R:S, Conners' Parent Rating Scale; DDE-2, battery for assessing developmental dyslexia and dysorthographia–2; Mental C, mental calculation; Written C, written calculation.

omissions, position changes, or additions), scoring no more than one error point for any given word. Self-corrections were not counted as errors. Reading performance was measured in terms of: (1) reading speed, i.e., the number of syllables read per second, expressed as the total reading time for each list; and (2) reading errors, i.e., the total number of words misread. Reliability varies from $r = 0.74$ to $r = 0.96$ (Di Brina et al., 2018).

Writing Task

DDE-2 (Sartori et al., 2007). Children's spelling competence was tested with a "homophones-not-homographs test." They were asked to write a list of sentences read aloud by the experimenter that contained some words with the same pronunciation but different spelling. The appropriate spelling depended on the word's meaning drawn from the overall context (i.e., "flower" and "flour"). Only errors relating to this type of word were considered, scoring no more than one error point for any given word. Reliability varies from $r = 0.74$ to $r = 0.96$ (Di Brina et al., 2018).

Arithmetic Task

AC-MT 6-11; 11-14 (Cornoldi and Cazzola, 2003; Cornoldi et al., 2012). Math competencies were assessed with the AC-MT battery, with the age-appropriate subtests. For the present study, children were administered the individual part of the AC-MT battery, consisting of mental and written calculation, transcoding, and fact retrieval tasks. Mental and written calculations involved additions, subtractions, multiplications, and divisions appropriate for the participant's age and school level. The transcoding and fact retrieval tasks assessed their basic numerical knowledge. For both mental and written calculations, problems were administered verbally only once, and primary-school children were allowed up to 30 s (mental calculation) or 60 s (written calculation) to answer them, while middle-school children were allowed 60 s for both types of calculation. The number of errors and the time taken to respond were recorded. In the transcoding task, the experimenter read one number at a time aloud, and only once. The fact retrieval task involved children directly retrieving simple solutions to arithmetical problems within 5 s. For both these tasks, only the number of errors was considered. Test-retest coefficients range from $r = 0.70$ to $r = 0.79$ for primary-school children, and from $r = 0.72$ to $r = 0.83$ for secondary-school children (Hill et al., 2016).

Math Fluency Task

AC-FL (Caviola et al., 2016). In this task, the children were asked to solve three sets of calculations (additions, subtractions, and multiplications). They had 2 min to complete each set of problems as quickly and accurately as possible. Each set contained 24 complex problems involving two- or three-digit numbers. The task implicitly assessed children's calculation strategies. The total number of correct solutions was recorded. Cronbach's α was 0.89, 0.90, and 0.82 for additions, subtractions, and multiplications, respectively (Caviola et al., 2016).

Executive Function Tasks

Inhibition and Shifting

NEPSY II (Korkman et al., 2007). This task assesses the ability to inhibit automatic responses in favor of novel answers, and the ability to switch automatic responses. The children were shown a series of black and white shapes or arrows pointing in different directions. The task involved two conditions: (a) an inhibition condition, in which participants had to name the opposite shapes (i.e., if they saw a square the children should say "circle" and vice versa) or arrow directions (i.e., if the arrow was pointing upwards they should say downwards, and vice versa) as rapidly and accurately as possible; and (b) a shifting condition, in which they had to name shapes (or directions of arrows) differently depending on their color (i.e., if the shape or arrow was black, they had to say what they were seeing; if it was white, they had to name the opposite shape or direction). Response times and errors were recorded. According to the manual, response times were first converted into standard scores, and errors were converted into percentiles. Then the two scores obtained were converted into a single standardized "combined score" that took both parameters into account. Test-retest reliability ranges between $r = 0.79$ to $r = 0.82$ for the inhibition condition, and between 0.75 and 0.93 for the shifting condition (Brooks et al., 2009).

Verbal and Visuospatial Updating

Two updating tasks were devised with different types of stimuli, verbal in one and visuospatial in the other. Both tests, administered using E-prime (Schneider and Zuccoloto, 2007) and a laptop computer with a 15-inch LCD screen, were characterized by four levels of difficulty depending on the increased number of target categories. Each level consisted of two items in which the memory span required stayed the same. The children were asked to recall the last verbal stimulus or its last positions belonging to *target categories* (among 2–5) shown on the computer screen. A detailed description of both verbal and visuospatial updating is reported in the **Supplementary Materials**.

Accuracy in both verbal and visuospatial tasks was considered, based on the proportion of items correctly remembered out of the total words or positions to remember. Cronbach's α based on the current sample was 0.71 for verbal updating and 0.76 for visuospatial updating.

Procedure

After obtaining the written consent of children's parents to their participation in the study, the children were tested during two different sessions in a quiet room outside their classrooms (for TD children) or at the Child Neuropsychiatry Department of the hospital to which they referred for their diagnosis (for children in the clinical groups). At the same time, parents completed a rating scale to assess their children's ADHD symptoms.

Participants completed both the group selection measures and the cognitive tasks, administered in a counterbalanced order, during two individual sessions lasting approximately 1 h each. Instructions were given for each task, and participants practiced with each task before starting the experiment. All experimental tasks were preceded by two practice trials. For the

computer-based tasks, the children sat in front of the computer screen and the experimenter sat on the child's right to present the tasks.

RESULTS

Data Analysis

Data analyses were conducted using R (RC Team, 2015). One-way ANOVAs were run for the group selection measures and the inhibition task, to examine the differences between groups.

The analyses were run in two stages. In the first, Group was included as an independent variable. In the second, to answer the question of whether or not the comorbid group has an additive profile, the same analyses as in the first stage were run, with the presence of ADHD (no/yes) and SLD (no/yes) as factors[2].

The Akaike information criterion (*AIC*, Akaike, 1974) was also taken into consideration for each of these models. It provided the best description of the relationships between the variables (Bentler, 1990; Schermelleh-Engel et al., 2003). Graphical effects were obtained using the "effects" package (Fox, 2003). The **Supplementary Results** contain detailed analyses of the updating tasks by span level.

The updating tasks (both verbal and visuospatial) allowed us to collect accurate data for each item from each participant. Generalized mixed-effects models were used (Baayen et al., 2008; Jaeger, 2008) and a "binomial" function family, using the "lme4" package (Bates et al., 2015). Participants were included as random effects. This latter analysis is extensively described in the **Supplementary Results** section.

Group Selection

In the first phase, the Conners' Parent Rating Scale-Revised, Short-Form (CPRS-R:S, Conners, 1997) was used to confirm their children's inattention and/or hyperactivity symptoms, and T-scores of 65 or more were required for inclusion in the ADHD group. To be assigned to the SLD group, children were required to show an impaired performance (>−2 SD) in at least one domain of academic achievement: reading (DDE-2; Sartori et al., 2007); spelling (DDE-2; Sartori et al., 2007); or math (AC-MT 6-11, Cornoldi et al., 2012; AC-MT 11–14, Cornoldi and Cazzola, 2003; AC-FL, Caviola et al., 2016). Confirmation of ADHD in comorbidity with SLD (ADHD + SLD group) required an impaired performance (>−2 SD) in at least one domain of academic achievement and a T-score of 65 or higher in the CPRS-R:S indexes for Inattention or ADHD.

As shown in **Table 1**, the group profiles were confirmed. Children with ADHD (with or without SLD) had significantly higher scores in CPRS-R indexes than those with TD and SLD, showing at least two clinically significant indices. Children with SLD (with or without ADHD) were more impaired in reading and writing than TD and ADHD. As for math abilities, all clinical groups performed significantly worse than children with TD. The ADHD group had a significantly better performance than SLD and ADHD + SLD in both transcoding and written calculation.

Executive Functions

Inhibition

Table 2 sums up the descriptive statistics by group (ADHD, SLD, ADHD + SLD, and TD) in the inhibition and shifting conditions. In the first stage, a main effect of Group emerged in both inhibition ($F_{(3,93)} = 6.80$, $p < 0.001$, $AdjustedR^2 = 0.15$), and shifting ($F_{(3,93)} = 3.27$, $p = 0.025$, $AdjustedR^2 = 0.07$). For both conditions, children with a clinical diagnosis performed significantly worse than TD children (inhibition: ADHD: $p < 0.001$, *Cohen's d* = 0.96; SLD: $p = 0.01$, *Cohen's d* = 0.83; ADHD + SLD: $p = 0.002$, *Cohen's d* = 0.89; shifting: ADHD: $p = 0.01$, *Cohen's d* = 0.66; SLD: $p = 0.05$, *Cohen's d* = 0.57; ADHD + SLD: $p = 0.056$, *Cohen's d* = 0.73). No other differences emerged between the groups. In the second stage, the same analyses were run using the presence of ADHD and SLD as factors. In the inhibition task, a main effect of ADHD emerged ($F_{(1,95)} = 11.04$, $p = 0.001$, full model: *AIC* = 451.96, model without ADHD *AIC* = 460.74) and SLD ($F_{(1,95)} = 4.30$, $p = 0.04$, model without SLD *AIC* = 454.30). As shown in **Figure 1A**, the interaction was not significant ($F_{(1,93)} = 2.40$, $p = 0.12$, model with interaction *AIC* = 451.49).

In the shifting task, a main effect emerged for ADHD ($F_{(1,95)} = 4.60$, $p = 0.03$, full model: *AIC* = 472.32, model without ADHD *AIC* = 474.96), but not for SLD ($F_{(1,95)} = 1.94$, $p = 0.16$, model without SLD *AIC* = 472.31). As shown in **Figure 1B**, the interaction was not significant ($F_{(1,93)} = 2.12$, $p = 0.15$ model with interaction *AIC* = 472.13).

Verbal and Visuospatial Updating

Table 2 sums up the descriptive statistics by group (ADHD, SLD, ADHD + SLD, and TD) in the Verbal Updating and Visuospatial Updating. In the first stage, a main effect of Group emerged in Verbal updating ($F_{(3,93)} = 3.40$, $p = 0.02$, $AdjustedR^2 = 0.07$), as children with a clinical diagnosis of SLD performed significantly worse than children with TD or ADHD (respectively: $p = 0.003$, *Cohen's d* = 0.83; and $p = 0.01$, *Cohen's d* = 0.83). There was also a main effect of Group in Visuospatial updating ($F_{(3,93)} = 3.59$, $p = 0.02$, $AdjustedR^2 = 0.07$), as children with ADHD and ADHD + SLD performed significantly worse than the TD or SLD groups (for TD: $p = 0.01$, *Cohen's d* = 0.65 and $p = 0.04$, *Cohen's d* = 0.63, respectively; for SLD: $p = 0.02$, *Cohen's d* = 0.94 and $p = 0.05$, *Cohen's d* = 0.96). No other differences emerged between the groups.

In the second stage, using ADHD and SLD as factors, a main effect on the Verbal updating task emerged for SLD ($F_{(1,95)} = 7.90$, $p = 0.006$, full model: *AIC* = 133.77, model without SLD *AIC* = 139.94), but not for ADHD ($F_{(1,95)} = 1.04$, $p = 0.31$, model without ADHD *AIC* = 140.69). As shown in **Figure 2A**,

[2]Additional analyses were run, controlling for the role of attentional difficulties derived from the CPRS: R-S. The results revealed no group differences for inhibition, switching, or visuospatial updating tasks after controlling for attentional difficulties. A slight difference emerged in the verbal updating task, with the SLD group performing worse than the other clinical groups (with ADHD or ADHD + SLD).

TABLE 2 | Measures of executive functions: means (M) and standard deviations (SD) by group.

		ADHD (*n* = 18) *M* (SD)	SLD (*n* = 18) *M* (SD)	ADHD + SLD (*n* = 13) *M* (SD)	TD (*n* = 48) *M* (SD)
Inhibition	Combined	7.33 (3.03)	8.00 (2.28)	7.31 (3.33)	9.73 (1.85)
Shifting	Combined	7.39 (3.11)	7.83 (2.85)	7.69 (1.65)	9.31 (2.65)
Verbal updating	Accuracy	0.65 (0.11)	0.56 (0.13)	0.63 (0.12)	0.66 (0.11)
Visuospatial updating	Accuracy	0.57 (0.19)	0.71 (0.09)	0.58 (0.17)	0.69 (0.18)

Note: ADHD, attention deficit and hyperactivity disorder; SLD, specific learning disabilities; ADHD + SLD, ADHD and SLD in comorbidity; TD, typical development.

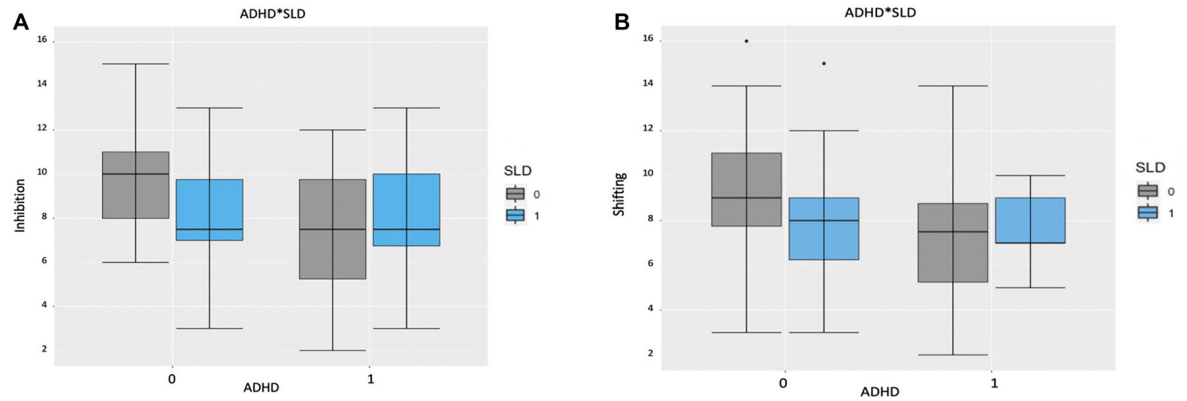

FIGURE 1 | **(A)** Boxplots representing the composite score by attention deficit and hyperactivity disorder (ADHD) and specific learning disorders (SLD) in the Inhibition task. The central mark is the median. The edges of the box are the 25th and 75th percentiles. The whiskers are the interquartile range. Note: 0 = absent; 1 = present. **(B)** Boxplots representing the composite score by ADHD and SLD in the Switching task. The central mark is the median. The edges of the box are the 25th and 75th percentiles. The whiskers are in the interquartile range and the symbols are outliers. Note: 0 = absent; 1 = present.

the interaction was not significant ($F_{(1,93)} = 1.85$, $p = 0.18$, model with interaction $AIC = 133.68$). In the Visuospatial updating task, there was a main effect of ADHD ($F_{(1,95)} = 10.87$, $p = 0.001$, full model: $AIC = 55.64$, model without ADHD $AIC = 64.26$), but not of SLD ($F_{(1,95)} = 0.15$, $p = 0.70$, model without SLD $AIC = 66.11$). Here again, the interaction was not significant ($F_{(1,93)} = 0.004$, $p = 0.95$, model with interaction $AIC = 62.27$), as shown in **Figure 2B**.

Finally, in the mixed-model analysis (extensively reported in the **Supplementary Results**) no main effect of the group emerged in the Verbal updating task. Instead, there was a significant main effect of Span ($\chi^2_{(3)} = 184.52$, $p < 0.001$, model without Span: $AIC = 1{,}993.9$). No significant interaction between Group and Span emerged. In the Visuospatial updating task, there was a main effect of Group ($\chi^2_{(3)} = 10.55$, $p = 0.01$, full model: $AIC = 2{,}013.5$, model without Group: $AIC = 2{,}018$) and Span ($\chi^2_{(3)} = 100.11$, $p < 0.001$, model without Span: $AIC = 2{,}107.6$). The interaction between Group and Span was also significant ($\chi^2_{(9)} = 33.63$, $p < 0.001$, model with Interaction: $AIC = 1{,}997.8$).

DISCUSSION

The main aim of our study was to examine the specific neuropsychological profiles of children with a clinical diagnosis of either ADHD or SLD—with major impairment in both reading and math, or both in comorbidity (ADHD + SLD), by comparison with TD children. We were particularly interested in understanding whether the EFs profiles of four groups differed and whether the comorbid group (ADHD + SLD) showed an additive (i.e., the sum of the deficits in the isolated groups) or rather an interactive effect (i.e., a distinct deficit profile). Children in the clinical groups had been previously diagnosed at centers specialized in neurodevelopmental disorders. In the first part of the assessment, all their diagnoses had been confirmed through specific questionnaires for parents and appropriate academic achievement tests.

To test potential differences in EFs profiles, children with a clinical diagnosis of ADHD, SLD, and comorbid ADHD + SLD were compared with TD children on measures of inhibition, shifting, and updating (verbal and visuospatial). In our analyses, we first compared our groups considering EF measures separately. Then, we ran the same analyses considering the presence of ADHD (no/yes) and/or SLD (no/yes) as factors to see whether the comorbid group reveals an additive profile. Finally, mixed-effects models were used to analyze in detail performances at different span levels for the updating tasks.

In the group comparisons, our findings showed that all clinical groups performed worse than the TD group, and no differences emerged between any of the clinical groups on measures of inhibition and shifting. A more specific pattern emerged when the groups were compared on updating measures. Children with SLD performed less well than the other groups in the verbal task, while the groups with ADHD or

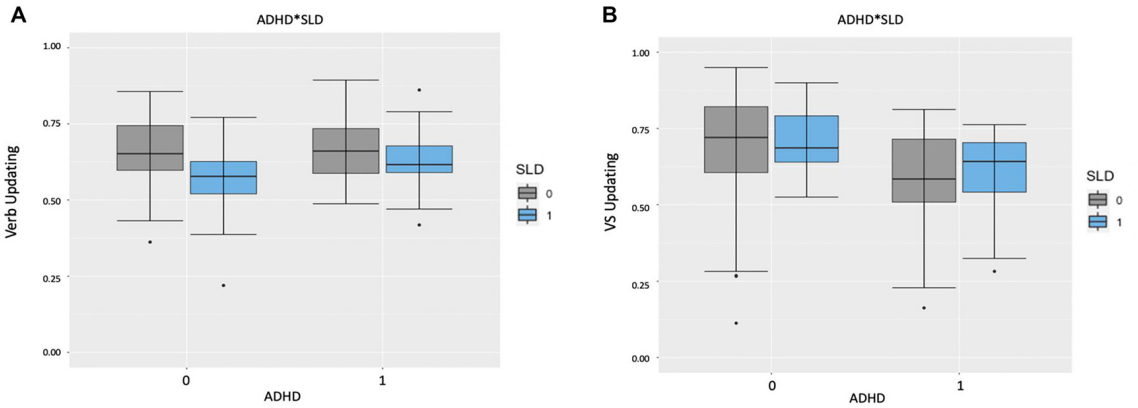

FIGURE 2 | (A) Boxplots representing the accuracy score by ADHD and SLD in the Verbal Updating Task. The central mark is the median. The edges of the box are the 25th and 75th percentiles. The whiskers are in the interquartile range and the symbols are outliers. Note: 0 = absent; 1 = present. **(B)** Boxplots representing the Accuracy Score by ADHD and SLD in the Visuospatial Updating Task. The central mark is the median. The edges of the box are the 25th and 75th percentiles. The whiskers are in the interquartile range and the symbols are outliers. Note: VS Updating = Visuospatial Updating; 0 = absent; 1 = present.

ADHD + SLD performed less well than either the SLD or the TD groups in the visuospatial task. This would contradict the idea of an additive effect of the two disorders combined (Seidman et al., 1995, 2001; Willcutt et al., 2013; Horowitz-Kraus, 2015). The pattern was slightly different when we considered the presence or absence of symptoms of SLD or ADHD: the effects of both SLD and ADHD could be seen in the inhibition task, but only those of ADHD in the shifting task. The effect of SLD was apparent for verbal updating and that of ADHD for visuospatial updating. Notably, from a qualitative perspective, children with ADHD + SLD were not more severely impaired than those with either ADHD or SLD alone. This would contradict the interactive hypothesis that children with several problems in comorbidity exhibit a qualitatively distinct condition (Pennington et al., 1993). Finally, by considering group performances at different span levels, a specific pattern emerged in the visuospatial updating task. Children with ADHD performed significantly worse on Span level 3 then showed a slight improvement on level 4, whereas the other groups had a more linear worsening performance with longer spans. Our results can be explained by altered motivational processes in ADHD (Sagvolden et al., 2005), or the children's inability to regulate their state of activation (Kuntsi and Klein, 2011).

The novelty of our investigation lies in that we compared these clinical groups with one another, as well as with a TD group, as previously reported. The results underlined that EFs are similarly compromised in all clinical groups, pointing to a comorbidity explanation based on a domain-general cognitive level. In particular, EF impairments, are not enough to differentiate between ADHD and SLD (Stern and Morris, 2013), shedding further light on the importance of comparisons across disorders and studies on comorbid conditions. Although ADHD is often associated with EF deficits (Barkley et al., 1992; Pennington and Ozonoff, 1996; Sergeant et al., 2003), this association did not seem sufficient to consider EF as core-deficits of the disorder (Willcutt et al., 2003), and impairments in inhibition (Booth et al., 2010; Mammarella et al., 2018a) and shifting (Van der Sluis et al., 2007; Andersson, 2008) have also been observed in children with SLD.

It is worth noting that SLD involves specific difficulties relating to achievement, particularly in reading (dyslexia) and math (dyscalculia). Dyslexia and dyscalculia seem to involve distinct cognitive profiles in terms of domain-specific processes (mainly phonological deficits for the former, and number processing deficits for the latter), but similar domain-general cognitive processes (particularly concerning WM). Domain-general cognitive processes like WM may therefore substantially overlap between dyslexia and dyscalculia (Peters and Ansari, 2019). In the present study, our SLD group consisted of children with major impairments in both math and reading abilities, unfortunately making it impossible to separately analyze the influence of reading or math. Our groups of children with either SLD or ADHD showed more specific patterns of results when looking at domain-general processes, linked to the presentation format of the WM tasks. In agreement with previous studies (Willcutt et al., 2001; de Jong et al., 2009), when verbal and visuospatial WM updating were compared, specific differences emerged between ADHD and SLD. Children with ADHD (with or without SLD) performed significantly worse than children with SLD in visuospatial updating (Kibby and Cohen, 2008; de Jong et al., 2009). In contrast, children with SLD were significantly more impaired than children with ADHD in verbal updating (Korkman and Pesonen, 1994; Willcutt et al., 2001; Kibby and Cohen, 2008). Our results thus suggest that the presentation format of an updating task (i.e., verbal or visuospatial), rather than the cognitive task *per se*, may be useful for distinguishing between ADHD and SLD.

As concerns comorbid ADHD + SLD, our data would support the claim that ADHD + SLD is not a third, separate disorder with a specific pattern of EF impairments since we could find

no specific profile distinctive of children with both conditions. Thus, we could not rule out the possibility of ADHD and SLD shared the same biological and environmental risk factors, increasing the likelihood of their co-occurrence and supporting the correlated liabilities hypothesis (Pennington et al., 2005; Pennington, 2006).

Although our study produced some interesting findings, our results should be considered explorative because it has some limitations. First of all, the sample size was small and the children in the SLD group had significant impairments in both reading and math, which prevented us from analyzing their influence separately. Second, the SLD group also had some attention-related problems, though they were not clinically relevant, and some differences in achievement emerged between groups of ADHD and typical development and SLD and ADHD + SLD. It is worth emphasizing that the children in our clinical groups had previously received a clinical diagnosis, and the heterogeneity of our sample's difficulties was typical of neurodevelopmental disorders and the impairments were not fulfilling criteria for different diagnoses. Another limitation of our study lies in that we only administered a limited set of EF tasks, without differentiating between verbal and visuospatial tasks for inhibition and shifting. We chose these particular tasks because the procedure was already long and hard, particularly for children with ADHD, and because they reflected our theoretical background (Miyake et al., 2000). Finally, our group with comorbid ADHD and SLD was smaller than the other two. This was because, we paid more attention to confirming the comorbid condition (ADHD + SLD, without any other comorbidities). Further research might replicate our methodology but increasing the numerosity of the clinical samples and including other cognitive tests.

Even with the above-mentioned limitations, our study has some important clinical implications. Understanding the specific type of interaction, the similarities, and differences between ADHD and SLD, and the combination of the two is fundamental to our ability to assess and treat all three conditions. The DSM-5 (American Psychiatric Association, 2013) made an important effort to operationalize the concept of a dimensional approach to neurodevelopmental disorders, but some issues persist (Pham and Riviere, 2015). We agree with previous studies that a neuropsychological assessment is not enough to convey a diagnosis (for further details, see Pham and Riviere, 2015). As, we have reported, children with ADHD can have learning difficulties, and children with SLD can have attention deficits, and our group of children with both disorders did not have a specific domain-general cognitive profile. Neuropsychological impairments and learning difficulties are not as uniquely associated with these disorders as was earlier supposed (Nigg and Huang-Pollock, 2003; Happé et al., 2006). Clinicians should therefore bear in mind the kinds of challenges they may encounter in the assessment process and the differential diagnosis. It is good practice not to focus on seeking specific neuropsychological deficits associated with a potential disorder, but rather to assess a child's abilities as a whole, to identify particular strengths and weaknesses.

To conclude, it is important to emphasize that no important differences emerged from our study between the clinical conditions considered as regards the children's EF impairments. All three clinical groups were significantly impaired by comparison with TD children. However, a more specific pattern emerged for the WM updating, in which verbal and visuospatial presentation format seems to better differentiate the SLD and ADHD profiles. Nevertheless, further studies are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Psychology Research Ethics Committee of the University of Padua. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SC and IM developed the study concept. Testing was performed by GC. RC and GC performed the data analysis. GC and SC drafted the manuscript and IM provided revisions. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.594234/full#supplementary-material.

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Intermediate lengths of the *C9ORF72* hexanucleotide repeat expansion may synergistically contribute to attention deficit hyperactivity disorder in child and his father: case report

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ABSTRACT

We have summarized the abstract section as follows: "We report a son and his father affected by Attention Deficit Hyperactivity Disorder (ADHD). They belonged to a larger cohort (116 ADHD children, 20 related parents, 77 controls) wholly genotyped for*C9ORF72* expansion. Ten ADHD susceptibility genes were further investigated in the family. We revealed that son and father shared an intermediate*C9ORF72* expansion and common variants in*CDH23*, *ITGAE* and *MTRR*. Bioinformatics highlighted a*C9ORF72-MTRR* interaction. This case-report underlines that in relatives with ADHD, carrying variants in ADHD susceptibility genes, the intermediate*C9ORF72* repeats might have a potentially pathogenetic synergistic effect, supporting the multifactorial polygenic aetiopathogenetic profile of disease".

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental, neuropsychiatric disorder with profound cognitive, behavioral, and psychosocial impairments across the life cycle. The disease prevalence is 5–7% in school-aged children, and 2.5–4.9% in adulthood (for review Bonvicini et al., 2018).

Increasing evidence suggests that ADHD is the result of a complicated interplay of genetic and environmental factors, with a heritability coefficient of 0.76 during childhood, one of the highest among psychiatric disorders. A recent review supported that both common and rare variants within a broad range of genes related to the development of motor, cognitive and impulsive ADHD symptoms are implicated in disease susceptibility (Faraone & Larsson, 2018). Among the genes generally engaged in motor and cognitive impairment, the *chromosome 9 Open Reading Frame 72* (*C9ORF72*) gene plays a preferential role. Involved in the classic phenotype of Motor Neuron Disease (or Amyotrophic Lateral Sclerosis, ALS) and Frontotemporal Dementia (FTD), with a GGGGCC (G_4C_2) hexanucleotide repeat mutation (DeJesus-Hernandez et al., 2011; Renton et al., 2011), *C9ORF72* has also implications in a wide spectrum of neurological conditions. In patients with *C9ORF72*-associated ALS/FTD, the G_4C_2 expansion ranges from several hundred to thousands of repeats (DeJesus-Hernandez et al., 2011; Souza et al., 2015). In addition to these well-established evidence of the involvement of the *C9orf72* gene in various neurological conditions, there are further studies – reviewed in Ducharme et al., 2017, Zucchi et al., 2019, and Devenney et al., 2018 (Devenney et al., 2018; Ducharme, Bajestan, Dickerson & Voon, 2017; Zucchi, Ticozzi & Mandrioli, 2019) – that documented the relatively high prevalence of psychiatric symptoms in cohorts of patients with FTD-related *C9ORF72* expansions. In this context, various research groups have investigated whether these repeats could be the cause of primary psychiatric disorders, mainly Schizophrenia and Bipolar Disorder (BD) in some patients. The revision of Ducharme et al., 2017 identified six studies on Schizophrenia and schizoaffective disorders spanning North America, Europe, and Asia, whereas four American and European studies investigated the frequency of the G_4C_2 expansion in large BD cohorts. Of note, the prevalence of *C9ORF72* expansions is estimated at approximately 0.1% in patients with typical schizophrenia or schizoaffective disorders or BD (Ducharme et al., 2017).

Discussion is open on how many repeats are truly needed to cause disease (Xi et al., 2012): some authors use an arbitrary value of 23 (DeJesus-Hernandez et al., 2011; Gijselinck et al.,

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ABBREVIATIONS*C9ORF72*: chromosome 9 Open Reading Frame 72; ADHD: Attention-deficit/hyperactivity disorder; CDH23: Cadherin-23; ITGAE: Integrin, alpha E; MTHFR: Methylene tetrahydrofolate reductase; MTRR Methionine synthase reductase; PON1: Paraoxonase 1; TPO: Thyroid Peroxidase; VDR: Vitamin D Receptor; NPSR1: Neuropeptide S Receptor 1; SRD5A2: 3-oxo-5α-steroid 4-dehydrogenase 2; WNK1: WNK Lysine Deficient Protein Kinase 1.

2012); others 30 units (Renton et al., 2011). Repeat alleles as short as 20 to 22 repeats have been observed in FTD patients and their siblings (Gomez-Tortosa et al., 2013), whereas the clinical phenotype of ALS cases with 24 and 28 units appear similar to those with 30 repeats (Byrne et al., 2014; Garcia-Redondo et al., 2013; Millecamps et al., 2012; Ng & Tan, 2017; Ratti et al., 2012; Van Mossevelde et al., 2017) suggesting that also the intermediate lengths expansion <30 could be pathogenetic. Interestingly, intermediate length expansions have been associated with BD and Schizophrenia (Fahey et al., 2014; Galimberti, Reif, Dell'osso et al., 2014, 2014; Meisler et al., 2013; Solje et al., 2016; Watson et al., 2016). For instance, 4/130 (3%) patients with psychosis from the Northern Finland Birth Cohort had intermediate repeat sizes (17–26 units) (Solje et al., 2016). In an Irish psychosis cohort, two Schizophrenia cases were found with 28 and 27 repeats (Fahey et al., 2014). Furthermore, Ng & Tan, 2017 supported that intermediate *C9ORF72* repeats cannot directly influence disease risk in common neurological diseases but may be associated with higher frequency of neuropsychiatric symptoms.

In the light of all these evidence, herein, we described a case of a child and his father both affected by ADHD in which the presence of an intermediate *C9ORF72* expansion was detected. A targeted Next Generation Sequencing (NGS) approach coupled with bioinformatics tools was further performed on the whole family investigating a panel of 10 well-known genes for their association with ADHD susceptibility.

2. Materials and methods

2.1. Participants

2.1.1 Entire sample

The family was enrolled along with 116 ADHD children and 20 adult related parents by a network of North Italian Clinical ADHD Centers. It belongs to the ten trios recruited by the ADHD Center of the Child and Adolescent Neuropsychiatry Department, Rho Hospital, Milan. Moreover, 77 age-matched subjects were also enrolled as controls.

The diagnosis of ADHD was performed according to the Diagnostic and Statistical Manual of Mental Disorders 4 (DSM-IV) criteria and the guidelines of the Italian Institute of Health (2005). Neurological examination for minor neurological dysfunctions was performed (Revised Touwen). The following exclusion criteria were adopted: childhood schizophrenia, autism, epilepsy, encephalitis, Tourette syndrome, conduct disorder, and Intelligence quotient (IQ) ≤ 70 (Wechsler Intelligence Scale for Children). Psychopathological features were assessed with specific clinical interviews and Child Behavior Check List. Depressive and anxious symptoms were addressed by using Children Depression Rating Scale.

The clinical assessment for the trios was conducted according to the following protocol. Family history was obtained by clinically interviewing one or both parents. In the assessment phase, demographics and clinical information were collected. The physical and neurological examination was performed by using: the Amsterdam Neuropsychological Test (ANT), a battery to evaluate executive functions and attention; the SNAP-IV Rating Scale - Revised (SNAP IV) for the evaluation of ADHD subsets of symptoms; the Conners' Rating Scale - Revised (CRS-R) for teachers and parents (Conners & Obi, 1968); the narrow band ADHD questionnaires for parents (SDAG) and teachers (SDAI); the Children Depression Rating Scale (derived from the Hamilton Rating Scale for Depression) and the Pediatric Anxiety Rating Scale were used to exclude mood and anxiety disorders. Electrocardiogram (ECG) was also performed.

The ADHD children's cohort (11.39 ± 2.83 years; male = 89.4%) included 70.8%, 27.8%, and 1.4% of ADHD combined, predominantly inattentive, and predominantly hyperactive-impulsive variants, respectively.

The control group consisted of unrelated volunteers (10.19 ± 2.19 years; male = 77.9%) not affected by mental retardation, chronic and medical diseases, inflammatory diseases, and allergies, undergoing blood tests for a pre-surgical screening. They were also selected to exclude ADHD or conduct disorder.

All the participants included in the case-control studies were unrelated, Caucasoid and living in Northern Italy. The study protocol was approved by the local ethics committee in accordance with the ethical standards of Declaration of Helsinki and its later amendments (Scassellati et al., 2014; Valbonesi et al., 2015).

2.1.2 Case report

The proband was a 15-year-old male with a diagnosis of ADHD combined subtype associated with Specific Learning Disorder (SLD) (Table 1). Currently, he is an adult (24 years) with persistent ADHD. The subject was treated with Atomoxetine 1.4 mg/kg/die for one year with a good clinical response, and with speech therapy for 2 years for the learning disabilities (Table 1).

The proband's father is 54 years old affected by ADHD. He has a low educational level (5-year course of studies). No information on ADHD onset is available, although attention problems were already present in childhood, and learning deficit were observed during primary school.

The proband's mother is 50 years old with the same low educational level of her husband. She had language developmental issues, but no attention or memory deficit in childhood.

The diagnoses were based on an accurate anamnestic interview following standard diagnostic criteria. A family history of neurodegenerative and/or other psychiatric disorders was absent in both father's and mother's families.

2.2 Molecular genetic investigation and bioinformatics

The genomic DNA (gDNA) of all participants was extracted from blood or saliva samples using commercial standard kits. The *C9ORF72* G_4C_2 repeat expansion was evaluated by sizing PCR using previously published primers (DeJesus-Hernandez et al., 2011) on an automated ABI3130xl genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The PCR reaction was carried out in a mixture containing 5% dimethylsulfoxide and 7-deaza-2-deoxy GTP in substitution for dGTP. Allele identification and scoring was performed using GeneMapper v4.0 software (Applied Biosystems).

Targeted NGS was performed on gDNA isolated from ADHD child and his parents through the Illumina MiSeq platform and the TruSight One Sequencing Panel (Illumina, Inc., San Diego,

Table 1. Clinical, neuropsychological and neurophysiological features of the child with ADHD carrying the *C9ORF72* hexanucleotide repeat expansion.

Features		Patient
ADHD rating scale		Combined type
Demographic features		
Age (years), Gender Age at onset (years)		24, Male 6
Height (cm)		167
Weight (Kg)		52,6
Treatment		Atomoxetine 1.4 mg/kg/die for one year Speech therapy for 2 years for the learning disabilities.
Cognitive and neuropsychological assessment		
IQ intellectual (WISC)		111
verbal IQ (WISC)		108
Performance IQ (WISC)		112
MT Cornoldi Test		Severe reading difficulties
Tressoldi Test:	Z score reading time of words.	6.06
	Z score syll/sec words	−2.75
	Z score errors words	4
	Z score reading time non words	4.05
	Z score syll/sec non words	−2.4
	Z score number of errors of non words	1
Amsterdam Neuropsychological Test:	Baseline simple reaction time	normal
	Encoding: perceptual abilities	normal
	Visual spatial memory	normal
	Memory search workload:	
	Memory rate	4.67 (z score)
	Memory Efficiency	2.08 (z score)
	Decision speed memory	1.52 (z score)
	Distraction factor	0.19 (z score)
	Focussed attention 4 Letters	normal
	Sustained attention task:	
	Impulsivity index	8.40 (z score)
	Number of misses	5.92 (z score)
	Pursuit	normal
	Tracking significant deficit of eye	
	Left hand coordination	4.14 (z score)
Conners for parents	Global score DSMIV for attention	6 (pathological >5)
	Global score DSMIV for hyperactivity	2 (pathological >5)
Conners for teachers	Global score DSMIV for attention	8 (pathological >5)
	Global score DSMIV for hyperactivity	1 (pathological >5)

(*Continued*)

Table 1. (Continued).

Features		Patient
Neurophysiological assessment	EEG	Absolute power: significant deficit in the delta band in frontal and central areas, significant deficit in the alfa band in parietal and occipital areas. Relative power: significant deficit in delta band in prefrontral areas and significant increased activity in the beta band in centro-parietal areas. Asymmetry: in all frequency bands in temporo-parietal areas. Coherence: significant hyper-coherence in prefrontal areas bilaterally in all frequency bands. This patient's discriminant score suggests ($p \leq 0.0025$) ADHD diagnosis confirmation. The features making the largest contribution to the ADHD statement are: Normed monopolar intrahemispheric coherence theta for Fp1-Fp3. Normed monopolar absolute power delta for Fp1. Normed monopolar coherence theta for Fp1-Fp2.
Comorbidity features	Type of dyslexia according to Boder's classification mixed developmental dyslexia (dysphonetic + dyseidetic)	
	TDLS test:	
	Reading quotient	64.18 (n.v.>90)
	Reading age	9.62
	Chronological age at the date of testing	13.5

TDLS test (Chiarenza and Bindelli. Il test diretto di lettura e scrittura (TDLS): versione computerizzata e dati normativi. Giornale di Neuropsichiatria dell'età evolutiva, 2001, 21, 163–179). Amsterdam Neuropsychological Test (ANT, De Sonneville L.M.J. Boom Testuitgevers; Amsterdam, The Netherlands: 2014. Handboek Amsterdam Neuropsychological Tasks), SNAP-IV ADHD scale revised (SNAP IV, Gaub M & Carlson CL. (1997). Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. J Abnorm Child Psychol, 25, 103–111; Swanson JM. School-Based Assessment and Interventions for ADD Students. Irvine, CA: KC Publications; 1992), Conners' rating scale-R for teachers and parents (CTRS-S, Conners CK. Conners' Rating Scales – Revised: Long Form. Multi-Heath Systems; North Tonawanda, NY: 1997), ADHD questionnaires for parents (SDAG) and for teachers (SDAI) (Cornoldi C, Gardinale M, Masi A & Pettenò L. "Impulsività e autocontrollo". Trento: Erickson 1996).

n.v. = normal values

CA, USA) that allows to explore a global gene list of 4.813 clinically relevant genes, harboring disease-causing variants. The obtained sequence reads were aligned to the hg19 human reference sequence using the Burrow-Wheeler Aligner (BWA version 0.7.12). Duplicated reads were removed with Picard tools.

To confirm the effective presence of all the identified variants, Sanger sequencing was performed. Briefly, standard Polymerase Chain Reaction (PCR) amplifications were conducted on 100 ng gDNA using empirically defined cycling conditions and primers specifically designed by Primer 3 plus program (http://primer3plus.com/cgi-bin/dev/primer3plus.cgi). The PCR products were electrophoresed in 1% agarose gel, stained with Safe DNA gel stain (Life Technologies), and visualized under UV light. PCR amplicons were then purified using the ExoSAP-IT kit (USB 269 Corporation, Cleveland, OH), and sequenced from both forward and reverse directions using the BigDye Terminator Cycle Sequencing kit v3.1 (Applied Biosystems, Foster City, CA) on an automated 271 ABI3130xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Local realignment, recalibration, and variant calling were conducted with the Genome Analysis Tool Kit (GATK version 3.30).

To facilitate variants filtering, we selected: a) variants within selected ADHD candidate genes (i.e. *Cadherin Related 23, CDH23; Integrin Subunit Alpha E, ITGAE; Methylenetetrahydrofolate Reductase, MTHFR; 5-Methyltetrahydrofolate-Homocysteine Methyltransferase Reductase, MTRR; Paraoxonase 1, PON1; Thyroid Peroxidase, TPO; Vitamin D Receptor, VDR; Neuropeptide S Receptor 1, NPSR1; Steroid 5-Alpha-Reductase 2, SRD5A2; Lysine Deficient Protein Kinase 1, WNK1*), as reported in literature data; b) coding variants with a frequency higher than 1% in at least one of the three reference databases (1000 Genomes Project (http://www.internationalgenome.org/), Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), and Exome Aggregation Consortium (http://exac.broadinstitute.org). All the identified NGS variants were annotated according to: a) type of mutations (synonymous; non-synonymous; ins/del non-frameshift and frameshift; stop gain/loss); b) annotation in single nucleotide polymorphism database (dbSNP, rs number); and c) frequency in the ExAC database.

For *in-silico* analysis, the Sorting Intolerant from Tolerant (SIFT) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) algorithms were used to predict the effect of the identified variants on protein structure and function. We classified a variant for its potential deleteriousness, if it was predicted to be as "damaging" (D) by the two considered algorithms.

The differences in the distributions of specific additive combinations were evaluated using the Monte Carlo style CLUMP analysis program. A correlation between age and *C9ORF72* repeat expansions among patients and controls was performed (Pearson Correlation).

For quality control, the best practice from Broad institute was followed (https://software.broadinstitute.org/gatk/best-practices/workflow?id=11145).

A GPS-Prot database was used to explore the gene–gene interaction among the investigated genes.

3. Results

3.1 Detection of C9ORF72 hexanucleotide repeat expansions in the whole cohort

In the entire cohort, the *C9ORF72* repeat expansions genotyping showed the following results. The estimated number of repeats in control and patient cohorts were <16; only two control subjects showed 20 and 18 repeats, respectively. The alleles distributions (CLUMPT1 $X^2 = 24.11$ df = 16 p = 0.06) and genotype frequencies (CLUMPT1 $X^2 = 39.85$ df = 35 p = 0.19, 10,000 permutations) were not different between controls and patients (Table 1S, A and B in supplementary material).

Within the explored family, we detected an intermediate size length of 24 repeats in the proband (0.86% of cases) and his father, but not in his mother not affected by ADHD (G_4C_2 expansion = 8 repeats).

A correlation between age and *C9ORF72* expansions did not reveal any significant result both in the whole ADHD sample cohort (including child/father with ADHD) (Pearson Correlation = 0-.005; p = 0.96) as well as in the control group (Pearson Correlation = −0.011; p = 0.96).

3.2 Genetic investigation by Next Generation Sequencing in the family case

To further explore the family's genetic background, we performed a targeted NGS on each member.

As preliminary data on global mutational profile, considering all the variants that passed the quality control filter (that is an average read depth of coverage per variant per sample > 20), we identified more than 8,000 variants in each subject (8,312 in patient, 8,418 in father, and 8,090 in mother).

To facilitate variants filtering and prioritization, we selected only coding variants (i.e., ins/del frameshift, stop gain/loss, and missense variants) within the selected genes. All the identified variants were confirmed by Sanger Sequencing.

As summarized in Table 2, we revealed common non-synonymous, stop loss/gain, and frameshift insertion variants, most predicted to be damaging by *in silico* approach.

Specifically, the proband showed common variants in all the 10 ADHD candidate genes and, interestingly, among these, the *MTRR* (rs1801394), *CDH23* (rs4747195) and *ITGAE* (rs1716) variants were shared only with his affected father, while they were not present in his unaffected mother. The most common polymorphism in *MTTR* is a substitution of A for G at nucleotide 66 that decreases the enzymatic activity and the rate of hyperhomocysteinemia remethylation (Olteanu et al., 2002). Rs1716 is a missense mutation on *ITGAE* gene (O'Brien et al., 2013).

The other seven variants identified in the patient were detected in both parents.

By using GPS-Prot database, we built a gene-gene interaction framework between *C9ORF72* and each of the 10 investigated genes. Thanks to this analysis, we found that *C9ORF72* was indirectly linked to *WNK1* by *EIF2B2* (Eukaryotic Translation Initiation Factor 2B Subunit Beta) and *MMS19* (Homolog, Cytosolic Iron-Sulfur Assembly Component); to *MTRR* by

Table 2. Genetic variants by targeted exome sequencing in common among ADHD child and his father both carrying the 24 repeats of the *C9orf72* expansion and his mother unaffected and no carrying of *C9ORF72* repeat expansion.

Proband	Father	Mother	Chr	dbSNP	Gene	Exonic Function	ExAC NFE	SIFT	PP2	Clinical significance
x	x	x	1	rs1801133	*MTHFR*	NS	0.35	D	D	Schizophrenia; Major Depressive Disorder; Antipsychotic/antiepileptic response; Autism Spectrum Disorder; Conduct Disorder; Cognitive decline
x	x	x	2	rs2175977	*TPO*	NS	0.60	D	D	Hypothyroidism; Deficiency of iodide peroxidase
x	x	x	2	rs142200057	*SRD5A2*	FI	1.00	-	-	Post-traumatic stress symptoms; Autistic-like traits; Schizophrenia spectrum Disorder; Epilepsy
x	x		5	rs1801394	*MTRR*	NS	0.55	D	D	Autism Spectrum Disorder; Behavioral problems; Bipolar Disorder; Schizophrenia; Antidepressant response
x	x	x	7	rs10275028	*NPSR1*	SL	0.34	-	-	Anxiety disorder; Obsessive-Compulsive Disorder; Panic disorder
x	x	x	7	rs854560	*PON1*	NS	0.37	D	D	Autistic Disorder; Epilepsy; Schizophrenia; Hyperhomocysteinemia
x	x		10	rs4747195	*CDH23*	NS	0.27	D	D	Major Depressive Disorder; Bipolar Disorder; Personality dimensions
x	x	x	12	rs397768556	*WNK1*	FI	0.57	-	-	Schizophrenia
x	x	x	12	rs2228570	*VDR*	NS	0.61	D	D	Autistic Disorder; Major Depressive Disorder; Epilepsy
x	x		17	rs1716	*ITGAE*	NS	0.33	D	D	-

Chr: Chromosome; *MTHFR*: Methylenetetrahydrofolate Reductase; *TPO*: Thyroid Peroxidase; *SRD5A2*: Steroid 5 Alpha-Reductase 2; *MTRR*: 5-Methyltetrahydrofolate-Homocysteine Methyltransferase Reductase; *NPSR1*: Neuropeptide S Receptor 1; *PON1*: Paraoxonase 1; *CDH23*: Cadherin Related 23; *WNK1*: WNK Lysine Deficient Protein Kinase 1; *VDR*: Vitamin D Receptor; *ITGAE*: Integrin Subunit Alpha E; SL: stop-loss; FI: frameshift insertion; PP2, PolyPhen2; SIFT, Sorting Intolerant from Tolerant NS: non-synonymous; D: Damaging; ExAC-NFE: Exome Aggregation Consortium-European non Finnish.

ELAVL1 (ELAV Like RNA Binding Protein 1); and *VDR* by *RUNX1T1* (RUNX1 Partner Transcriptional Co-Repressor 1) and *SRPK1* (SRSF Protein Kinase 1) genes (Figure 1S in supplementary material).

4. Discussion

This work describes a case report of a child and his father both affected by ADHD carrying an intermediate *C9ORF72* expansion (G_4C_2 = 24 repeats). They belong to a larger sample cohort of 116 ADHD children and 20 adult related parents, with 77 age-matched control subjects, whom were all genotyped for *C9ORF72* repeat expansion. The investigated family was further analyzed by a targeted NGS approach followed by Sanger sequencing confirmation, exploring a panel of 10 ADHD associated genes (*CDH23, ITGAE, MTHFR, MTRR, PON1, TPO, VDR, NPSR1, SRD5A2 WNK1*) (Lesch et al., 2008; Gokcen et al., 2011; Saha et al., 2018; Bonvicini et al., 2018; Päkkilä et al., 2014; Sahin, Altun, Kurutas & Balkan, 2018; van der Meer et al., 2017; Zettergren et al., 2016). Of note, genetic exploration allowed to discover that the proband and his father also shared three common variants with a functional impact in *MTRR, CDH23*, and *ITGAE* genes, in addition to the peculiar *C9ORF72* intermediate expansion. Instead, the other detected variants were present also in the unaffected mother and not carrying of 24-repeat expansion, excluding their potential aetiopathogenetic role. Moreover, the bioinformatics analyses showed a gene–gene interaction between *C9ORF72* and *WNK1, MTRR, VDR*. Excluding *VDR* gene, this finding supports that alterations in autophagic mechanisms could be involved in ADHD (Tsetsos et al., 2016). Interestingly, among the genes for which a direct/indirect interaction with *C9ORF72* was identified, *MTRR* is involved with a demonstrated functional variant (rs1801394; Olteanu et al., 2002).

Some crucial points emerge from this study. 1. We detected for the first time an intermediate size length of 24 repeats in one ADHD child with a mutation frequency of 0.86% in the whole ADHD explored cohort. This finding is in line with literature data for neuropsychiatric phenotypes. Other authors found a frequency of 0.5% (Meisler et al., 2013), 1.0% (Galimberti et al., 2014) in BD, and 0.7% (Galimberti et al., 2014), 0.2% (Fahey et al., 2014), and 3% (Solje et al., 2016) in schizophrenia. In both schizophrenia and BD, the prevalence of *C9ORF72* mutation is estimated at approximately 0.1% in patients with typical schizophrenia, schizoaffective disorders, or BD (Ducharme et al., 2017). Interestingly, the same number of repeats was found in his father, also affected by ADHD. 2. Repeat G_4C_2 expansions in *C9ORF72* cause familial FTD, ALS, and mixed phenotype with symptomatic expansion carriers displaying higher rates of psychotic and other psychiatric symptoms than non-carriers (Silverman et al., 2019). If it remains still unknown how many repeats are truly needed for causing disease (Xi et al., 2012), intermediate lengths (20–28 repeats) have been observed in dementia patients (Byrne et al., 2014; Garcia-Redondo et al., 2013; Gomez-Tortosa et al., 2013; Millecamps et al., 2012; Ratti et al., 2012), but also and more

frequently in presence of neuropsychiatric phenotypes (Ng & Tan, 2017). In these phenotypes, these sizes also display an increased methylation as compared to large expansions and affect normal transcriptional activity of the *C9ORF72* promoter already with 24-unit, compared with 2-unit repeat allele (Ng & Tan, 2017). 3. The intermediate lengths of *C9ORF72* repeat expansion were found in ADHD subjects, which are relatives with different age, carrying also the same clinically recognized variants in ADHD susceptibility genes, such as *MTRR, ITGAE,* and *CDH23* (Gokcen et al., 2011; Lesch et al., 2008; Saha et al., 2018). Of note, these three genes play a key role in cell-cell communication and folate pathways known to be impaired in ADHD (Gokcen et al., 2011; Lesch et al., 2008; Saha et al., 2018). Moreover, all the variants in these genes showed common frequencies in reference databases, and were non-synonymous predicted to be deleterious, underling the role of the common variants in contributing to disease risk and further that ADHD, as it is already known is a polygenic disorder. 4. Among *CDH23, ITGAE* and *MTRR*, in which the same variants were detected for both the affected subjects, the bioinformatics analysis conducted by using GPS-Prot database highlighted an interesting gene–gene interaction specifically between *C9ORF72* and *MTRR*. This link is not directly but involves intermediate genes. Anyway, this result suggests that the intermediate *C9ORF72* repeats might have a synergistic potentially pathogenetic effect with important implications both in childhood and in adulthood ADHD. Recent studies (Budini et al., 2017) have identified a role of *C9ORF72* in the control of autophagy. Interestingly, also *MTRR* seems to be implicated in this pathway (Gallolu Kankanamalage et al., 2017). Autophagy has been identified as the main process underlying protein degradation and that, if altered, it impairs cell homeostasis and physiology. Deregulation of autophagy leads thus to multiple diseases, including ADHD (Tsetsos et al., 2016). 5. The other seven variants identified in the patient were detected in both parents. The fact that these variants are present also in the mother, unaffected and not carrying the 24 *C9ORF72* repeats, permits to exclude their potential aetiopathogenetic role. 6. We did not find a correlation between age and G_4C_2 repeat size both in patients including child/father with ADHD and in controls sample, in line with other authors who did not detect correlations for *C9ORF72* repeat expansion carriers affected by ALS or FTD (Chen et al., 2016).

In the light of all these evidence, we speculate that, in a polygenic and multifactorial aetiopathogenetic scenario, therefore extremely complex, such as that underlying ADHD, intermediate expansions in *C9ORF72* gene could have a causative effect on ADHD development if in presence of other relevant causes. We hope that this study will represent the starting point for future investigations in larger cohorts.

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