NEWSLETTER

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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD FEBBRAIO 2022

Addict Biol. 2022 Mar;27:e13137.

EFFECTS OF FAMILY HISTORY OF SUBSTANCE USE DISORDER ON REWARD PROCESSING IN ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Paraskevopoulou M, Van RD, Schene AH, et al.

Patients with attention-deficit/hyperactivity disorder (ADHD) often develop early onset substance use disorder (SUD) and show poor treatment outcomes. Both disorders show similar reward-processing alterations, but it is unclear whether these are associated with familial vulnerability to SUD. Our aim was to investigate effects of family history of SUD (FH) on reward processing in individuals with and without ADHD, without substance misuse. Behavioural and functional magnetic resonance imaging (fMRI) data from a modified monetary incentive delay task were compared between participants with and without FH (FH positive [FH+]: n = 76 and FH negative [FH-]: n = 69; 76 with ADHD, aged 16.74 ± 3.14, 82 males), while accounting for continuous ADHD scores. The main analysis showed distinct positive association between ADHD scores and reaction times during neutral versus reward condition. ADHD scores were also positively associated with anticipatory responses of dorsolateral prefrontal cortex, independent of FH. There were no main FH effects on brain activation. Yet, FH+ participants showed distinct neural alterations in ventrolateral prefrontal cortex (VLPFC), dependent on ADHD. This was driven by positive association between ADHD scores and VLPFC activation during reward outcome, only in FH+. Sensitivity analysis with stricter SUD index showed hyperactivation of anterior cingulate cortex for FH+, independent of ADHD, during reward anticipation. There were no FH or ADHD effects on activation of ventral striatum in any analysis. Findings suggest both FH and ADHD effects in circuits of reward and attention/memory during reward processing. Future studies should examine whether these relate to early substance use initiation in ADHD and explore the need for adjusted SUD prevention strategies

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

Am J Med Genet A. 2021 Dec;185:3664-74.

EARLY DEVELOPMENTAL IMPACT OF SEX CHROMOSOME TRISOMIES ON ATTENTION DEFICIT-HYPERACTIVITY DISORDER SYMPTOMOLOGY IN YOUNG CHILDREN.

Kuiper K, Swaab H, Tartaglia N, et al.

Individuals with sex chromosome trisomies ([SCT], XXX, XXY, and XYY)) are at increased risk for neurodevelopmental problems, given that a significant portion of the sex chromosome genes impact brain functioning. An elevated risk for psychopathology has also been described, including attention deficit-hyperactivity disorder (ADHD). The present study aimed at identifying early markers of ADHD, providing the first investigation of ADHD symptomology in very young children with SCT. The variety, type, and severity of ADHD symptomology in 1-6-year-old children with SCT (n =104) were compared with population-based controls (n =101) using the strengths and weaknesses of ADHD symptoms and normal-behavior (SWAN) parent-report questionnaire. ADHD symptomology was significantly more prevalent in SCT and already present from toddlerhood on, compared to controls. ADHD inattention symptoms were significantly increased in all karyotypes (XXX, XXY, and XYY), boys with XYY also showed significantly more hyperactivity/impulsivity symptoms than controls. Inattentiveness was more pronounced with increasing age for SCT, in contrast to controls. Within the SCT group, 24% of the children had significantly elevated ADHD symptoms at a clinical level. Already from an early age on, SCT is associated with a risk for ADHD, suggesting that its neurodevelopmental risk lies anchored in early brain maturation. Studying this genetically vulnerable population allows for the prospective study of risk markers to facilitate early and preventive interventions

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Am J Occup Ther. 2022 Mar;76.

PILOT STUDY OF THE COGNITIVE-FUNCTIONAL INTERVENTION FOR ADULTS (COG-FUN A): A METACOGNITIVE-FUNCTIONAL TOOL FOR ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kastner L, Velder-Shukrun Y, Bonne O, et al.

IMPORTANCE: Adults with attention deficit hyperactivity disorder (ADHD) often experience chronic challenges in their life roles. There is a need for evidence-based occupational therapy interventions to help enhance their functioning.

OBJECTIVE: To determine the preliminary effectiveness of the Cognitive-Functional Intervention for Adults (Cog-Fun A), a metacognitive-functional occupational therapy tool for the improvement of occupational performance (OP) and quality of life (QoL) in adults with ADHD.

DESIGN: One-group pretest-posttest design with a 3-mo follow-up.

SETTING: Community setting in Jerusalem, Israel.

PARTICIPANTS: Fourteen adults, ages 18-60 yr, with a valid diagnosis of ADHD and an indication of executive function (EF) impairment.

INTERVENTION: Participants received 15 1-hr weekly sessions that addressed self-awareness of strengths and challenges through education and guided discovery as well as strategy acquisition and implementation within a context of occupational goal attainment.

OUTCOMES AND MEASURES: The Behavioral Rating Inventory of Executive Function-Adult version, an adult ADHD QoL measure, the Canadian Occupational Performance Measure, and the Self-Regulation Skills Interview were administered. RESULTS: Twelve participants completed the intervention. Posttreatment scores revealed statistically significant improvements in EF, awareness, OP, and QoL. Gains in QoL showed a modest reduction at the 3-mo follow-up.

CONCLUSIONS AND RELEVANCE: The Cog-Fun A is a promising intervention for improving OP and QoL among adults with ADHD and should be investigated further. What This Article Adds: The Cog-Fun A offers an effective nonpharmacological, metacognitive-functional, occupation-centered treatment option for adults with ADHD

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Asia Pac Psychiatry. 2022 Mar;14:e12448.

CHANGING PARENTING STYLE BETWEEN TWO GENERATIONS AND ITS IMPACTS ON THE SEVERITY OF BEHAVIORAL AND EMOTIONAL SYMPTOMS.

Ghorbani S, Gharraee B, Hosseini F, et al.

OBJECTIVE: The purpose of this study is to compare the perceived parenting dimensions in mothers and their daughters (differences between two generations), and study the relationship between these dimensions and the severity of daughters' behavioral and emotional symptoms.

MATERIALS AND METHODS: 300 participants (150 daughters with their mothers) participated in this study. They responded to the perceived parenting styles questionnaire (PSQ), and mothers were additionally asked to answer the child symptoms inventory-4 (CSI-4). Data analysis was done by the SPSS using the paired sample t-test and multiple regressions.

RESULTS: The results indicated a significant difference between perceived parenting dimensions in mothers and their daughters; specifically, acceptance and control dimensions increased through generation. It was also found that daughters' acceptance-rejection dimension could predict the severity of the symptoms of attention-deficit/hyperactivity disorders, autism spectrum disorders, depression, dysthymia, conduct disorders, and opposite defiant disorders. The control-autonomy dimension could also predict the severity of schizophrenia symptoms.

CONCLUSION: The results indicate the different parenting styles between two generations and the critical role of parenting in developing the children's psychopathology symptoms

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Autism Res. 2022.

DECREASED INTEROCEPTIVE ACCURACY IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND WITH COMORBID ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Yang HX, Zhou HY, Li Y, et al.

Interoception refers to the awareness of internal physiological state. Several previous studies reported that people with autism spectrum disorders (ASD) and adults with attention-deficit/hyperactivity disorder (ADHD) have diverse patterns of interoception, but the extent of literature is limited and inconsistent. This study aimed to investigate the interoceptive accuracy (IA) in children with ASD, children with comorbid ASD and ADHD, and typically developing (TD) children with high and low levels of autistic traits. We administered the eye-tracking interoceptive accuracy task (EIAT) to 30 children with ASD, 20 children with comorbid ASD and ADHD, and 63 TD controls with high and low levels of autistic traits. Parent-report scales concerning ASD and ADHD symptoms were collected. ASD children with and without comorbid ADHD both exhibited lower IA than TD children. Reduced IA was also found in TD children with high-autistic traits relative to those with low-autistic traits. IA was negatively correlated with autistic and ADHD symptoms. Atypical cardiac interoception could be found in children with ASD. Difficulties in sensing and comprehending internal bodily signals in childhood may be related to both ASD and ADHD symptoms

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Behav Genet. 2021;51:631-53.

THE DIFFERENTIAL RELATIONS BETWEEN ADHD AND READING COMPREHENSION: A QUANTILE REGRESSION AND QUANTILE GENETIC APPROACH.

Shero JA, Logan JAR, Petrill SA, et al.

This paper extends the understanding of the relation between ADHD and reading comprehension, through examining how this relation differs depending on the quantile an individual falls in for each. Samples from three twin projects around the United States were used (Florida Twin Project, Colorado component of International Longitudinal Twin Study of Early Reading Development, & Western Reserve Reading and Math Projects). Phenotypic analysis using quantile regression showed relations between ADHD related behaviors and reading comprehension to be stronger in the lower quantiles of reading comprehension in two of three samples. A new method was developed extending this analysis into the bivariate genetic space. Results of this quantile genetic analysis revealed that overlapping common environmental influences accounted for a larger proportion of variance in the lower quantiles of these variables in two of three samples. Finally, in all

three samples the phenotypic relation was strongest when shared environmental influences accounted for a larger proportion of the overall variance

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Biomedical and Biopharmaceutical Research. 2018;15:259.

THE PERCEPTION OF FIRST-CYCLE TEACHERS REGARDING THE THERAPEUTICS OF THE ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ferreira R, Mendes LC, Fernandes AS.

The Attention Deficit Hyperactivity Disorder (ADHD) is characterized by a persistent pattern of inattention and / or hyperactivity-impulsivity, with personal, academic, family and social impact, affecting 5-7% of the school-age population. Methylphenidate is the first-line drug, and its use had a large increase in recent years. The management of the pathology, including the monitoring of the response to therapy, should involve health professionals, family members and teachers. Teachers have a greater contact with children and can thus easily detect behavioral changes upon the beginning of medication. However, few studies have focused role of teachers in the management of ADHD, especially in the context of therapeutics. The present work aims to characterize the perception of 1st cycle teachers regarding the impact of ADHA therapeutics on their students. In the absence of an adequate instrument to collect these data, a specific questionnaire was constructed. The questionnaire was focused on teachers' training regarding ADHD and its therapy; the experience with students with ADHD; the changes upon beginning of medication; and the observation of adverse drug reactions (ADR) and possible notification to the physicians, family members and National Pharmacovigilance System (SNF). The feasibility of the questionnaire was verified in a pre-test applied personally to a convenience sample of 12 teachers from a school of Lisboa e Vale do Tejo region. Subsequently an online version of the questionnaire was developed and distributed to the teachers from the schools of this region. A total of 107 responses was received. In addition, pediatric psychiatrists were interviewed by telephone, in order to gather experiences regarding their interaction with teachers in the management of ADHA therapeutics. The results indicate that more than 40% of the inquired teachers have received training in ADHA, but in most cases the theme of therapeutics was not included. About 87% of the teachers mentioned the need for more training. The vast majority of teachers (91.6%) have had students with ADHD. Most of the teachers observed alterations in their students upon starting medication, generally in a beneficial way. More than 60% of the teachers answered that they are aware of the ADR and 24% have already detected them in their students. The teachers reported the observed ADR to the parents in 93% of the cases and to the doctors in 28% of the cases, but never to the SNF. From the preliminary results of the interviews, pediatric psychiatrists highlighted the interaction with teachers. Importantly, physicians mentioned that they do not report ADR to the SNF due to lack of information about the notification process. In conclusion, the results show the need to reinforce teachers' training in ADHD and its therapeutics, as well as the need to disseminate the SNF amongst teachers and physicians. This study allows to characterize the perception of the teachers towards the ADHD therapeutics, contributing to the identification of strategies for the better follow up of the children with this pathology

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BMC Pediatr. 2022;22.

NUTRIENT INTAKE, DIETARY PATTERNS, AND ANTHROPOMETRIC VARIABLES OF CHILDREN WITH ADHD IN COMPARISON TO HEALTHY CONTROLS: A CASE-CONTROL STUDY.

Salvat H, Mohammadi MN, Molavi P, et al.

Background: Poor health behaviors and variables are recently more documented in attention-deficit hyperactivity disorder (ADHD) lifestyle which might be relevant to the pathophysiology of this disorder. The objective of this case-control study was to assess the nutrient intake, dietary patterns, and anthropometric variables-áin children with-ADHD compared to normal peers.

Method: One hundred children diagnosed with ADHD were included and compared to 100 healthy, sex-matched normal children as the control group. Anthropometric indices, macronutrients, and micronutrients were measured and compared in both groups.

Results: ADHD children were significantly consuming more simple sugars, tea, ready-made meals but less protein, vitamin B1, vitamin B2, vitamin C, zinc and calcium compared to the control group. The body mass

index (BMI) and waist circumference of children with-ADHD were significantly higher and were related to the severity and type of the disease.
Conclusion: Unhealthy eating behavior is more frequent in children with-ADHD, compared to normal children which might warrant lifestyle intervention in this disorder

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BMC Psychiatry. 2022;22.

COGNITIVE, EMOTIONAL, AND SOCIAL FUNCTIONING OF PRESCHOOLERS WITH ATTENTION DEFICIT HYPERACTIVITY PROBLEMS.

Biele G, Overgaard KR, Friis S, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is associated with deficits in different functional domains. It remains unclear if deficits in different domains are equally strong in early childhood, and which deficits are specific to ADHD. Here, we describe functional domains in preschoolers and assess deficits in children with ADHD problems, by comparing them to preschoolers with other mental health problems or who develop typically.
Methods: The ADHD Study assessed 1195 ca. 3.5 years old preschoolers through a semi-structured parent interview, parent questionnaires, and with neuropsychological tests. We determined functional domains by applying factor analytic methods to a broad set of questionnaire- and test-scales. Using resulting factor scores, we employed a Bayesian hierarchical regression to estimate functional deficits in children with ADHD.
Results: We found that preschoolersΓÇÖ functioning could be described along the seven relatively independent dimensions activity level and regulation, executive function, cognition, language, emotion regulation, introversion, and sociability. Compared to typically developing preschoolers, those with ADHD had deficits in all domains except introversion and sociability. Only deficits in activity level regulation and executive functions were larger than 0.5 standardised mean deviations and larger than deficits of children with other mental health problems.
Conclusions: Preschoolers with ADHD have deficits in multiple functional domains, but only impairments in activity level and regulation and executive functions are specific for ADHD and large enough to be clinically significant. Research on functioning in these domains will be important for understanding the development of ADHD, and for improving treatment and prevention approaches

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BMC Psychiatry. 2022 Jan;22:61.

SYMPTOMATOLOGY OF ATTENTION DEFICIT, HYPERACTIVITY AND DEFIANT BEHAVIOR AS PREDICTORS OF ACADEMIC ACHIEVEMENT.

Flores J, et al.

BACKGROUND: It is essential to understand the factors that affect the academic achievement of schoolchildren, both in general and in terms of the major subsectors of each grade. Although symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and Negative Defiant Disorder (NDD-which are commonly recognized as externalizing problems in childhood and adolescence-have been associated with lower academic achievement in the international literature, few studies have addressed this problem in Latin America. This study aimed to analyze the possible predictive relationship of attention problems, hyperactivity, and defiant behavior on academic achievement.
METHODS: We recruited a sample of 4580 schoolchildren (50.9% female, 1754 belonging to primary school, and 2826 to secondary school, ranging from 9 to 18 years old). This cross-sectional study used the scales pertaining to attention problems, hyperactivity, and challenging behavior from the Child and Adolescent Evaluation System.
RESULTS: The analysis showed that attention problems significantly affected all academic achievement areas, while hyperactivity and challenging behavior affected only some of them. The regression models explained 24% of the variability in overall academic achievement in primary school and 17% in secondary school. Other predictors included sex, age, socioeconomic level, and school attendance.
CONCLUSIONS: It is important to consider this symptomatology in the design of educational interventions

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BMC Psychiatry. 2022 Jan;22:4.

THE USEFULNESS OF VIRTUAL, AUGMENTED, AND MIXED REALITY TECHNOLOGIES IN THE DIAGNOSIS AND TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN: AN OVERVIEW OF RELEVANT STUDIES.

Goharinejad S, Goharinejad S, Hajesmaeel-Gohari S, et al.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by attention problems, excessive physical activity, and impulsivity. ADHD affects not only the patients but also their families. The development and use of technologies such as virtual reality (VR), augmented reality (AR), and mixed reality (MR) for ADHD has increased over recent years. However, little is known about their potential usefulness. This overview aimed to clarify the current knowledge about the use of these three innovative technologies for the diagnosis and treatment of children with ADHD.

METHODS: This overview was conducted using the PubMed, Web of Science, and Scopus databases until January 24th, 2021. The following descriptive information was compiled from the identified studies: country, year of publication, sample size, study design, ADHD diagnosis methods, applied technology, hardware equipment, clinical target, and main findings.

RESULTS: The initial database searches yielded 409 articles, but 103 were removed as duplicates. Eventually, 30 eligible studies remained for analysis, the majority of which were case-control (n =22, 73%). Regarding the applied technology/hardware equipment, VR (n =27; 90%), head-mounted displays (n =19, 63%), VR-based continuous performance tests (VR-CPT) (n =21, 70%) were most frequently used. Most studies (n=21, 70%) used the DSM criteria for the diagnosis of childhood ADHD. They primarily evaluated the utility of these technologies in assessing ADHD symptoms (n=10, 33%) and improving the ADHD diagnostic process (n =7, 23%).

CONCLUSION: This comprehensive overview evaluated the studies on the use of VR, AR, and MR technologies for children with ADHD. These technologies seem to be promising tools for improving the diagnosis and management of ADHD in this population

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BMJ Open. 2021 Dec;11:e048222.

CASE-CONTROL STUDY ON CLINICAL CHARACTERISTICS OF CHILD AND ADOLESCENT PSYCHIATRIC OUTPATIENTS WITH CHILD-TO-PARENT VIOLENCE.

Sasaki Y, Usami M, Sasaki S, et al.

OBJECTIVES: To the best of our knowledge, no case-control study on child and adolescent psychiatric outpatients has investigated the clinical characteristics of patients with child-to-parent violence (CPV). The current study aimed to evaluate the clinical characteristics of child and adolescent psychiatric patients with CPV.

SETTING AND PARTICIPANTS: This research included child and adolescent psychiatric patients who were aged 10-15 years during their initial consultation. The participants were allocated to one of two groups: children with CPV (CPV group, n=109) and without CPV (non-CPV group, n=713).

OUTCOME MEASURES: This study analysed data including age, sex, diagnostic classification of the primary diagnosis, antisocial behaviour, suicidal attempt or self-harm and refusal to attend school. Moreover, a history of abuse by parents was investigated. Psychological rating scales such as the Spence Children's Anxiety Scale, Depression Self-Rating Scale for Children, Tokyo Autistic Behavior Scale, Attention-deficit/Hyperactivity Disorder-Rating Scale and Oppositional Defiant Behavior Inventory were used.

RESULTS: Of 822 patients who sought consultation in our department, 109 (13.26%) were included in the CPV group during the first consultation. Compared with the non-CPV group, the CPV group had significantly higher proportions of patients who experienced physical abuse, psychological abuse and who witnessed violence between parents. Meanwhile, the proportion of patients with neurodevelopmental disorders was significantly higher in the CPV group than in the non-CPV group. Regarding developmental characteristics, impulsivity might be correlated with CPV. Moreover, violence and behavioural problems outside of home were associated with CPV.

CONCLUSIONS: In patients with CPV who sought consultation, the findings of the current study should be considered to understand invisible side and to facilitate the use of appropriate treatment approaches. However, a prospective study should be performed to investigate the causality between CPV and clinical characteristics

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BMJ Paediatr Open. 2021;5:e001209.

ADVERSE CHILDHOOD EXPERIENCES-HOUSEHOLD STRESSORS AND CHILDREN'S MENTAL HEALTH: A SINGLE CENTRE RETROSPECTIVE REVIEW.

Holmes H, Darmanthe N, Tee K, et al.

OBJECTIVE: To determine the prevalence of reported 'household stressor' adverse childhood experiences (ACEs) in families of children presenting with neurodevelopmental, behavioural or emotional difficulties and to determine whether family vulnerabilities, individually or cumulatively, were associated with particular clinical symptomatology.

DESIGN: Retrospective chart review followed by statistical analysis of family stressors and clinical symptomatology.

SETTING: A community paediatric clinic in Australia.

PARTICIPANTS: All 267 children who attended an initial paediatric appointment during 2018. RESULTS: 162 (60.7%) children had been exposed to one or more household stressor ACEs, including 116 (43.4%) children exposed to parental mental illness. Behavioural disturbance occurred in 144 (53.9%) children and externalising behaviours (other than attention deficit hyperactivity disorder) were more frequent than internalising behaviours. Externalising and internalising behaviours were associated with individual and cumulative household stressor ACEs. Most other symptomatology apart from genetic/neurological conditions, autistic symptoms and some developmental delays appeared to be partially associated with ACEs.

CONCLUSION: Household stressor ACEs were common, frequently occurred concurrently, and were associated with much of the symptomatology, in this cohort. Parental mental illness was the most prevalent stressor and behavioural disturbance the most prevalent symptomatology. These findings may have implications for clinical practice and service provision

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Br J Anaesth. 2022 Mar;128:e221-e222.

UNDIAGNOSED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MAY BE A RISK FACTOR FOR REQUIRING ANAESTHESIA.

Conway MA, Conway MA.

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Brain Behav Immun. 2022 Feb;100:105-11.

KAWASAKI DISEASE IN CHILDHOOD AND PSYCHIATRIC DISORDERS: A POPULATION-BASED CASE-CONTROL PROSPECTIVE STUDY IN TAIWAN.

Chen DT, Chang JP, Cheng SW, et al.

Background: Kawasaki disease (KD) is a common childhood acute inflammatory disease and potentially triggers a chronic inflammation. Although some researches have investigated neurodevelopmental consequences following KD, the findings have been inconsistent. This is the first population-based study targeted on KD and common psychiatric disorders.

Objectives: We aimed to investigate the association between KD and psychiatric disorders and hypothesized that standard anti-inflammatory treatment by intravenous immunoglobulin (IVIG) may protect against development of psychiatric disorders.

Method: We retrieved data from Taiwan's National Health Insurance Research database (NHIRD). Patients (n = 282,513) with psychiatric disorders (the case group) during 1997-2013 were included, and the control group was matched with age, sex, income and urbanization (1:1). We calculated the prevalence of KD in both groups and estimated odd ratios (ORs) and 95% confidence intervals (CIs) in the subgroup analyses for KD in conditions of age, severity, and common psychiatric comorbidity.

Results: Numbers of patients with KD were 460 in the cases and 380 in the controls (p = .006), and the crude OR of KD was 1.21 times greater (95% CI = 1.06-1.39, p = .006) in the case than the control groups. KD patients without IVIG treatment (n = 126) were higher in the cases than those in the controls (n = 54), with the OR of 2.33 (95% CI = 1.70-3.21, p < .0001). Subgroup analyses showed that KD survivors were at significant risk for autism spectrum disorders (ASD) (OR = 2.15, 95% CI = 1.27-3.65; p = .005) and attention

deficit and hyperactivity disorders (ADHD) (OR = 1.19, 95% CI = 1.02-1.39; p = 0.03), and a trend of increased risk for anxiety disorders (OR = 1.36, 95%CI = 0.99-1.86; p = 0.05).
Conclusions: Patients with KD were more likely to have comorbid psychiatric disorders, including ASD and ADHD. Moreover, anti-inflammatory treatment with IVIG may have potential prophylactic effects against the development of psychiatric disorders

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Brain Behav Immun. 2022 Jan;99:281-88.

MYCOPLASMA PNEUMONIAE IGG POSITIVITY IS ASSOCIATED WITH TIC SEVERITY IN CHRONIC TIC DISORDERS.

Schnell J, Bond M, Moll N, et al.

Infectious pathogens may represent an environmental risk factor for chronic tic disorders (CTD). This cross-sectional study aimed to determine whether Mycoplasma pneumoniae (M. pneumoniae) IgG positivity is associated with the presence or severity of tics. We compared M. pneumoniae IgG positivity across three groups: children and adolescents (3-16 years) with CTD (CTD group; n = 302); siblings (3-10 years) of people with CTD who developed tics within a seven-year follow-up period (tic onset group; n = 51); siblings (4-10 years) who did not develop tics within the study period and were ≥10-years-old at their last assessment (unaffected group; n = 88). The relationship between M. pneumoniae IgG positivity and the presence and severity of tics was analysed using multilevel models controlling for site, family relatedness, sex, age, presence of comorbid obsessive-compulsive and/or attention-deficit/hyperactivity disorder and use of psychotropic medication. M. pneumoniae IgG positivity was not associated with the presence of CTD, or the first onset of tics as compared to siblings who remained unaffected. M. pneumoniae IgG positivity was associated with a higher tic severity score within the CTD group (β = 2.64, s.e. = 1.15, p = 0.02). It is possible that M. pneumoniae infection influences tic severity in CTD or, that having more severe tics, increases the risk of infection. However, it is more likely that the association observed in this study reflects a propensity toward enhanced immune responses in people with CTD and that, rather than a causal relationship, infection and greater tic severity are indirectly linked via shared underlying immune mechanisms

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Brain Dev. 2021 Nov;43:997-1003.

A RETROSPECTIVE ANALYSIS OF MEMANTINE USE IN A PEDIATRIC NEUROLOGY CLINIC.

Bouhadoun S, Poulin C, Berrahmoune S, et al.

BACKGROUND: Memantine is an N-methyl-D-aspartate receptor (NMDA-R) antagonist, approved for dementia, but also studied in pediatric autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD).
METHODS: We reviewed children treated with memantine in a single-centre pediatric neurology clinic. Clinical data extracted included age, sex, weight, clinical history, reason for memantine prescription, period of treatment trial and dosage, treatment response, side effects, and concomitant medications.
RESULTS: Eight patients met inclusion criteria with diagnoses including developmental and epileptic encephalopathy, focal epilepsy, ASD, ADHD. Four reported clear cognitive improvement, though two of these started other concurrent treatments at the time of memantine initiation. One of three patients with poorly-controlled epilepsy, a girl with a GRIN2A variant of uncertain significance, had a clear reduction in seizure frequency. No serious adverse events were noted.
CONCLUSIONS: Memantine is generally well-tolerated in children, and may have potential benefit for a broad range of pediatric neurodevelopmental disorders

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Brain Imaging Behav. 2022.

SEX DIFFERENCES IN MICROSTRUCTURAL ALTERATIONS IN THE CORPUS CALLOSUM TRACTS IN DRUG-NA+»VE CHILDREN WITH ADHD.

Lin Q, Bu X, Chen H, et al.

Widespread alterations in the corpus callosum (CC) microstructure and organization have been found in children with attention-deficit/hyperactivity disorder (ADHD); however, few studies have investigated the diffusion characteristics and volume of transcallosal fiber tracts defined by specific cortical projections in

ADHD, which is important for identifying distinct functional interhemispheric connection abnormalities. In the current study, an automated fiber-tract quantification (AFQ) approach based on diffusion tensor imaging identified seven CC tracts according to their cortical projections and estimated diffusion parameters and volume among 76 drug-na+»ve ADHD patients (53 boys and 23 girls) and 37 typically developing children (TDC) (20 boys and 17 girls) matched for age, IQ, and handedness. We found significantly lower fractional anisotropy (FA) in the occipital and superior parietal tracts and higher mean diffusivity (MD) in the posterior, superior parietal and anterior frontal tracts in children with ADHD compared with TDC. In addition, lower FA and higher radial diffusivity (RD) in the occipital callosal tract were significantly associated with higher hyperactivity and impulsivity performance in ADHD. In addition, sex-by-diagnosis interactions were observed in the occipital, posterior and superior parietal tracts. Girls with ADHD showed decreased FA and volume in the occipital tract, which were significantly associated with increased impulsivity performance and poor response control, and increased MD in the posterior and superior parietal callosal tracts, which were significantly associated with increased inattention performance, whereas boys with ADHD merely showed decreased volume in the frontal tract. Our results elucidated that sex-specific alterations in the CC tracts potentially underlie ADHD symptomatology and further suggested a differential contribution of abnormalities in different CC tracts to impulsivity and inattention among girls with ADHD

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Br J Psychiatry. 2022;220:64-72.

METHYLPHENIDATE AND MORTALITY IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: POPULATION-BASED COHORT STUDY.

Chen VCH, Chan HL, Wu SI, et al.

Background Little is known about methylphenidate (MPH) use and mortality outcomes.

Aims To investigate the association between MPH use and mortality among children with an attention-deficit hyperactivity disorder (ADHD) diagnosis.

Method This population-based cohort study analysed data from Taiwan's National Health Insurance Research Database (NHIRD). A total of 68 096 children and adolescents aged 4-17 years with an ADHD diagnosis and prescribed MPH between 2000 and 2010 were compared with 68 096 without an MPH prescription, matched on age, gender and year of first ADHD diagnosis. All participants were followed to death, migration, withdrawal from the National Health Insurance programme or 31 December 2013. MPH prescriptions were measured on a yearly basis during the study period, and the association between MPH use and mortality was analysed using a repeated-measures time-dependent Cox regression model. The outcome measures included all-cause, unnatural-cause (including suicide, accident and homicide) and natural-cause mortality, obtained from linkage to the National Mortality Register in Taiwan.

Results The MPH group had lower unadjusted all-cause, natural-, unnatural- and accident-cause mortality than the comparison group. After controlling for potential confounders, MPH use was associated with a significantly lower all-cause mortality (adjusted hazard ratio AHR = 0.81, 95% CI 0.67-0.98, P = 0.027), delayed use of MPH was associated with higher mortality (AHR = 1.05, 95% CI 1.01-1.09) and longer MPH use was associated with lower mortality (AHR = 0.83, 95% CI 0.70-0.98).

Conclusions MPH use is associated with a reduced overall mortality in children with ADHD in this cohort study, but unmeasured confounding cannot be excluded absolutely

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Clin Genet. 2021 Nov;100:573-600.

SPECTRUM OF NEURO-GENETIC DISORDERS IN THE UNITED ARAB EMIRATES NATIONAL POPULATION.

Saleh S, Beyyumi E, Al KA, et al.

Clinical and molecular characterization of neuro-genetic disorders among UAE national patients seen in the Genetic Clinic at Tawam hospital over a period of 3â€‰years. A retrospective chart review of all Emirati patients assessed by clinical geneticists due to neuro-genetic disorders including global developmental delay, ASD, ID, ADHD, and epilepsy in combination with abnormalities of other organ systems. Each patient had proper assessment including detailed history, three-generation family history, developmental history and detailed physical examination looking for other system involvement. Hearing test and ophthalmological examination were performed when needed. Magnetic resonance imaging (MRI) of the brain,

echocardiogram, and renal ultrasound were pursued as indicated. Detailed psychological evaluation and psychometric assessment were done when indicated. The review was done for a period between January 2018 and December 2020. Genetic investigations included chromosome karyotype, FISH study, metabolic/biochemical tests, chromosome microarray, gene sequencing, targeted mutation testing, trio whole exome and trio genome sequencing. A total of 644 patients with developmental delay, ID, learning difficulty, ASD, ADHD, or NNDs, were seen in genetic clinic from January 2018 to December 2020. A total of 506 patients were included in this review, all completed the genetic evaluations during the study period. There were 398 (61.8%) males and 246 (38.2%) females, with a ratio of 1.6:1. Positive family history of NDD was documented in 132 families, while 115 families had negative history and family history was unknown/unclear in the remaining. Fifty seven (11.26% [57/506]) patients had positive microarray results. Hundred ninety seven (38.9% [197/506]) patients had positive molecular testing. Genetic disorders were found in 133 (67.5% [133/197]) and inborn errors of metabolism were found in 42 (21.3% [42/197]). Consanguinity was documented in 139 patients with positive molecular diagnoses (139/197, 70.5%). Sixty nine (35% [69/197]) patients had autosomal dominant disorders, majority were De Novo (84%). Ninety-five (48% [95/197]) patients had autosomal recessive diseases, 40 mutations involved inborn errors of metabolism and 50 mutations involved genetic disorders. Pathogenic variants causing both autosomal dominant and recessive disorders were found in 98 patients (49.7% [98/197]), likely pathogenic variants causing both autosomal dominant and recessive disorders were found in 66 patients (33.5% [66/197]). X-linked related disorders were found in 10 patients (5% [10/197]). Mitochondrial mutation was found in one patient. Novel mutations were found in 76 patients (76/197 i.e., 38.56%). Twenty two patients had variants of unknown significant. The remaining 252 studied patients (252/506 i.e., 49.8%), remained undiagnosed. This study shows that neuro-genetic disorders in the UAE are very heterogeneous at clinical and molecular levels. Using microarray, WES and WGS a diagnosis was reached in 50% of the patients while no diagnosis was reached in other half of the studied patients. It is possible that some mutations were missed by WGS and WES. However, it is also possible that many of disorders in UAE population are novel and the causative mutation is not yet discovered. More researches need to be done in this population to uncover the molecular basis of these disorders

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Clin Pediatr. 2022;61:222-27.

THE TOLL OF COVID-2019 ON DIVERSE, URBAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND THEIR FAMILIES: A CASE SERIES.

Lejeune JA, Sikov J, Loubeau JK, et al.

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Clin Psychopharmacol Neurosci. 2022;20:109-17.

INCREASED SERUM LEVEL OF CCL5 IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: FIRST RESULTS ABOUT SERUM CHEMOKINES.

Ozaslan A, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder and its aetiology is not fully understood. This study aimed to determine whether the CCL5 and CCL11 influence the ADHD aetiology by comparing serum CCL5 and CCL11 levels of children with ADHD and typical development.

Methods: This study included 45 (27 males, mean age = 8.9 -¦ 1.7 years) treatment-naive patients diagnosed with ADHD and 35 (20 males, mean age = 8.8 -¦ 1.6 years) healthy controls. Participants ranged in age between 6-12 years and completed the Conners Teacher Rating Scale that assesses ADHD presentation and severity. CCL5 and CCL11 serum levels were also measured using enzyme-linked immunosorbent assay kits.

Results: Significantly higher serum CCL5 levels were found in children with ADHD compared to healthy controls (p 0.001). No significant difference was found between the mean serum CC11 level of the patients and controls (p = 0.93). In addition, there was no significant correlation between the serum CCL5 and CCL11 levels and predominant presentations of ADHD and disease severity.

Conclusion: This study suggests that there are higher levels of serum CCL5 in drug naive children with ADHD, this findings suggest that CCL5 might play a role in the pathophysiology of ADHD. Moreover, these

changes in peripheral blood may have therapeutic value. In addition, these results help to understand the role of chemokines in elucidating the etiopathogenesis of ADHD. Our results can be considered as the first step in investigating the role of CCL5 in ADHD, and further research is needed to support these initial findings

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Clin Psychopharmacol Neurosci. 2022;20:126-34.

PREVALENCE AND COMORBIDITIES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG ADULTS AND CHILDREN/ADOLESCENTS IN KOREA.

Seo JC, Jon DI, Shim SH, et al.

Objective: This study investigated the prevalence and comorbidities of attention deficit hyperactivity disorder (ADHD) among adults and children/adolescents in Korea.

Methods: This study used data from the Korea Health Insurance Review and Assessment Service collected from 2008 to 2018. Study participants comprised patients with at least one diagnosis of ADHD (International Statistical Classification of Diseases and Related Health Provisions, 10th revision code F90.0). Prevalence rates and psychiatric comorbidities were also analyzed.

Results: We identified 878,996 patients diagnosed with ADHD between 2008 and 2018. The overall prevalence rate of diagnosed ADHD increased steeply from 127.1/100,000 in 2008 to 192.9/100,000 in 2018; it increased 1.47 times in children/adolescents (Γëñ 18 years) and 10.1 times in adults (18 years) during this period. Among adult and children/adolescent ADHD patients, 61.84% (95% confidence interval [95% CI] 61.74-61.93) and 78.72% (95% CI 78.53- 78.91) had at least one psychiatric comorbidity, respectively.

Conclusion: Our results showed that the prevalence rate of diagnosed ADHD has increased in Korea; however, it is lower than the global average. Further studies are required to identify and treat vulnerable populations appropriately

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CMAJ. 2022 Feb;194:E235-E241.

ANTENATAL CORTICOSTEROID ADMINISTRATION AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD: A REGRESSION DISCONTINUITY STUDY.

Hutcheon JA, Strumpf EC, Liauw J, et al.

BACKGROUND: Antenatal corticosteroids reduce respiratory morbidity in preterm infants, but their use during late preterm gestation (34-36 weeks) is limited because their safety for longer-term child neurodevelopment is unclear. We sought to determine if fetuses with higher probability of exposure to antenatal corticosteroids had increased rates of prescriptions for attention-deficit/hyperactivity disorder (ADHD) medication in childhood, using a quasiexperimental design that better controls for confounding than existing observational studies.

METHODS: We identified 16 358 children whose birthing parents were admitted for delivery between 31 + 0 (31 weeks, 0 days) and 36 + 6 weeks' gestation in 2000-2013, using a perinatal data registry from British Columbia, Canada, and linked their records with population-based child ADHD medication data (2000-2018). We used a regression discontinuity design to capitalize on the fact that pregnancies presenting for delivery immediately before and immediately after the clinical cut-off for antenatal corticosteroid administration of 34 + 0 weeks' gestation have very different levels of exposure to corticosteroids, but are otherwise similar with respect to confounders.

RESULTS: Over a median follow-up period of 9 years, 892 (5.5%) children had 1 or more dispensations of ADHD medication. Children whose birthing parents were admitted for delivery just before the corticosteroid clinical cut-off of 34 + 0 weeks' gestation did not appear to be more likely to be prescribed ADHD medication than those admitted just after the cut-off (rate ratio 1.1, 95% confidence interval [CI] 0.8 to 1.6; 1.3 excess cases per 100 children, 95% CI -2.5 to 5.7).

INTERPRETATION: We found little evidence that children with higher probability of exposure to antenatal corticosteroids have higher rates of ADHD prescriptions in childhood, supporting the safety of antenatal corticosteroids for this neurodevelopmental outcome

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CNS Spectr. 2021 Oct;26:448-56.

CLOSING THE GAP: UNMET NEEDS OF INDIVIDUALS WITH IMPULSIVE AGGRESSIVE BEHAVIOR OBSERVED IN CHILDREN AND ADOLESCENTS.

Robb AS, Connor DF, Amann BH, et al.

Impulsive aggressive (IA, or impulsive aggression) behavior describes an aggregate set of maladaptive, aggressive behaviors occurring across multiple neuropsychiatric disorders. IA is reactive, eruptive, sudden, and unplanned; it provides information about the severity, but not the nature, of its associated primary disorder. IA in children and adolescents is of serious clinical concern for patients, families, and physicians, given the detrimental impact pediatric IA can have on development. Currently, the ability to properly identify, monitor, and treat IA behavior across clinical populations is hindered by two major roadblocks: (1) the lack of an assessment tool designed for and sensitive to the set of behaviors comprising IA, and (2) the absence of a treatment indicated for IA symptomatology. In this review, we discuss the clinical gaps in the approach to monitoring and treating IA behavior, and highlight emerging solutions that may improve clinical outcomes in patients with IA

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Current Neuropharmacology. 2021;19:1794-804.

THE EFFECTS OF DRUGS USED FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) ON PREGNANCY OUTCOME AND BREAST-FEEDING: A CRITICAL REVIEW.

Ornoy A, Koren G.

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral condition found in 5-10% of school-age children and in 2-5% of adults. Stimulants affecting the dopaminergic, noradrenergic and/or serotonergic systems are commonly used for treatment in children and adults, including women of childbearing age. The data on the effects of stimulants (methylphenidate and amphetamines) in pregnancy are generally reassuring, but methylphenidate might slightly increase the rate of cardiac malformations and of spontaneous abortions, while amphetamines might slightly increase the risk for premature birth, low birth weight and other pregnancy complications. Bupropion, a dopamine and norepinephrine reuptake inhibitor, when used as an antidepressant, appears to be safe in pregnancy. The data on the use of atomoxetine, guanfacine and clonidine in pregnancy are scarce. Importantly, there are practically no data on the long-term neurodevelopmental effects of most of these drugs. The published data on the development of children born to methamphetamine-abusing women may be misleading since these women generally use other drugs, including alcohol, and the home environment where the child is raised may not be optimal. The treating physician should judge the need for treatment during pregnancy in relation to the severity of the clinical symptoms. If needed, methylphenidate is preferred over amphetamines because breast feeding is possible. If one uses non-stimulant medications, bupropion seems to be the preferred drug

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Current Opinion in Psychiatry. 2022;35:90-100.

TOWARDS EQUITABLE DIAGNOSES FOR AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ACROSS SEXES AND GENDERS.

Lai MC, Lin HY, Ameis SH.

Purpose of review Sex/gender-related factors contribute to contextual issues influencing the recognition of autism and attention-deficit/hyperactivity disorder (ADHD), and modulate how neurodevelopmental characteristics are manifested. This review summarizes the empirical literature to provide directions for improving clinical diagnostic practices. Recent findings Timing of autism and/or ADHD diagnosis, particularly in girls/women, is related to the individual's developmental characteristics and co-occurring diagnoses, and expectancy, alongside gender stereotype biases, of referral sources and clinicians. This is further compounded by sex and gender modulations of behavioural presentations. The emerging'female autism phenotype' concept may serve as a helpful illustration of nuanced autism phenotypes, but should not be viewed as essential features of autism in a particular sex or gender. These nuanced phenotypes that can present across sexes and genders include heightened attention to socially salient stimuli, friendship and social groups, richness in language expression, and more reciprocal behaviours. The nuanced female-predominant ADHD phenotypes are characterized by subtle expressions in hyperactivity-impulsivity (e.g.,

hyper-verbal behaviours). Optimizing neurodevelopmental diagnoses across sexes and genders also requires an understanding of sex-related and gender-related variations in developmental trajectories, including compensation/masking efforts, and the influences of co-occurring conditions on clinical presentations. Summary Equitable diagnoses across sexes and genders for autism and ADHD require understanding of the nuanced presentations and the Gestalt clinical-developmental profiles, and addressing contextual biases that influence diagnostic practices

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Curr Psychiatry Rep. 2022.

ADHD AND ANXIETY DISORDER COMORBIDITY IN CHILDREN AND ADULTS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES.

Koyuncu A, Ayan T, Ince Guliyev E, et al.

Purpose of the-áReview: In this review, we focus on overlapping features of ADHD and anxiety disorders, and will discuss how an anxiety disorder comorbidity leads to diagnostic and treatment challenges in patients with ADHD, in consideration of the accumulated available knowledge. Recent Findings: The presence of overlapping symptoms, changes in the diagnostic criteria, and the use of divergent diagnostic tools and informant effects can complicate the diagnosis of this comorbidity. Due to the ongoing debate about the etiology, psychopathology, and diagnostic features of the association between ADHD and anxiety disorders, choosing appropriate treatment options emerges as a challenge. Summary: A novel methodology, standardized interview tools, and new statistical analysis methods are needed to define the phenotype of this co-occurrence more clearly. It is important to uncover the developmental nature of this comorbidity with follow-up studies that may explain the etiology and underlying neurobiological basis, and ultimately lead to more effective treatment approaches

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Depress Anxiety. 2022 Mar;39:233-45.

PATERNAL PREVALENCE AND RISK FACTORS FOR COMORBID DEPRESSION AND ANXIETY ACROSS THE FIRST 2 YEARS POSTPARTUM: A NATIONWIDE CANADIAN COHORT STUDY.

Dennis CL, Marini F, Dol J, et al.

OBJECTIVE: To determine the prevalence of comorbid depression and anxiety symptoms in fathers and investigate the predictors for comorbidity during the first- and second-year following birth.

METHODS: In a longitudinal Canadian study, couples were recruited within 3 weeks of childbirth. Fathers completed a survey after the birth of their child followed by questionnaires at 3, 6, 9, 12, 18, and 24 months postpartum on paternal depression and anxiety symptoms and potential risk factors. Sequential logistic regression was used for analysis.

RESULTS: Of the 3217 enrolled fathers, 2544 (79.08%) provided data for at least one time point during the first year postpartum and 2442 (75.29%) in the second year. Overall, 569 fathers (22.4%) had comorbid depression and anxiety symptoms at some point during the first year postpartum (2.2% at baseline to 8.9% at 6 months), and 323 fathers (13.2%) had comorbidity at some point during their second year postpartum (8.1% at 18 months and 8.6% at 24 months). Strongest risk factors associated with paternal comorbidity were poor or fair perceived health at 4 weeks postpartum, depression before pregnancy, anxiety in the current pregnancy, significant adverse childhood experiences, positive ADHD screen, and victim of intimate partner violence.

CONCLUSION: High rates of comorbidity among fathers in the first 2 years postpartum demonstrate the importance of perinatal mental health management at a family level. The identification of important modifiable comorbidity risk factors highlights areas for further research and the development of interventions to support paternal mental health to optimize child and family outcomes

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Dev Neuropsychol. 2022 Jan;47:42-59.

INHIBITORY CONTROL, CONDUCT PROBLEMS, AND CALLOUS UNEMOTIONAL TRAITS IN CHILDREN WITH ADHD AND TYPICALLY DEVELOPING CHILDREN.

Waschbusch DA, Babinski DE, Fosco WD, et al.

Compared children with CP/ADHD, CPCU/ADHD, ADHD-only, and controls on two measures of inhibitory control: a Simon/flanker task that measured response selection and a stop signal task that measured response inhibition. Results showed: (a) ADHD was associated with both measures of inhibitory control; (b) control children had better overall performance and ADHD-only had worse response selection than the CP groups; and (c) children with CPCU/ADHD had better response inhibition than children with ADHD-only or CP/ADHD. Results suggest inhibitory control dysfunction is associated with ADHD rather than CP and that response inhibition dysfunction distinguishes children with CP/ADHD from children with CPCU/ADHD

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Dev Neuropsychol. 2022 Mar;47:61-77.

MODELING THE SPEEDED DETERMINANTS OF ADOLESCENTS' ACADEMIC AND ATTENTIONAL FUNCTIONING.

Wakeman HN, Leopold DR, Olson RK, et al.

The current study utilized a large, unselected sample of adolescent twins to examine whether processing speed (PS) is an important shared predictor that accounts for covariance among reading, math, ADHD, and rapid naming (RN). The best fitting model included correlated but distinguishable latent measures of PS, RN, reading, math, inattention, hyperactivity/impulsivity, and academic fluency. PS was a shared predictor across all outcomes, while RN was uniquely associated with reading, fluency, and (albeit weakly) math. The results add to a growing literature suggesting that PS and RN may be important components of comprehensive neuropsychological models of academics, ADHD, and their covariation

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Dev Psychopathol. 2021 Dec;33:1803-20.

LONGITUDINAL NETWORK MODEL OF THE CO-DEVELOPMENT OF TEMPERAMENT, EXECUTIVE FUNCTIONING, AND PSYCHOPATHOLOGY SYMPTOMS IN YOUTH WITH AND WITHOUT ADHD.

Karalunas SL, Antovich D, Goh PK, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a common, chronic, and impairing disorder, yet presentations of ADHD and clinical course are highly heterogeneous. Despite substantial research efforts, both (a) the secondary co-occurrence of ADHD and complicating additional clinical problems and (b) the developmental pathways leading toward or away from recovery through adolescence remain poorly understood. Resolving these requires accounting for transactional influences of a large number of features across development. Here, we applied a longitudinal cross-lagged panel network model to a multimodal, multilevel dataset in a well-characterized sample of 488 children (nADHD=296) to test Research Domain Criteria initiative-inspired hypotheses about transdiagnostic risk. Network features included DSM symptoms, trait-based ratings of emotional functioning (temperament), and performance-based measures of cognition. Results confirmed that ADHD symptom domains, temperamental Irritability, and Working Memory are independent transdiagnostic risk factors for psychopathology based on their direct associations with other features across time. ADHD symptoms and working memory each had direct, independent associations with depression. Results also demonstrated tightly linked co-development of ADHD symptoms and temperamental Irritability, consistent with the possibility that this type of anger dysregulation is a core feature that is co-expressed as part of the ADHD phenotype for some children

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Dev Sci. 2022 Mar;25:e13168.

THE RELATIONSHIP BETWEEN EXECUTIVE FUNCTION, PROCESSING SPEED, AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN MIDDLE CHILDHOOD.

Sabhlok A, Malanchini M, Engelhardt LE, et al.

Attention-Deficit Hyperactivity Disorder (ADHD) is a heterogeneous disorder that is highly impairing. Early, accurate diagnosis maximizes long-term positive outcomes for youth with ADHD. Tests of executive functioning (EF) are potential tools for screening and differential diagnosis of ADHD subtypes. However,

previous research has been inconsistent regarding the specificity and magnitude of EF deficits across ADHD subtypes. Here, we advance knowledge of the EF-ADHD relationship by using: (1) dimensional latent factor models of ADHD that captures the heterogeneity of expression, and (2) a comprehensive, reliable battery of EF tasks and modeling relationships with a general factor of EF ability. We tested 1548 children and adolescents (ages 7-15 years) from the Texas Twin Project, a population-based cohort with a diverse socioeconomic and ethnic composition. We show that EF deficits were specific to the inattention domain of ADHD. Moreover, we found that the association between EF task performance and inattention was stable across sociodemographic groups. Our results demonstrate that failures of executive control are selectively manifested as covert inattentive symptoms, such as trouble with organization, forgetfulness, and distractedness, rather than overt symptoms, such as inappropriate talkativeness and interruption. Future research, utilizing a bifactor characterization of ADHD in clinical samples, is needed to further refine understanding of the nature of cognitive deficits in ADHD across the full range of symptom variation

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Diabetologia. 2021 Apr;64:767-77.

POOR GLYCAEMIC CONTROL IS ASSOCIATED WITH INCREASED RISK OF NEURODEVELOPMENTAL DISORDERS IN CHILDHOOD-ONSET TYPE 1 DIABETES: A POPULATION-BASED COHORT STUDY.

Liu S, Kuja-Halkola R, Larsson H, et al.

AIMS/HYPOTHESIS: The aim of this study was to investigate the effect of childhood-onset type 1 diabetes on the risk of subsequent neurodevelopmental disorders, and the role of glycaemic control in this association. We hypothesised that individuals with poor glycaemic control may be at a higher risk of neurodevelopmental disorders compared with the general population, as well as compared with individuals with type 1 diabetes with adequate glycaemic control.

METHODS: This Swedish population-based cohort study was conducted using data from health registers from 1973 to 2013. We identified 8430 patients with childhood-onset type 1 diabetes (diagnosed before age 18Â years) with a median age of diabetes onset of 9.6 (IQR 5.9-12.9) and 84,300 reference individuals from the general population, matched for sex, birth year and birth county. Cox models were used to estimate the effect of HbA(1c) on the risk of subsequent neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and intellectual disability.

RESULTS: During a median follow-up period of 5.6Â years, 398 (4.7%) individuals with type 1 diabetes received a diagnosis of any neurodevelopmental disorder compared with 3066 (3.6%) in the general population, corresponding to an adjusted HR (HR(adjusted)) of 1.31 (95% CI 1.18, 1.46) after additionally adjusting for other psychiatric morbidity prior to inclusion, parental psychiatric morbidity and parental highest education level. The risk of any neurodevelopmental disorder increased with HbA(1c) levels and the highest risk was observed in patients with mean HbA(1c) >8.6% (>70Â mmol/mol) (HR(adjusted) 1.90 [95% CI 1.51, 2.37]) compared with reference individuals without type 1 diabetes. In addition, when compared with patients with diabetes with HbA(1c) <7.5% (<58 mmol/mol), patients with HbA(1c) >8.6% (>70 mmol/mol) had the highest risk of any neurodevelopmental disorder (HR(adjusted) 3.71 [95% CI 2.75, 5.02]) and of specific neurodevelopmental disorders including ADHD (HR(adjusted) 4.16 [95% CI 2.92, 5.94]), ASD (HR(adjusted) 2.84 [95% CI 1.52, 5.28]) and intellectual disability (HR(adjusted) 3.93 [95% CI 1.38, 11.22]).

CONCLUSIONS/INTERPRETATION: Childhood-onset type 1 diabetes is associated with an increased risk of neurodevelopmental disorders, with the highest risk seen in individuals with poor glycaemic control. Routine neurodevelopmental follow-up visits should be considered in type 1 diabetes, especially in patients with poor glycaemic control

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Diabetologia. 2021 Aug;64:1897-98.

ADHD SHOULD BE CONSIDERED IN ADOLESCENTS WITH TYPE 1 DIABETES AND POOR METABOLIC CONTROL.

Nylander C, Fernell E.

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Diagnostics. 2022;12.

NEVUS COMEDONICUS SYNDROME ASSOCIATED WITH PSYCHIATRIC DISORDER.

Woo HY, Kim SK.

Nevus comedonicus (NC) is a rare hamartoma of the pilosebaceous unit origin. The association with extracutaneous abnormalities defines NC syndrome (NCS). Fewer than 50 cases of NCS have been reported in the English literature. A 31-year-old woman presented with grouped and linear comedonal papules present from birth and located on the left buttock along BlaschkoΓÇÖs lines. She had a history of pediatric mood disorder combined with attention-deficit hyperactivity disorder (ADHD) from 5 years of age and was recently diagnosed with sinus bradycardia. Her skin lesion was surgically removed and microscopic findings revealed the aggregation of dilated follicular in-fundibula filled with prominent laminated keratin plugs, a characteristic finding of NC. This is the first report presenting NCS associated with mood disorder and ADHD. Psychiatric symptoms may represent systemic manifestation of NCS

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Drug Alcohol Depend. 2021;228.

EFFECTS OF SUBSTANCE MISUSE AND CURRENT FAMILY HISTORY OF SUBSTANCE USE DISORDER ON BRAIN STRUCTURE IN ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Novi M, Paraskevopoulou M, van Rooij D, et al.

Background: Alterations in brain structure in attention-deficit/hyperactivity disorder (ADHD) show considerable overlap with those observed in substance use disorder (SUD). These overlapping structural alterations in ADHD and SUD might be explained by family history (FH-trait) effects of SUD, and/or substance misuse (state) effects. Our aim was to investigate effects of 1) current parental SUD (SUD-FH) and 2) recent substance misuse (SM) on brain structure in a cohort of ADHD patients and controls.

Design: Cortical thickness and subcortical volumes were measured using structural MRI. We compared ADHD subjects and controls with or without SUD-FH (aim 1) and additionally explored differences between SUD-FH- and SUD-FH + subjects with one versus two parents with SUD. We also compared ADHD groups with and without SM (ADHD + SM and ADHD-only, respectively) and controls (aim 2).

Findings: There was no association between SUD-FH and brain structure. Exploratory analysis on SUD-FH showed decreased IFG thickness ($p = 0.032$) and nucleus accumbens (NAcc) volume ($p = 0.017$) in subjects with two versus one SUD parent, regardless of ADHD. ADHD + SM showed decreased inferior frontal gyrus (IFG) thickness compared to controls (pars opercularis $p = 0.025$, pars orbitalis $p = 0.010$, pars triangularis $p = 0.049$), while no difference was found between ADHD-only and either ADHD + SM or controls.

Conclusions: Despite negative findings in the primary trait-analysis, exploratory trait-analysis on SUD-FH loading suggested potential SUD trait-effects on IFG thickness and NAcc volume. Substance misuse state effects in ADHD were linked to lower IFG thickness. Future studies should confirm these findings and investigate their clinical relevance, including the functional consequences of decreased IFG thickness

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Drugs and Therapy Perspectives. 2022;38:77-83.

VILOXAZINE FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A NEW FORMULATION FOR A NEW INDICATION.

Balasundaram MK, Singh A.

Viloxazine (SPN-812), an age-old antidepressant, has recently been approved by the US FDA for the treatment of attention-deficit hyperactivity disorder (ADHD) in children aged 6-17 years, at a dose range of 100-400 mg/day. Viloxazine acts primarily by norepinephrine reuptake inhibition and may also modulate the serotonergic system. The efficacy of viloxazine for the treatment of ADHD in children aged 6-17 years has been demonstrated in a series of short-term clinical trials. The most common adverse events include somnolence and gastrointestinal upset, while the FDA has issued a black-box warning regarding suicidal ideation or behavior. This article summarizes the information regarding viloxazine based on previously published narrative reviews, preclinical studies, and blinded controlled clinical trials

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Dyslexia. 2022.

CHILDREN'S VOCABULARY AND FRIENDSHIPS: A COMPARATIVE STUDY BETWEEN CHILDREN WITH AND WITHOUT SPECIFIC LEARNING DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kouvava S, Antonopoulou K, Ralli AM, et al.

Language skills are important in the formation and maintenance of friendships. Children with specific learning disorder (SLD) or attention-deficit/hyperactivity disorder (ADHD) experience difficulties with their relationships and have language-related problems. This study aims to examine how expressive and receptive vocabulary may relate to friendships of children with and without SLD or ADHD. Participants were 64 children with SLD, 64 children with ADHD, and 64 typically developing (TD) children, aged 8-12 years (Mage=-9.77 years, SD=1.22), attending Grades 3 to 6 in inclusive primary schools of Attica, Greece. The Greek versions of the Peabody Picture Vocabulary Test and the expressive vocabulary subscale of the WISC-III were administered along with the sociometric nominations of friends and the self-reports of best friendship duration. Results showed that children with SLD and ADHD reported best friendships of shorter duration and had significantly poorer receptive and expressive vocabulary. Children with ADHD had significantly fewer close and best friends than children with SLD, who in turn had significantly fewer close and best friends than the TD children. Children's vocabulary in all three groups was positively correlated with the duration of their best friendships and was found to moderately predict children's close friendships

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Early Interv Psychiatry. 2022 Jan;16:17-25.

SOCIAL IMPAIRMENT IN RELATION TO CLINICAL SYMPTOMS IN YOUTH AT HIGH RISK FOR BIPOLAR DISORDER.

Weintraub MJ, Keenan-Miller D, Schneck CD, et al.

AIM: Social impairment is common in individuals with bipolar disorder (BD), although its role in youths at high-risk for BD (i.e., mood symptoms in the context of a family history of BD) is not well understood. Social impairment takes many forms including social withdrawal, relational aggression, physical aggression, and victimization. The aim of this study was to explore the links between social impairment and clinical symptoms in youth at high-risk for BD.

METHODS: The sample included 127 youths with elevations in mood symptoms (depression or hypomania) and at least one first and/or second degree relative with BD. Measures of youths' current psychopathology (i.e., depressive and manic severity, suicidality, anxiety, and attention-deficit/hyperactivity disorder [ADHD]) were regressed onto youths' self-reports of social impairment (i.e., social withdrawal, relational aggression, physical aggression, and victimization).

RESULTS: Depressive symptoms, suicidal ideation, and anxiety symptoms were related to social withdrawal. Suicidal ideation was also related to reactive aggression. ADHD symptoms related to reactive and proactive aggression as well as relational victimization. Manic symptoms were not associated with social impairment in this sample.

CONCLUSIONS: Although cross-sectional, study findings point to potential treatment targets related to social functioning. Specifically, social withdrawal should be a target for treatment of childhood depressive and anxiety symptoms. Treatments that focus on social skills and cognitive functioning deficits associated with BD may also have clinical utility

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Environ Int. 2022;161.

THE ASSOCIATION OF PRENATAL AND CHILDHOOD PYRETHROID PESTICIDE EXPOSURE WITH SCHOOL-AGE ADHD TRAITS.

Lee KS, Lim YH, Lee YA, et al.

Background: Pyrethroid insecticides are commonly used in residential settings, and their use has increased rapidly. Although research has been scarce, they have been reported to be associated with impaired neurodevelopment. Moreover, susceptible exposure windows and the long-term effects of pyrethroids have not been investigated. We examined the association between pyrethroid exposure and attention-deficit/hyperactivity disorder (ADHD) symptoms over time, with exposure windows spanning from the prenatal period to school-age.

Methods: Using 524 motherΓÇôchild pairs, we measured urinary concentrations of 3-phenoxybenzoic acid (3-PBA), a major pyrethroid metabolite, and asked parents to fill-out the ADHD Rating Scale IV (ARS). We used Poisson regression to identify the susceptible periods of pyrethroid exposure, by correlating various 3-PBA exposure windows (prenatal, ages 2, 4, 6 and 8) with ADHD symptoms at ages 6 and 8.
Results: Doubling of prenatal and age 2 3-PBA concentrations was associated with increased ADHD symptoms at age 6 (2.7% change, 95% confidence interval [CI]: 0.3, 5.2; 5.2% change [95% CI: 0.5, 10.2], respectively). The 3-PBA concentrations at age 4 and age 6 were linked with ADHD symptoms at age 8 (2.7% change [95% CI: 0.3, 5.3]; 3.3% change [95% CI: 0.2, 6.4], respectively). There were no clear sex-specific patterns in association.
Discussion: Both prenatal and early-childhood exposure to 3-PBA were found to be associated with ADHD symptoms. Exposure during pregnancy, and at ages 2 to 6 were found to be susceptible periods for pyrethroid neurotoxicity at ages 6 and 8

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Environ Int. 2022;161.

ASSOCIATION OF BISPHENOL A, BISPHENOL F, AND BISPHENOL S WITH ADHD SYMPTOMS IN CHILDREN.

Kim JI, Lee YA, Shin CH, et al.

Background: Bisphenol A (BPA) has been linked to attention-deficit/hyperactivity disorder (ADHD) symptoms, but the neurotoxic effects of bisphenol substitutes such as bisphenol F (BPF) and S (BPS) have not been well investigated. We investigated the associations between BPA, BPF, and BPS with ADHD symptoms at multiple time points in children.
Methods: The levels of BPA (at ages 4, 6, and 8), BPF (at ages 6 and 8), and BPS (at ages 6 and 8) were measured in 619 children. Because of the low detection frequency of BPF and BPS levels, participants were divided into categories (<or ΓëÑ limit of detection (LOD) for BPF; < LOD, LOD and < median, or median for BPS). ADHD symptoms were assessed using the ADHD Rating Scale IV (ARS). The relationship between bisphenols and ARS scores was analyzed using Poisson regression models, and generalized additive models and piecewise regression models were further explored for BPA.
Results: BPA was detected in most participants (>97%), whereas BPF and BPS were less frequently detected (age 6: 17.5% for BPF and 42.0% for BPS; age 8: 51.6% for BPF and 73.3% for BPS). Doubling in BPA levels was associated with increased ARS scores by 4.7% (95% confidence intervals [CI]: 0.5, 9.2) at age 6. The association was greater with BPA levels higher than 3.0 ++g/g creatinine (24.2% [95% CI: 15.5, 33.6] increase). The BPF LOD group had 10.8% (95% CI: 1.2, 21.4) higher ARS scores than the BPF < LOD group. The BPS median group had 11.4% (95% CI: 2.0, 21.7) higher ARS scores than the BPS < LOD group.
Conclusion: All bisphenols, in particular those at or above the LOD or median levels, were associated with ADHD symptoms at age 6. Further prospective studies are warranted to determine causal inference

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Environ Res. 2022;208.

ATTENTION DEFICIT AMONG PRESCHOOL AND SCHOOL-AGED CHILDREN LIVING NEAR FORMER METAL-PROCESSING PLANTS IN ROMANIA.

Nedelescu M, Stan M, Ciobanu AM, et al.

Industrial areas affected by high and long-term heavy metal pollution have a great impact on health of the resident population. Children represent a group at high-risk with an increased susceptibility to chronic heavy metal intoxication. Our work included the assessment of attention particularities through a case-control study in pre-school and school-aged children (4ΓÇô6 years and 8ΓÇô11 years) from two study areas, Cop+ƒa Mic-â and Zlatna, compared to a non-polluted locality with no history of heavy metal pollution. Cop+ƒa Mic-â and Zlatna are two of the most polluted heavy metals regions in Romania due to non-ferrous metallurgy for a long period of time. Recruitment of participants was made by a random selection of an entire class for each age within the schools and kindergartens from the study areas (Cop+ƒa Mic-â and Zlatna) and from the non-polluted region. Interpretation of data was performed using statistical analysis (ANOVA and Student's t-test). Preschool children (4ΓÇô6 years) were tested using Wechsler Preschool and Primary Scale of Intelligence (WPPSI) tests, Animal House and labyrinth samples. The results of the attention tests applied to pre-school children were lower in the study areas compared to the control group, but no statistical differences were

found. The results of the attention tests applied to children aged between 8 and 11 years (Toulouse-Pieron test and Traffic light test) indicate lower average scores within the study groups from polluted areas, compared to the control group. Differences with statistically significance were registered for the 8 years age group (p = 0.037). In these areas efficient strategies and precise intervention measures are needed in order to limit or remove the heavy metal exposure and protect the human health, especially the groups exposed to a high level of risk

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Eur J Cardiothorac Surg. 2021 Dec;60:1428-36.

INTERMEDIATE-TERM NEURODEVELOPMENTAL OUTCOMES AND QUALITY OF LIFE AFTER ARTERIAL SWITCH OPERATION BEYOND EARLY NEONATAL PERIOD.

Ramanan S, Sundaram S, Gopalakrishnan A, et al.

OBJECTIVES: The study objective was to evaluate the cardiac, neurodevelopmental, psycho-social and health-related quality of life (HRQOL) outcomes of children who underwent an arterial switch operation (ASO).

METHODS: Children who underwent ASO were evaluated on follow-up at 3-5 years with cardiovascular, neurodevelopmental and HRQOL assessment using validated tools. Children with developmental delay, attention-deficit hyperactivity disorder, autism spectrum disorder, neuromotor and speech and language impairment were considered to have neurodevelopmental disorder (NDD). The impact of socioeconomic status (Kuppuswamy classification), perioperative cardiac, nutritional and psycho-social factors on outcomes was analysed.

RESULTS: There were 61 (89.7%) survivors at a mean follow-up of 50.9 ±7.6 months. The median age at surgery was 41 days (22-74.5). One-third of patients had growth restriction. Two children had residual cardiovascular lesions requiring intervention. The mean HRQOL score was >90 in all scales of the Paediatric Quality of Life Inventory 3.0 Cardiac Module. Neurological abnormalities were seen in 19 patients (31.1%) of whom 17 (27.9%) patients had NDD and 12 had developmental delay. Speech and language impairment, attention-deficit hyperactivity disorder, and neuromotor impairment were found in 16.4%, 3.3% and 6.7% patients, respectively. On multivariate analysis, increasing time to lactate normalization and low socioeconomic status were associated with developmental delay after ASO.

CONCLUSIONS: While intermediate-term cardiac outcomes and HRQOL after ASO were fairly satisfactory, NDD was identified in one-fourth of these children. Increasing time to lactate normalization after ASO and low socioeconomic status were associated with suboptimal intermediate neurodevelopment outcomes after ASO

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Eur J Psychotraumatol. 2021;12:1995264.

DOG TRAINING ALLEVIATES PTSD SYMPTOMATOLOGY BY EMOTIONAL AND ATTENTIONAL REGULATION.

Maoz I, Zubedat S, Dolev T, et al.

BACKGROUND: Post-Traumatic Stress Disorder (PTSD) symptoms include re-experiencing, avoidance, hyperarousal, and cognitive deficits, reflecting both emotional and cognitive dysregulation. In recent years, non-pharmacological approaches and specifically animal-assisted therapy have been shown to be beneficial for a variety of disorders such as Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and PTSD. However, little is mentioned in the literature about the reciprocal effects of the animal-human interaction.

OBJECTIVE: To evaluate the effects of a one-year dog training programme on PTSD symptomatology in youngsters with PTSD and on dogs' behaviour.

METHODS: Fifty-three adolescents, previously exposed to interpersonal trauma, were clinically diagnosed with PTSD and assigned to a dog-training programme group (n = 30) and a control group (n = 23) that engaged in other training programmes (e.g. cooking, hairstyling, etc.). Both groups were evaluated at baseline and following 12-months by The Clinician-Administered PTSD Scale for DSM-5 in Children and Adolescents (CAPS-CA-5) and Beck-Depression Inventory (BDI). Additionally, we physiologically measured both emotional and attention dysregulation.

RESULTS: Post-12-months training, a significant alleviation of PTSD symptomatology accompanied by lower depression severity was observed in the dog-training group, compared with a insignificant recovery in the control group. Furthermore, improved emotional and attentional regulation was observed in the dog-training group. Measuring the dogs' behaviour revealed increased anxiety and decreased selective attention performance, which was inversely correlated with the beneficial effects observed in the dog-training programme group.
CONCLUSIONS: Our findings emphasize the role of emotional and attentional regulations on the dog-handler interface, as evidence-based support for the beneficial effects of the dog-training programme, as either a non-pharmacological intervention or as complementary to anti-depressants treatment of PTSD. Though pharmacological treatments increase the patients' well-being by treating certain PTSD symptoms, our suggested dog-training programme seems to influence the PTSD diagnostic status, thus may be implemented in civilians and veterans with PTSD

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Eur Arch Psychiatry Clin Neurosci. 2022.

DEPRESSIVE SYMPTOMS IN YOUTH WITH ADHD: THE ROLE OF IMPAIRMENTS IN COGNITIVE EMOTION REGULATION.

Mayer JS, Brandt GA, Medda J, et al.

Youth with attention-deficit/hyperactivity disorder (ADHD) are at increased risk to develop co-morbid depression. Identifying factors that contribute to depression risk may allow early intervention and prevention. Poor emotion regulation, which is common in adolescents, is a candidate risk factor. Impaired cognitive emotion regulation is a fundamental characteristic of depression and depression risk in the general population. However, little is known about cognitive emotion regulation in youth with ADHD and its link to depression and depression risk. Using explicit and implicit measures, this study assessed cognitive emotion regulation in youth with ADHD (N = 40) compared to demographically matched healthy controls (N = 40) and determined the association with depressive symptomatology. As explicit measure, we assessed the use of cognitive emotion regulation strategies via self-report. As implicit measure, performance in an ambiguous cue-conditioning task was assessed as indicator of affective bias in the processing of information. Compared to controls, patients reported more frequent use of maladaptive (i.e., self-blame, catastrophizing, and rumination) and less frequent use of adaptive (i.e., positive reappraisal) emotion regulation strategies. This pattern was associated with the severity of current depressive symptoms in patients. In the implicit measure of cognitive bias, there was no significant difference in response of patients and controls and no association with depression. Our findings point to depression-related alterations in the use of cognitive emotion regulation strategies in youth with ADHD. The study suggests those alterations as a candidate risk factor for ADHD-depression comorbidity that may be used for risk assessment and prevention strategies

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Eur Child Adolesc Psychiatry. 2022.

A RANDOMIZED CONTROLLED STUDY OF REMOTE COMPUTERIZED COGNITIVE, NEUROFEEDBACK, AND COMBINED TRAINING IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Luo X, Guo X, Zhao Q, et al.

There is an increasing interest in non-pharmacological treatments for children with attention-deficit/hyperactivity disorder (AD/HD), especially digital techniques that can be remotely delivered, such as neurofeedback (NFT) and computerized cognitive training (CCT). In this study, a randomized controlled design was used to compare training outcomes between remotely delivered NFT, CCT, and combined NFT/CCT training approaches. A total of 121 children with AD/HD were randomly assigned to the NFT, CCT, or NFT/CCT training groups, with 80 children completing the training program. Pre- and post-training symptoms (primary outcome), executive and daily functions were measured using questionnaires as well as resting EEG during eyes-closed (EC) and eyes-open (EO) conditions. After 3 months of training, the inattentive and hyperactive/impulsive symptoms, inhibition, working memory, learning and life skills of the three groups of children were significantly improved. The objective EEG activity showed a consistent increase in the relative alpha power in the EO condition among the three training groups. Training differences were not observed between groups. There was a positive correlation between pre-training EO relative alpha power and symptom improvement scores of inattention and hyperactivity/impulsivity, as well as a negative

correlation between pre-training inattention scores and change in EO relative alpha. This study verified the training effects of NFT, CCT, and combined NFT/CCT training in children with AD/HD and revealed an objective therapeutic role for individual relative alpha activity. The verified feasibility and effectiveness of home-based digital training support promotion and application of digital remote training

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Eur Child Adolesc Psychiatry. 2022.

INTERRELATIONSHIPS AMONG GROWTH HORMONE, THYROID FUNCTION, AND ENDOCRINE-DISRUPTING CHEMICALS ON THE SUSCEPTIBILITY TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang LJ, Huang YH, Chou WJ, et al.

Abnormal growth hormones and thyroid function may be linked to pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Phthalates and bisphenol-A (BPA), two endocrine-disrupting chemicals (EDCs), may affect the human endocrine system. In this study, we aimed to perform a comprehensive investigation of whether growth hormone, thyroid function, and EDCs exhibited differential levels between ADHD patients and healthy controls. In total, 144 children with ADHD and 70 healthy control subjects were enrolled. Their endocrine systems were evaluated using the serum levels of insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3), thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and Free T4. The urinary levels of EDCs, including monoethyl phthalate (MEP), mono-methyl phthalate (MMP), monoethylhexyl phthalate (MEHP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), and BPA, were also examined. Patients with ADHD had lower IGF-1 levels than healthy controls ($p = 0.003$), but we observed no significant difference in IGFBP-3, TSH, T3, T4, or Free T4. Compared to the control group, patients with ADHD demonstrated higher MEHP levels ($p = 0.043$), MnBP ($p = 0.033$), and MBzP ($p = 0.040$). Furthermore, MEHP levels ($p < 0.001$) and BPA levels ($p = 0.041$) were negatively correlated with IGF-1 levels, while IGF-1 levels were negatively correlated with principal components consisting of ADHD clinical symptoms and neuropsychological performance variables. We suggest that MEHP exposure may be associated with decreased serum levels of IGF-1 and increased risk of ADHD. The mechanism underlying this association may be important for protecting children from environmental chemicals that adversely affect neurodevelopment

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Eur J Neurosci. 2021;54:7654-67.

SURFACE VALUES, VOLUMETRIC MEASUREMENTS AND RADIOMICS OF STRUCTURAL MRI FOR THE DIAGNOSIS AND SUBTYPING OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shi L, Liu X, Wu K, et al.

Attention-deficit/hyperactivity disorder (ADHD) is diagnosed subjectively based on an individual's behaviour and performance. The clinical community has no objective biomarker to inform the diagnosis and subtyping of ADHD. This study aimed to explore the potential diagnostic biomarkers of ADHD among surface values, volumetric metrics and radiomic features that were extracted from structural MRI images. Public data of New York University and Peking University were downloaded from the ADHD-200 Consortium. MRI T1-weighted images were pre-processed using CAT12. We calculated surface values based on the DesikanΓÇôKilliany atlas. The volumetric metrics (mean grey matter volume and mean white matter volume) and radiomic features within each automated anatomical labelling (AAL) brain area were calculated using DPABI and IBEX, respectively. The differences among three groups of participants were tested using ANOVA or KruskalΓÇôWallis test depending on the normality of the data. We selected discriminative features and classified typically developing controls (TDCs) and ADHD patients as well as two ADHD subtypes using least absolute shrinkage and selection operator and support vector machine algorithms. Our results showed that the radiomics-based model outperformed the others in discriminating ADHD from TDC and classifying ADHD subtypes (area under the curve [AUC]: 0.78 and 0.94 in training test; 0.79 and 0.85 in testing set). Combining grey matter volumes, surface values and clinical factors with radiomic features can improve the performance for classifying ADHD patients and TDCs with training and testing AUCs of 0.82 and 0.83, respectively. This study demonstrates that MRI T1-weighted features, especially radiomic features, are potential diagnostic biomarkers of ADHD

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Eur Neuropsychopharmacol. 2022;57:69-74.

THE DYNAMICAL ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND AFFECT IN THE DAILY LIFE OF INDIVIDUALS WITH ADHD.

Koch ED, Freitag CM, Mayer JS, et al.

Exercise interventions in mental disorders have evidenced a mood-enhancing effect. However, the association between physical activity and affect in everyday life has not been investigated in adult individuals with ADHD, despite being important features of this disorder. As physical activity and affect are dynamic processes in nature, assessing those in everyday life with e-diaries and wearables, has become the gold standard. Thus, we used an mHealth approach to prospectively assess physical activity and affect processes in individuals with ADHD and controls aged 14ΓÇô45 years. Participants wore accelerometers across a four-day period and reported their affect via e-diaries twelve times daily. We used multilevel models to identify the within-subject effects of physical activity on positive and negative affect. We split our sample into three groups: 1. individuals with ADHD who were predominantly inattentive (n = 48), 2. individuals with ADHD having a combined presentation (i.e., being inattentive and hyperactive; n = 95), and 3. controls (n = 42). Our analyses revealed a significant cross-level interaction (F(2, 135.072)=5.733, p = 0.004) of physical activity and group on positive affect. In details, all groups showed a positive association between physical activity and positive affect. Individuals with a combined presentation significantly showed the steepest slope of physical activity on positive affect (slope_inattentive=0.005, p<0.001; slope_combined=0.009, p<0.001; slope_controls=0.004, p = 0.008). Our analyses on negative affect revealed a negative association only in the individuals with a combined presentation (slope=-0.003; p = 0.001). Whether this specifically pronounced association in individuals being more hyperactive might be a mechanism reinforcing hyperactivity needs to be empirically clarified in future studies

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European Radiology. 2022.

QUANTITATIVE SUSCEPTIBILITY MAPPING REVEALS BRAIN IRON DEFICIENCY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A WHOLE-BRAIN ANALYSIS.

Chen Y, Su S, Dai Y, et al.

Objectives: To quantitatively measure and compare the whole-brain iron deposition between attention-deficit/hyperactivity disorder (ADHD) patients and typically developing (TD) children using the quantitative susceptibility mapping (QSM) technique.

Methods: This study was approved by the institutional review board of our institution (No. [2019]328). Fifty-one patients between 6 and 14-áyears with clinical diagnosis of ADHD and 51 age- and gender-paired TD children were enrolled. For each participant, the 3D T1 and multi-echo GRE sequence were performed to acquire the whole-brain data with 3.0-T MRI. The QSM maps were calculated using STISuite toolbox. After normalizing the QSM images to MNI space, the voxel-based analysis was used to compare the iron content between the two groups. Pearson's correlation test was used to assess the associations between the iron content and the score of the tablet-PC-based cancellation test, which was done to evaluate the attention concentration level.

Results: Iron deficiency was observed in several brain regions in children with ADHD, including bilateral striatums, anterior cingulum, olfactory gyrus, and right lingual gyri. In further correlation analysis, the left anterior cingulum was found to show positive correlation with the symptom severity (r = 0.326, p < 0.05).

Conclusions: Our study demonstrated that the iron deficiency in several brain regions might be related with ADHD, which might be valuable for further studies. And QSM might have the potential efficacy in the auxiliary diagnosis of ADHD. Key Points: ΓÇó Iron deficiency was observed in several brain regions in children with ADHD, which include bilateral striatums, the critical regions in the dopaminergic transmitter system. The iron content in the left ACG may have association with the symptom severity of ADHD. QSM might have the potential efficacy in the auxiliary diagnosis of ADHD

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European Review for Medical and Pharmacological Sciences. 2022;26:138-43.

THE EFFECTIVENESS OF MINDFUL PARENTING TRAINING ON ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN MALE STUDENTS.

Amiri M, Fatemi SAM, Jabbari S, et al.

OBJECTIVE: One of the main influential factors in the occurrence of behavioral problems in children with attention deficit/ hyperactivity disorder (ADHD) is the behavior related to the parenting styles. This study aimed at investigating the effect of mindful parenting training on mothers of children with ADHD in reducing the symptoms of hyperactivity/impulsivity and inattention behaviors.

MATERIALS AND METHODS: The research method was quasi-experimental with a pretest- posttest control group. The study population consisted of all mothers of children from 8 to 12 years. Therefore, 24 mothers of children with ADHD whose scores in the Connors questionnaire (parent form) were above the cut-off point score and diagnostic interview were selected and randomly paired and assigned into two experimental and control groups. All the mothers were between 30 to 38 years old. The research tools included the Connors questionnaire. Mindful parenting training was accomplished in eight 90-minute sessions for the experimental group. In the end, the two groups completed the questionnaires as post-test. Analysis of covariance was used to analyze the data.

RESULTS: The analysis of the results showed the effect of mindful parenting training on reducing the symptoms of hyperactivity/impulsivity and inattention behaviors of children with ADHD in the experimental group compared to the control group (p-value <0.05).

CONCLUSIONS: The educational and behavioral methods that parents and especially mothers use in response to their children's problematic and undesirable behaviors can increase the incidence of these behavioral problems in the long run. Hence, it is addressed in this study due to the great importance of changing the behavioral and educational methods of such parents. The findings generally show that mindful parenting education has affected the emotional climate governing parent-child interactions and has reduced behavioral problems in children suffering from ADHD

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Evidence-Based Practice in Child and Adolescent Mental Health. 2022.

EXECUTIVE DYSFUNCTION, PSYCHIATRIC SYMPTOMS, AND BEHAVIORAL DYSREGULATION IN PRESCHOOLERS: PRELIMINARY FINDINGS IN A CLINICAL SAMPLE.

Martin SE, Kavanaugh BC, Paszek C, et al.

Children with deficits in executive function are at risk for poor outcomes in academic, social-emotional, and behavioral domains. These deficits have been particularly well documented in school-aged children with attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders. However, there have been fewer studies exploring the links between executive function and psychopathology in preschool-aged children, particularly among young children with diagnosed psychiatric disorders and significant clinical impairment. This study examined associations between executive dysfunction, psychiatric symptoms, and behavioral dysregulation in a sample of 44 preschoolers participating in an intensive psychiatric day treatment program. The NIH Toolbox Early Childhood Cognition Battery was used to assess EF, including inhibitory control and cognitive flexibility, and parent-reported assessments were used to examine child psychiatric symptoms and behavioral dysregulation. Analyses using linear and logistic regression equation modeling suggest that executive dysfunctionΓÇôparticularly cognitive inflexibilityΓÇôis a significant predictor of ADHD symptoms and behavioral dysregulation in clinically-referred preschoolers. Findings are discussed with respect to the role of executive dysfunction in early childhood psychopathology, with implications for treatment. Findings also suggest the NIH Toolbox is feasible for use in an early childhood psychiatric treatment setting and provides valid neurocognitive results to inform treatment planning and clinical care

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Front Behav Neurosci. 2021;15.

SYNAPTOSOMAL-ASSOCIATED PROTEIN 25 GENE POLYMORPHISMS AFFECT TREATMENT EFFICIENCY OF METHYLPHENIDATE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: AN FNIRS STUDY.

Li J, Yan WJ, Wu Y, et al.

Methylphenidate (MPH) is the first-line drug for the treatment of children with attention-deficit hyperactivity disorder (ADHD); however, individual curative effects of MPH vary. Many studies have demonstrated that synaptosomal-associated protein 25 (SNAP-25) gene MnlI polymorphisms may be related to the efficacy of MPH. However, the association between SNAP-25MnlI polymorphisms and changes in brain hemodynamic responses after MPH treatment is still unclear. This study used functional near-infrared spectroscopy (fNIRS) to preliminarily investigate the interaction of MPH treatment-related prefrontal inhibitory functional changes with the genotype status of the SNAP-25 gene in children with ADHD. In total, 38 children with ADHD aged 6.76ΓÇô12.08 years were enrolled in this study and divided into the following two groups based on SNAP-25 gene MnlI polymorphisms: T/T genotype group (wild-type group, 27 children) and G allele carrier group (mutation group, 11 children). The averaged oxygenated hemoglobin concentration changes [+öavg oxy-Hb] and deoxyhemoglobin concentration changes [+öavg deoxy-Hb] in the frontal cortex before MPH treatment and after 1.5 h (post-MPH1.5h) and 4 weeks (post-MPH4w) of MPH treatments were monitored using fNIRS during the go/no-go task. SNAP-IV scores were evaluated both pre-MPH and post-MPH4w treatments. In the T/T genotype group, [avg oxy-Hb] in the dorsolateral prefrontal cortex was significantly higher after 4 weeks of MPH (post-MPH4W) treatment than pre-treatment; however, in the G allele group, no significant differences in [avg oxy-Hb] were observed between pre- and post-treatments. In the go/no-go task, the accuracy was significantly increased post-MPH4w treatment in the T/T genotype group, while no significant differences were observed in response time and accuracy of the go sand no-go task in the G allele group for pre-MPH, post-MPH1.5h, and post-MPH4w treatments. The T/T genotype group exhibited a significant decrease in SNAP-IV scores after MPH treatment, while the G allele group showed no significant difference. In conclusion, fNIRS data combined with SNAP-25 MnlI polymorphism analysis may be a useful biomarker for evaluating the effects of MPH in children with ADHD

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Front Integr Neurosci. 2022;15.

ASSOCIATION OF ADHD AND OBESITY IN HISPANIC CHILDREN ON THE US-MEXICO BORDER: A RETROSPECTIVE ANALYSIS.

Salcido A, Robles EH, Chaudhary K, et al.

Pediatric obesity and Attention Deficit Hyperactivity Disorder (ADHD) are rising health concerns in the United States, especially among Hispanic children and adolescents. Research on Hispanic children and adolescents indicates disproportionately higher prevalence rates of obesity in this community but scant data on ADHD prevalence rates. In contrast, a plethora of research studies across the general population examines the relationship between childhood obesity and ADHD. In addition, there is a lack of research that examines the role of ethnicity and sub-ethnic group correlations in ADHD, particularly in the Hispanic population. Existing studies in the general population indicate ADHD may be a risk factor for being overweight compared to normal controls. The objective of the present study is to examine the prevalence of obesity in children with ADHD compared to children in the general population in a predominately Hispanic sample on the US-Mexico border. A total of 7,270 pediatric medical records were evaluated. The retrospective analysis included Body Mass Index (BMI) and related health variables, and ethnicity and showed that children with ADHD are more likely to be underweight. In conclusion, no significant relationship existed between obesity and ADHD among Hispanic children on the US-Mexico Border, and instead we found the opposite correlation

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Frontiers in Neurology. 2022;12.

LIFETIME HISTORY OF CONCUSSION AMONG YOUTH WITH ADHD PRESENTING TO A SPECIALTY CONCUSSION CLINIC.

Cook NE, Teel E, Iverson GL, et al.

Child and adolescent student athletes with attention-deficit/hyperactivity disorder (ADHD) report a greater lifetime history of concussion than those without ADHD. This case-control study compared youth with and

without ADHD presenting for care at a specialty concussion clinic on their lifetime history of concussion. We hypothesized that a greater proportion of youth with ADHD would report a history of prior concussion. Archival clinical data from patients presenting to a specialty concussion clinic in Montreal, Qu+®bec, Canada between September 2015 and August 2019 were analyzed. The sample included 2,418 children and adolescents (age: M = 13.6, SD = 2.7, range 5ΓÇô18 years; 50.9% girls), including 294 (12.2%) with ADHD and 2,124 (87.8%) without ADHD. The proportion with prior concussion among youth with ADHD (43.9%) was significantly greater than youth without ADHD [37.5%, ¤ç2 = 4.41, p = 0.04, OR = 1.30, 95% confidence interval (CI): 1.02ΓÇô1.67]. A significantly higher proportion of boys with ADHD had a prior concussion history (48.1%) than boys without ADHD [38.4%, ¤ç2 = 5.33, p = 0.02, OR = 1.48 (95% CI: 1.06ΓÇô2.09)], but this difference was not observed for girls (¤ç2 = 0.31, p = 0.58). Youth with ADHD did not differ with regard to their estimated longest duration of symptoms from a prior concussion (Z = 1.52, p = 0.13) and the proportion who reported taking longer than 28 days to recover from a prior concussion did not differ between those with ADHD (15.3%) and without ADHD (12.2%), ¤ç2 = 2.20, p = 0.14. Among youth presenting to a specialty clinic, ADHD was associated with greater lifetime history of concussion but not a greater duration of symptoms from a prior injury

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Frontiers in Pediatrics. 2022;9.

PHYSICAL ACTIVITY AND EXECUTIVE FUNCTION IN CHILDREN WITH ADHD: THE MEDIATING ROLE OF SLEEP.

Liang X, Li R, Wong SHS, et al.

This study examined the mediating role of sleep in the relationship between physical activity and executive function in children with attention deficit hyperactivity disorder (ADHD). Fifty-six children with ADHD were recruited from Shenzhen Children's Hospital. Participants wore an accelerometer for seven consecutive days to measure physical activity and sleep quality. Activity counts were analyzed to measure moderate-to-vigorous physical activity (MVPA). Four sleep parameters, including sleep latency (SL), sleep efficiency, total sleep time, and wake after sleep onset were recorded from the actigraph. Three core executive functions, inhibitory control; working memory (WM); and cognitive flexibility (CF), were assessed from computer-based tasks: the flanker task, and the Tower of London and Trail Making Tests, respectively. The regression results showed that MVPA was negatively associated with SL (ΓêÆ0.169; 95%CI [ΓêÆ0.244, ΓêÆ0.112]). WM (total scores) was positively related to MVPA (0.028, 95%CI [0.008, 0.048]), but negatively related to SL (ΓêÆ0.105, 95%CI [ΓêÆ0.167, ΓêÆ0.030]). CF (part B errors) was negatively associated with MVPA (ΓêÆ0.031, 95%CI [ΓêÆ0.055, ΓêÆ0.005]) and positively correlated with SL (0.184, 95%CI [0.092, ΓêÆ0.260]). The indirect effect of SL was found for MVPA and WM (0.018, 95%CI [0.015, 0.034]), supporting the indirect partial mediation. Similarly, the indirect effect of SL was found between MVPA and CF (ΓêÆ0.031, 95%CI [ΓêÆ0.060, ΓêÆ0.012]), supporting the indirect partial mediation. The mediating role of SL in children with ADHD suggests that the intensity of physical activity plays a key role in linking sleep quality and executive function in this group

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Front Psychiatry. 2021;12.

EFFECTS OF THE DRD4 521 C/T SNP ON LOCAL NEURAL ACTIVITY AND FUNCTIONAL CONNECTIVITY IN CHILDREN WITH ADHD.

Zhang H, Yang B, Peng G, et al.

Objective: The present study aimed to investigate the effects of the dopamine receptor D4 (DRD4) ΓêÆ521 C/T single-nucleotide polymorphism on brain function among children with attention deficit hyperactivity disorder (ADHD) and to evaluate whether brain function is associated with behavioral performance among this demographic.

Methods: Using regional homogeneity, fractional amplitude low-frequency fluctuation, and functional connectivity as measurement indices, we compared differences in resting-state brain function between 34 boys with ADHD in the TT homozygous group and 37 boys with ADHD in the C-allele carrier group. The Conners' Parent Rating Scale, the SNAP-IV Rating Scale, the Stroop Color Word Test, the go/no-go task, the n-back task, and the working memory index within the Wechsler Intelligence Scale for Children-Fourth Edition were selected as comparative indicators in order to test effects on behavioral performance.

Results: We found that TT homozygotes had low behavioral performance as compared with C-allele carriers. The regional homogeneity for TT homozygotes decreased in the right middle occipital gyrus and increased in the right superior frontal gyrus as compared with C-allele carriers. In addition, the right middle occipital gyrus and the right superior frontal gyrus were used as the seeds of functional connectivity, and we found that the functional connectivity between the right middle occipital gyrus and the right cerebellum decreased, as did the functional connectivity between the right superior frontal gyrus and the angular gyrus. No statistically significant differences were observed in the respective brain regions when comparing the fractional amplitudes for low-frequency fluctuation between the two groups. Correlation analyses demonstrated that the fractional amplitude low-frequency fluctuation in the precentral gyrus for TT homozygotes were statistically significantly correlated with working memory.
Conclusions: We found differing effects of DRD4 521 C/T polymorphisms on brain function among boys with ADHD. These findings promote our understanding of the genetic basis for neurobiological differences observed among children with ADHD, but they must be confirmed in larger samples

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Front Psychiatry. 2022;12.

TRAJECTORIES OF HEALTHCARE UTILIZATION AMONG CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER AND/OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN JAPAN.

Aoki A, Niimura M, Kato T, et al.

Background: Early intervention and prevention of psychiatric comorbidities of children with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are urgent issues. However, the differences in the diagnoses of ASD and ADHD and psychiatric comorbidities associated with age, long-term healthcare utilization trajectories, and its associated diagnostic features have not been fully elucidated in Japan.
Method: We conducted a retrospective observational study using the medical records. Member hospitals of three major consortiums of hospitals providing child and adolescent psychiatric services in Japan were recruited for the study. Children who accessed the psychiatry services of the participating hospitals in April 2015 were followed up for 5 years, and data on their clinical diagnoses, consultation numbers, and hospitalizations were collected. Non-hierarchical clustering was performed using two 10-timepoint longitudinal variables: consultation numbers and hospitalization. Among the major clusters, the differences in the prevalence of ASD, ADHD, comorbid intellectual disability, neurotic disorders, and other psychiatric disorders were assessed.
Results: A total of 44 facilities participated in the study (59.5%), and 1,003 participants were enrolled. Among them, 591 diagnosed with ASD and/or ADHD (58.9%) and 589 without missing data were assessed. The mean age was 10.1 years, and 363 (70.9%) were boys. Compared with the pre-schoolers, the school-aged children and adolescents had fewer ASD, more ADHD, and fewer comorbid intellectual disability diagnoses, as well as more diagnoses of other psychiatric disorders. A total of 309 participants (54.7%) continued consultation for 2 years, and 207 (35.1%) continued for 5 years. Clustering analysis identified three, two, and three major clusters among pre-schoolers, school-aged children, and adolescents, respectively. The largest cluster was characterized by early termination of the consultation and accounted for 55.4, 70.6, and 73.4% of pre-schoolers, school-aged children, and adolescents, respectively. Among the school-aged children, the diagnosis of ADHD was associated with a cluster that required longer periods of consultations. Among the adolescents, comorbid psychiatric disorders other than intellectual disability and neurotic disorders were associated with clusters that required hospitalization.
Conclusion: Continuous healthcare needs were common and psychiatric comorbidities were associated with complex trajectory among adolescents. The promotion of early intervention and prevention of comorbidities are important

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Genes (Basel). 2021 Jul;12.

BRAIN ANATOMICAL MEDIATORS OF GRIN2B GENE ASSOCIATION WITH ATTENTION/HYPERACTIVITY PROBLEMS: AN INTEGRATED GENETIC-NEUROIMAGING STUDY.

Nobile M, Maggioni E, Mauri M, et al.

This study aims to investigate the genetic and neural determinants of attention and hyperactivity problems. Using a proof-of-concept imaging genetics mediation design, we explore the relationship between the glutamatergic GRIN2B gene variants and inattention/hyperactivity with neuroanatomical measures as intermediates. Fifty-eight children and adolescents were evaluated for behavioral problems at three time points over approximately 7 years. The final assessment included blood drawing for genetic analyses and 3T magnetic resonance imaging. Attention/hyperactivity problems based on the Child Behavior Checklist/6-18, six GRIN2B polymorphisms and regional cortical thickness, and surface area and volume were estimated. Using general linear model (GLM) and mediation analyses, we tested whether GRIN2B exerted an influence on stable inattention/hyperactivity over development, and to what extent this effect was mediated by brain morphology. GLM results enlightened the relation between GRIN2B rs5796555-/A, volume in the left cingulate isthmus and inferior parietal cortices and inattention/hyperactivity. The mediation results showed that rs5796555-/A effect on inattention/hyperactivity was partially mediated by volume in the left isthmus of the cingulate cortex, suggesting a key role of this region in translating glutamatergic GRIN2B variations to attention/hyperactivity problems. This evidence can have important implications in the management of neurodevelopmental and psychiatric disorders

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Genes (Basel). 2021 Sep;12.

COMMON AND UNIQUE GENETIC BACKGROUND BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EXCESSIVE BODY WEIGHT.

Dmitrzak-Weglarz M, Paszynska E, Bilska K, et al.

Comorbidity studies show that children with ADHD have a higher risk of being overweight and obese than healthy children. This study aimed to assess the genetic alternations that differ between and are shared by ADHD and excessive body weight (EBW). The sample consisted of 743 Polish children aged between 6 and 17 years. We analyzed a unique set of genes and polymorphisms selected for ADHD and/or obesity based on gene prioritization tools. Polymorphisms in the KCNIP1, SLC1A3, MTHFR, ADRA2A, and SLC6A2 genes proved to be associated with the risk of ADHD in the studied population. The COMT gene polymorphism was one that specifically increased the risk of EBW in the ADHD group. Using the whole-exome sequencing technique, we have shown that the ADHD group contains rare and protein-truncating variants in the FBXL17, DBH, MTHFR, PCDH7, RSPH3, SPTBN1, and TNRC6C genes. In turn, variants in the ADRA2A, DYNC1H1, MAP1A, SEMA6D, and ZNF536 genes were specific for ADHD with EBW. In this way, we confirmed, at the molecular level, the existence of genes specifically predisposing to EBW in ADHD patients, which are associated with the biological pathways involved in the regulation of the reward system, intestinal microbiome, and muscle metabolism

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Genes (Basel). 2021 Dec;13.

LRRTM4 TERMINAL EXON DUPLICATED IN FAMILY WITH TOURETTE SYNDROME, AUTISM AND ADHD.

Clarke RA, Eapen V.

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by motor and vocal tics and strong association with autistic deficits, obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD). The genetic overlap between TS and autism spectrum disorder (ASD) includes those genes that encode the neurexin trans-synaptic connexus (NTSC) inclusive of the presynaptic neurexins (NRXNs) and postsynaptic neuroligins (NLGNs), cerebellin precursors (CBLNs in complex with the glutamate ionotropic receptor deltas (GRIDs)) and the leucine-rich repeat transmembrane proteins (LRRTMs). In this study, we report the first evidence of a TS and ASD association with yet another NTSC gene family member, namely LRRTM4. Duplication of the terminal exon of LRRTM4 was found in two females with TS from the same family (mother and daughter) in association with autistic traits and ASD

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Genes (Basel). 2021 Dec;13.

EXPLORING THE CONTRIBUTION TO ADHD OF GENES INVOLVED IN MENDELIAN DISORDERS PRESENTING WITH HYPERACTIVITY AND/OR INATTENTION.

Fernandez-Castillo N, et al.

Attention-deficit hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by hyperactivity, impulsivity, and/or inattention, which are symptoms also observed in many rare genetic disorders. We searched for genes involved in Mendelian disorders presenting with ADHD symptoms in the Online Mendelian Inheritance in Man (OMIM) database, to curate a list of new candidate risk genes for ADHD. We explored the enrichment of functions and pathways in this gene list, and tested whether rare or common variants in these genes are associated with ADHD or with its comorbidities. We identified 139 genes, causal for 137 rare disorders, mainly related to neurodevelopmental and brain function. Most of these Mendelian disorders also present with other psychiatric traits that are often comorbid with ADHD. Using whole exome sequencing (WES) data from 668 ADHD cases, we found rare variants associated with the dimension of the severity of inattention symptoms in three genes: KIF11, WAC, and CRBN. Then, we focused on common variants and identified six genes associated with ADHD (in 19,099 cases and 34,194 controls): MANBA, UQCC2, HIVEP2, FOPX1, KANSL1, and AUH. Furthermore, HIVEP2, FOXP1, and KANSL1 were nominally associated with autism spectrum disorder (ASD) (18,382 cases and 27,969 controls), as well as HIVEP2 with anxiety (7016 cases and 14,475 controls), and FOXP1 with aggression (18,988 individuals), which is in line with the symptomatology of the rare disorders they are responsible for. In conclusion, inspecting Mendelian disorders and the genes responsible for them constitutes a valuable approach for identifying new risk genes and the mechanisms of complex disorders

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Genes (Basel). 2021 Jul;12.

STUDY OF THE INTERACTION BETWEEN EXECUTIVE FUNCTION AND ADAPTIVE BEHAVIOR AT SCHOOL IN GIRLS WITH FRAGILE X SYNDROME.

Joga-Elvira L, Martinez-Olmo J, Joga ML, et al.

The aim of this research is to analyze the relationship between executive functions and adaptive behavior in girls with Fragile X syndrome (FXS) in the school setting. This study is part of a larger investigation conducted at the Hospital Parc Tauli in Sabadell. The sample consists of a total of 40 girls (26 with FXS and 14 control) aged 7-16 years, who were administered different neuropsychological tests (WISC-V, NEPSY-II, WCST, TOL) and questionnaires answered by teachers (ABAS-II, BRIEF 2, ADHD Rating Scale). The results show that there is a greater interaction between some areas of executive function (cognitive flexibility, auditory attention, and visual abstraction capacity) and certain areas of adaptive behavior (conceptual, practical, social, and total domains) in the FXS group than in the control group. These results suggest that an alteration in the executive functions was affecting the daily functioning of the girls with FXS to a greater extent

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Genes (Basel). 2021 Aug;12.

ATTENTION DEFICIT HYPERACTIVITY AND AUTISM SPECTRUM DISORDERS AS THE CORE SYMPTOMS OF AUTS2 SYNDROME: DESCRIPTION OF FIVE NEW PATIENTS AND UPDATE OF THE FREQUENCY OF MANIFESTATIONS AND GENOTYPE-PHENOTYPE CORRELATION.

Sanchez-Jimeno C, Blanco-Kelly F, LÃ³pez-Grondona F, et al.

Haploinsufficiency of AUTS2 has been associated with a syndromic form of neurodevelopmental delay characterized by intellectual disability, autistic features, and microcephaly, also known as AUTS2 syndrome. While the phenotype associated with large deletions and duplications of AUTS2 is well established, clinical features of patients harboring AUTS2 sequence variants have not been extensively described. In this study, we describe the phenotype of five new patients with AUTS2 pathogenic variants, three of them harboring loss-of-function sequence variants. The phenotype of the patients was characterized by attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) or autistic features and mild global developmental delay (GDD) or intellectual disability (ID), all in 4/5 patients (80%), a frequency higher than previously reported for ADHD and autistic features. Microcephaly and short stature were found in 60% of the patients; and feeding difficulties, generalized hypotonia, and ptosis, were each found in 40%. We also provide

the aggregated frequency of the 32 items included in the AUTS2 syndrome severity score (ASSS) in patients currently reported in the literature. The main characteristics of the syndrome are GDD/ID in 98% of patients, microcephaly in 65%, feeding difficulties in 62%, ADHD or hyperactivity in 54%, and autistic traits in 52%. Finally, using the location of 31 variants from the literature together with variants from the five patients, we found significantly higher ASSS values in patients with pathogenic variants affecting the 3' end of the gene, confirming the genotype-phenotype correlation initially described

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Health Commun. 2022 May;37:637-47.

"MENTAL HEALTH" AS DEFINED BY TWITTER: FRAMES, EMOTIONS, STIGMA.

Pavlova A, Berkers P.

This study analyzes the general public's framing of 'mental health' and critically assesses the implications of these findings. A mismatch between how people think about mental health and what messages are used in mental health campaigns may hinder attempts to improve mental health awareness and reduce stigma. We have conducted frame analysis by using a combination of topic modeling and sentiment analysis, examining 10Â years of mental health-related tweets (nÂ =Â 695,414). The results reveal seven distinctive mental health frames: 'Awareness', 'Feelings and Problematization', 'Classification', 'Accessibility and Funding', 'Stigma', 'Service', and 'Youth' (arranged by salience). In analyzing these frames, we have learned that (1) the general awareness about mental health relates to mental illness, while health and well-being framing, although present, is prone to low quality of information, (2) mental health discourse is often used to problematize social issues and externalize personal anxieties, which tends toward trivialization and, possibly, treatment delays, (3) mental health discourse often revolves around popularized mental illness (e.g., depression, anxiety, but not neurocognitive diseases), (4) the mental health 'Stigma' frame is not overly pronounced; it revolves around violence, fear, and madness, (5) mental health is frequently politicized, especially concerning gun laws in the US and service accessibility and funding in the UK. Additionally, some narrower frames discovered may warrant further examination. For instance, PTSD is mostly framed around veterans and suicide, ADHD around youth, and substance abuse in relation to women, teens, and impoverished

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Hosp Pediatr. 2022 Mar;12:e101-e105.

ASSOCIATION OF PSYCHIATRIC COMORBIDITIES WITH TREATMENT AND OUTCOMES IN PEDIATRIC MIGRAINES.

Kafle M, Mirea L, Gage S.

BACKGROUND AND OBJECTIVES: Migraine headache is a common disorder in pediatrics, sometimes leading to hospital admission. Psychiatric comorbidities are prevalent in adults with migraine headache, but there is limited evidence in the pediatric population. This study aimed to examine the prevalence of psychiatric comorbidity in children hospitalized for migraine headache and assess the association of this comorbid state on treatment interventions and outcomes.

METHODS: This multicenter, retrospective cohort study examined data from the Pediatric Health Information System. Subjects included patients aged 6 to 18 hospitalized for migraine headache between 2010 and 2018, excluding those with complex chronic conditions. Associations of psychiatric comorbidity with treatments, length of stay (LOS), cost, and 30-day readmissions were assessed using the Fisher-exact, Wilcoxon-rank-sum test, and adjusted linear or logistic regression models.

RESULTS: The total 21-436 subjects included 6796 (32%) with psychiatric comorbidity, with prevalence highest for anxiety (2415; 11.2%), depression (1433; 6.7%), and attention-deficit/hyperactivity disorder (1411; 6.5%). Patients with psychiatric comorbidity were significantly more likely ($P < .001$) to receive dihydroergotamine (61% vs 54%), topiramate (23% vs 18%), and valproate (38% vs 34%), and have longer mean LOS (2.6 vs 2.0 days), higher average costs ($8749 vs $7040), and higher 30-day readmission (21% vs 17%).

CONCLUSIONS: Of children hospitalized for migraine headache, 32% have comorbid psychiatric disorders associated with increased use of medications, longer LOS, and increased cost of hospitalization and readmission. Prospective studies are recommended to identify optimal multidisciplinary care models for children with migraine headaches and psychiatric comorbidities in the inpatient setting

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Hum Mol Genet. 2021 Jun;30:1160-71.

A RARE MISSENSE VARIANT IN THE ATP2C2 GENE IS ASSOCIATED WITH LANGUAGE IMPAIRMENT AND RELATED MEASURES.

Martinelli A, Rice ML, Talcott JB, et al.

At least 5% of children present unexpected difficulties in expressing and understanding spoken language. This condition is highly heritable and often co-occurs with other neurodevelopmental disorders such as dyslexia and ADHD. Through an exome sequencing analysis, we identified a rare missense variant (chr16:84405221, GRCh38.p12) in the ATP2C2 gene. ATP2C2 was implicated in language disorders by linkage and association studies, and exactly the same variant was reported previously in a different exome sequencing study for language impairment (LI). We followed up this finding by genotyping the mutation in cohorts selected for LI and comorbid disorders. We found that the variant had a higher frequency in LI cases (1.8%, N=360) compared with cohorts selected for dyslexia (0.8%, N=520) and ADHD (0.7%, N=150), which presented frequencies comparable to reference databases (0.9%, N=24 046 gnomAD controls). Additionally, we observed that carriers of the rare variant identified from a general population cohort (N=42, ALSPAC cohort) presented, as a group, lower scores on a range of reading and language-related measures compared to controls (N=1825; minimum P=0.002 for non-word reading). ATP2C2 encodes for an ATPase (SPCA2) that transports calcium and manganese ions into the Golgi lumen. Our functional characterization suggested that the rare variant influences the ATPase activity of SPCA2. Thus, our results further support the role of ATP2C2 locus in language-related phenotypes and pinpoint the possible effects of a specific rare variant at molecular level

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Hum Brain Mapp. 2022.

QUANTITATIVE SUSCEPTIBILITY MAPPING SHOWS LOWER BRAIN IRON CONTENT IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Tang S, Zhang G, Ran Q, et al.

To investigate the feasibility of quantitative susceptibility mapping in children with attention-deficit hyperactivity disorder (ADHD), 53 children with ADHD aged 5ΓÇô16 years were prospectively selected as the study group and 49 healthy children matched with age and gender were selected as the control group. All children underwent magnetic resonance imaging conventional sequence, 3D-T1, and enhanced T2*-weighted magnetic resonance angiography (ESWAN) sequence scanning. The iron content of brain regions was obtained through software postprocessing, and the iron content of brain regions of children with ADHD and healthy children was compared and analyzed to find out the characteristics of the iron content of brain regions of children with ADHD. The iron content in frontal lobe, globus pallidus, caudate nucleus, substantia nigra, putamen, and hippocampus of children with ADHD was lower than that of healthy children ($p < .05$). There was no significant difference in the content of iron in the left and right brain regions of children with ADHD ($p > .05$). The volume of frontal lobe and hippocampus of children with ADHD was lower than that of healthy children ($p < .05$). Iron content in brain areas such as globus pallidus, caudate nucleus, hippocampus, and putamen could distinguish children with ADHD (Area under curve [AUC] > 0.5, $p < .05$). Quantitative susceptibility mapping showed decreased iron content in some brain regions of children with ADHD

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Int J Environ Res Public Health. 2022 Jan;19.

MODERATORS AND OTHER PREDICTORS OF METHYLPHENIDATE RESPONSE IN CHILDREN AND ADOLESCENTS WITH ADHD.

D'Aiello B, Di VS, de RP, et al.

Methylphenidate (MPH) is the treatment of first choice for developmental ADHD. To date, no reliable method to predict how patients will respond to MPH exists and conflicting results are reported on clinical characteristics of responders. The present study aims to give a more precise characterization of the patients who will respond best to MPH to help clinicians in defining the treatment plan. Age, neuropsychological functioning (i.e., attention and working memory), and behavioral/emotional symptoms of 48 drug-naïve children and adolescents with ADHD (42 boys and 6 girls, age-range 6-16 years, mean age 10.5 ± 2.5 years,

mean IQ 101.3 Â± 11.2) were studied to assess how these different characteristics affected a single-dose MPH response. Four hierarchical linear regression models were used to explore whether age, neuropsychological measures at baseline, and behavioral/emotional symptoms could predict attention and working memory measures after a single-dose MPH administration. We found that improvement in attention and working memory was predicted by age, neuropsychological measures at baseline, and severity of ADHD symptoms. No behavioral and emotional symptoms predicted single-dose MPH response with the exception of conduct symptoms

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Int J Environ Res Public Health. 2022 Feb;19.

SENSORY PROCESSING, PERCEIVED STRESS AND BURNOUT SYMPTOMS IN A WORKING POPULATION DURING THE COVID-19 CRISIS.

van den Boogert F, Spaan P, Sizoo B, et al.

Although previous research suggests an association between sensory processing and perceived stress in a broad spectrum of mental health conditions, it remains unclear whether this phenomenon occurs independently from psychopathology. The present study investigated the association between sensory processing patterns, perceived stress and occupational burnout as a stress-related condition in a working population. We focused on different aspects of sensory processing and used the momentum of a particularly stressful period: during the first months of the global COVID-19 crisis. A total of 116 workers at a mental healthcare institution in The Netherlands completed the Adolescent/Adult Sensory Profile (AASP), the Perceived Stress Scale (PSS-10) and the Burnout Assessment Tool (BAT). Our results demonstrated that higher scores on sensory sensitivity and low registration were associated with higher scores on perceived stress and core burnout symptoms. Sensory hypersensitivity was also associated with more secondary burnout symptoms. Associations were not driven by underlying sensory-related disorders (e.g., ASD or ADHD). In conclusion, sensory processing difficulties are relevant predictors of stress and occupational burnout, also in healthy employees. This phenomenon warrants further attention, as relatively simple adjustments in working environment may possess important preventive effects

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Int J Environ Res Public Health. 2022 Jan;19.

ARTIFICIAL INTELLIGENCE ENABLED PERSONALISED ASSISTIVE TOOLS TO ENHANCE EDUCATION OF CHILDREN WITH NEURODEVELOPMENTAL DISORDERS-A REVIEW.

Barua PD, Vicnesh J, Gururajan R, et al.

Mental disorders (MDs) with onset in childhood or adolescence include neurodevelopmental disorders (NDDs) (intellectual disability and specific learning disabilities, such as dyslexia, attention deficit disorder (ADHD), and autism spectrum disorders (ASD)), as well as a broad range of mental health disorders (MHDs), including anxiety, depressive, stress-related and psychotic disorders. There is a high co-morbidity of NDDs and MHDs. Globally, there have been dramatic increases in the diagnosis of childhood-onset mental disorders, with a 2- to 3-fold rise in prevalence for several MHDs in the US over the past 20 years. Depending on the type of MD, children often grapple with social and communication deficits and difficulties adapting to changes in their environment, which can impact their ability to learn effectively. To improve outcomes for children, it is important to provide timely and effective interventions. This review summarises the range and effectiveness of AI-assisted tools, developed using machine learning models, which have been applied to address learning challenges in students with a range of NDDs. Our review summarises the evidence that AI tools can be successfully used to improve social interaction and supportive education. Based on the limitations of existing AI tools, we provide recommendations for the development of future AI tools with a focus on providing personalised learning for individuals with NDDs

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Int J Neural Syst. 2022 Mar;32:2250008.

SUPPORTED DIAGNOSIS OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER FROM EEG BASED ON INTERPRETABLE KERNELS FOR HIDDEN MARKOV MODELS.

Maya-Piedrahita MC, Herrera-Gomez PM, BerrÃ-o-Mesa L, et al.

As a neurodevelopmental pathology, Attention Deficit Hyperactivity Disorder (ADHD) mainly arises during childhood. Persistent patterns of generalized inattention, impulsivity, or hyperactivity characterize ADHD that may persist into adulthood. The conventional diagnosis relies on clinical observational processes yielding high rates of overdiagnosis due to varying interpretations among specialists or missing information. Although several studies have designed objective behavioral features to overcome such an issue, they lack significance. Despite electroencephalography (EEG) analyses extracting alternative biomarkers using signal processing techniques, the nonlinearity and nonstationarity of EEG signals restrain performance and generalization of hand-crafted features. This work proposes a methodology to support ADHD diagnosis by characterizing EEG signals from hidden Markov models (HMM), classifying subjects based on similarity measures for probability functions, and spatially interpreting the results using graphic embeddings of stochastic dynamic models. The methodology learns a single HMM for EEG signal from each patient, so favoring the inter-subject variability. Then, the Probability Product Kernel, specifically developed for assessing the similarity between HMMs, fed a support vector machine that classifies subjects according to their stochastic dynamics. Lastly, the kernel variant of Principal Component Analysis provided a means to visualize the EEG transitions in a two-dimensional space, evidencing dynamic differences between ADHD and Healthy Control children. From the electrophysiological perspective, we recorded EEG under the Stop Signal Task modified with reward levels, which considers cognitive features of interest as insufficient motivational circuits recruitment. The methodology compares the supported diagnosis in two EEG channel setups (whole channel set and channels of interest in frontocentral area) and four frequency bands (Theta, Alpha, Beta rhythms, and a wideband). Results evidence an accuracy rate of 97.0% in the Beta band and in the channels where previous works found error-related negativity events. Such accuracy rate strongly supports the dual pathway hypothesis and motivational deficit concerning the pathophysiology of ADHD. It also demonstrates the utility of joining inhibitory and motivational paradigms with dynamic EEG analysis into a noninvasive and affordable diagnostic tool for ADHD patients

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Int J Environ Res Public Health. 2022;19.

MEETING THE 24-HOUR MOVEMENT GUIDELINES AND OUTCOMES IN ADOLESCENTS WITH ADHD: A CROSS-SECTIONAL OBSERVATIONAL STUDY.

Wang W, Haegele JA, Wu Y, et al.

According to the 24-Hour Movement Guidelines, meeting daily recommendations for physical activity, sleep, and screen time is important for obtaining optimal health benefits. This cross-sectional observational study aimed to examine (a) the prevalence of meeting the movement guidelines; and (b) the associations between meeting the guidelines and selected outcomes in adolescents with attention-deficit/hyperactivity disorder (ADHD). Data from the 2018ΓÇô2019 National Survey for Children's Health dataset was used. Participants were adolescents (10ΓÇô17 years) with ADHD and without other chronic conditions. Outcomes were flourishing, school engagement, and body weight status. Exposures of interest were adherence to the movement guidelines. The frequency of the participants adherence to the guidelines was estimated, and regression analyses were con-ducted to examine the associations between adherence to the guidelines and outcomes, adjusting for potential confounders. Complete observations were available for 634 adolescents with ADHD. Overall, 46.8% of the participants met at least one movement guideline, but only 6.5% met all three. The number of guidelines met had a significant and positive association with flourishing and school engagement (+¦ = 0.21/0.17, ptrend < 0.001). Compared with meeting all three guidelines, significant associations with lower flourishing levels were found in participants who met none, sleep only, and sedentary time only (+¦ = 0.38 0.13, p < 0.05). Similar findings were identified in the school engagement outcome. Adherence to the guidelines was, however, not significantly associated with the odds of being overweight or obese. Collectively, the findings suggest the movement guidelines may be appropriate for extending to adolescents with ADHD and there is a need to increase adherence to the guidelines in this group

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Int J Mol Sci. 2022;23.

CHARACTERIZATION OF THE L-ARGININE/NITRIC OXIDE PATHWAY AND OXIDATIVE STRESS IN PEDIATRIC PATIENTS WITH ATOPIC DISEASES.

Hanusch B, Sinningen K, Brinkmann F, et al.

Introduction: L-Arginine (Arg) is a semi-essential amino acid. Constitutive and inducible nitric oxide synthase (NOS) isoforms convert Arg to nitric oxide (NO), a potent vaso-and broncho-dilator with multiple biological functions. Atopic dermatitis (AD) and bronchial asthma (BA) are atopic diseases affecting many children globally. Several studies analyzed NO in airways, yet the systemic synthesis of NO in AD and BA in children with BA, AD or both is elusive.

Methods: In a multicenter study, blood and urine were obtained from 130 of 302 participating children for the measurement of metabolites of the Arg/NO pathway (BA 31.5%; AD 5.4%; AD + BA 36.1%; attention deficit hyperactivity disorder (ADHD) 12.3%). In plasma and urine amino acids Arg and homoargi-nine (hArg), both substrates of NOS, asymmetric dimethylarginine (ADMA) and symmetric dime-thylarginine (SDMA), both inhibitors of NOS, dimethylamine (DMA), and nitrite and nitrate, were measured by gas chromatography-mass spectrometry. Malondialdehyde (MDA) was measured in plasma and urine samples to evaluate possible effects of oxidative stress.

Results: There were no differences in the Arg/NO pathway between the groups of children with different atopic diseases. In comparison to children with ADHD, children with AD, BA or AD and BA had higher plasma nitrite ($p < 0.001$) and nitrate ($p < 0.001$) concentrations, suggesting higher systemic NO synthesis in AD and BA. Urinary excretion of DMA was also higher ($p = 0.028$) in AD and BA compared to patients with ADHD, suggesting elevated ADMA metabolization.

Discussion/Conclusion: The Arg/NO pathway is activated in atopic diseases independent of severity. Systemic NO synthesis is increased in children with an atopic disease. Plasma and urinary MDA levels did not differ between the groups, suggesting no effect of oxidative stress on the Arg/NO pathway in atopic diseases

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Int J Psychophysiol. 2022;174:83-91.

AGE-RELATED CHANGES IN THE EEG IN AN EYES-OPEN CONDITION: II. SUBTYPES OF AD/HD.

Mason LM, Clarke AR, Barry RJ.

This study investigated age-related changes in the EEG of subtypes of Attention-Deficit/Hyperactivity Disorder (AD/HD) compared with neurotypical controls, using an eyes-open resting condition. Two hundred and twenty five children between the ages of 5 and 16 years participated in this study. Groups consisted of AD/HD of the combined (AD/HDcom) and inattentive (AD/HDin) types, which were compared with controls for each of three age ranges: Young (5ΓÇô8 years), Middle (9ΓÇô12 years), and Old (13ΓÇô16 years). The EEG was recorded and analyzed using AMLAB hardware and software, and Fourier transformed to provide estimates for total power, and absolute and relative power in the delta, theta, alpha and beta bands. Compared to controls, the AD/HD groups had globally increased relative theta. Regional differences were found for absolute and relative alpha and beta. Compared to AD/HDcom, AD/HDin had globally reduced total power, absolute and relative theta, and absolute alpha. Regional differences only were found for absolute and relative delta, absolute beta, and relative alpha. No simple interactions were found for diagnostic factors with age. These results indicate that maturational effects can be observed between subtypes of AD/HD and controls in the eyes-open condition with similarities to those reported in eyes-closed conditions, although substantial differences are apparent in the maturation of fast wave activity, primarily alpha. These results provide evidence of maturational differences between subtypes of AD/HD in eyes-open conditions, and provide additional support for the suggestion that subtypes of AD/HD differ in severity rather than the nature of underlying neurological impairment

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Int J Psychophysiol. 2022;174:29-42.

EVENT-RELATED BRAIN OSCILLATIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A SYSTEMATIC REVIEW AND META-ANALYSIS.

Michelini G, Salmastyan G, Vera JD, et al.

Previous studies have associated attention-deficit/hyperactivity disorder (ADHD) with several alterations in electroencephalographic (EEG) activity. Time-frequency analyses capturing event-related power modulations are becoming an increasingly popular approach, but a systematic synthesis of the time-frequency literature in ADHD is currently lacking. We conducted the first systematic review and meta-analysis of time-frequency studies of children and adults with ADHD in comparison to neurotypical controls. Searches via Medline, Embase, and Web of Science, as well as reference lists, identified 28 eligible articles published until March 2021. Of these, 13 articles with relevant data were included in a multi-level meta-analysis. Most studies examined power modulations of alpha, theta and/or beta frequencies (N = 21/28), and focused on children (N = 17/28). Meta-analyses showed significantly weaker theta increases (Cohen's d = ΓêÆ0.25, p = 0.039; NADHD = 346, NCONTROL = 327), alpha decreases (d = 0.44, p < 0.001; NADHD = 564, NCONTROL = 450), and beta increases (Cohen's d = ΓêÆ0.33, p < 0.001; NADHD = 222, NCONTROL = 263) in individuals with ADHD relative to controls. These patterns indicate broad brain-oscillatory alterations in individuals with ADHD with small (theta) and small-to-moderate (alpha and beta) effect sizes. These group differences were partly consistent when repeating analyses by age group (<18 and 18+ years) and task type (cognitive control, working memory, and simple attention tasks). Overall, our findings identify widespread event-related brain-oscillatory alterations in individuals with ADHD during a range of neurocognitive functions. Future research requires larger samples, a broader range of frequency bands (including delta and gamma) during a wider type of cognitive-affective processes, and should clarify whether atypical event-related power profiles are ADHD-specific or shared with other neuropsychiatric conditions

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J Affect Disord. 2022 Apr;302:33-40.

TASK-BASED FUNCTIONAL CONNECTIVITY PATTERNS: LINKS TO ADOLESCENT EMOTION REGULATION AND PSYCHOPATHOLOGY.

Poon JA, Thompson JC, Chaplin TM.

Adolescence is a developmental period characterized by heightened emotional reactivity, neurobiological changes, and increased rates of anxiety and depression. Emotion regulation (ER) difficulties-or the inability to effectively regulate one's emotions-have been theoretically and empirically conceptualized as a transdiagnostic factor implicated in virtually all forms of psychopathology among youth. The current fMRI study investigates how young adolescents' ER abilities longitudinally mediate the relationship between their task-based (n=67) limbic-prefrontal functional connectivity values and subsequent levels of internalizing and externalizing symptoms. Findings revealed that adolescents with stronger limbic-prefrontal connectivity when viewing negative emotional images reported more ER difficulties one year later which, in turn, predicted higher levels of adolescent-reported internalizing and externalizing symptoms (with the exception of ADHD) two years later. This is the only study to date that provides compelling-albeit preliminary-evidence that ER problems longitudinally mediate the association between task-based functional connectivity patterns and future psychological symptoms among adolescents. Of note, participants were only scanned at baseline, limiting our ability to assess change in adolescents' task-based functional connectivity patterns as a function of developing ER abilities or burgeoning psychological symptomology. In sum, rather than conferring risk for any particular disorder, our results suggest that functional connectivity and subsequent ER abilities may serve a transdiagnostic risk factor for psychopathology. These findings may inform future emotion-focused prevention and intervention efforts aimed at youth susceptible to future internalizing and externalizing problems

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J Affect Disord. 2022 Apr;302:185-93.

HIGHER SOCIOECONOMIC STATUS AND LESS PARENTAL PSYCHOPATHOLOGY IMPROVE PROGNOSIS IN YOUTHS WITH BIPOLAR DISORDER.

Diler RS, Merranko JA, Hafeman D, et al.

BACKGROUND: To identify prospectively ascertained individual and family factors that are associated with improvement in Bipolar Disorder (BD) among youths who initially presented with poor course.

METHODS: 82 youths with BD with persistent poor mood symptomatology ("predominantly ill course") were compared to 70 youths with BD who at intake had poor course, but showed improvement during the follow-up ("ill with improving course"), (ages 12.3± 3.3, vs. 11.7± 3.3 years old, at intake). Improvement was measured by the percentage of time euthymic during a mean follow-up of 12.8 years. Youths and parents were interviewed to assess psychopathology, functioning, treatment, and familial functioning and psychopathology.

RESULTS: Compared to the ill group, since intake, the improving group showed significantly lower subthreshold depression and hypo/mania, Attention Deficit Hyperactivity Disorder, and Disruptive Behavior Disorders. Parental Socioeconomic Status (SES) remained unchanged over time in the ill group, but progressively increased in the improving group. Importantly, the change in SES predated the improvement in the mood trajectory. The most influential variables that predicted improvement were higher SES, and absence of parental BD and Substance Use Disorder (SUD). Parental SUD also negatively affected the parental SES, which was directly associated with worse mood course.

LIMITATIONS: Predominantly self-reported White samples may limit generalizability; other factors potentially associated with outcome (e.g., treatment adherence), were not ascertained.

CONCLUSIONS: In addition to treating mood/comorbid psychopathology in symptomatic BD youths, to improve their prognosis, it is crucial to address their parent's BD and SUD and promote parental education/employment

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J Am Acad Dermatol. 2021 Oct;85:893-900.

REAL-WORLD COMORBIDITIES OF ATOPIC DERMATITIS IN THE PEDIATRIC AMBULATORY POPULATION IN THE UNITED STATES.

Huang AH, Roh YS, Sutaria N, et al.

BACKGROUND: Increasing evidence has suggested the systemic nature of atopic dermatitis (AD), a common inflammatory skin condition in children. However, comprehensive analyses of real-world comorbidities in pediatric AD are limited.

OBJECTIVE: To characterize comorbidity burden in patients with AD aged <18Â years old. METHODS: The MarketScan commercial claims database was queried from January 1, 2017, to December 31, 2017. Age- and sex-matched analyses were used to compare patients with AD with general population controls.

RESULTS: A total of 86,969 pediatric patients with AD and 116,564 matched controls were identified. Increased anxiety (odds ratio [OR], 1.20) and attention-deficit hyperactivity disorder (OR, 1.11) were noted in patients with AD. In addition to dermatologic/allergic diseases, AD was also associated with infections, including methicillin-resistant Staphylococcus aureus (OR, 3.76), and autoimmune conditions, including vitiligo (OR, 2.98) and alopecia areata (OR, 4.32). Pediatric patients with AD had higher likelihoods of lymphoid/hematologic malignancies (OR, 1.94), ocular disorders (OR, 1.37-2.02), metabolic syndrome (OR, 1.61), and obesity (OR, 1.81). For all the ORs mentioned above, P was <.001.

LIMITATIONS: Retrospective analysis of health care claims data.

CONCLUSIONS: AD in pediatric patients was associated with a wide range of psychologic and systemic comorbidities. Increased awareness can help minimize its negative effects on the quality of life andÂ prevent long-term health consequences in young patients with AD

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J Atten Disord. 2022 Jan;26:125-39.

ADHD MAY ASSOCIATE WITH REDUCED TOLERANCE TO ACUTE SUBCONCUSSIVE HEAD IMPACTS: A PILOT CASE-CONTROL INTERVENTION STUDY.

Nowak MK, Ejima K, Quinn PD, et al.

OBJECTIVE: To test our hypothesis that individuals with ADHD would exhibit reduced resiliency to subconcussive head impacts induced by ten soccer headings.

METHOD: We conducted a case-control intervention study in 51 adults (20.6 ± 1.7 years old). Cognitive assessment, using ImPACT, and plasma levels of neurofilament-light (NF-L), Tau, glial-fibrillary-acidic protein (GFAP), and ubiquitin-C-terminal hydrolase-L1 (UCH-L1) were measured.

RESULTS: Ten controlled soccer headings demonstrated ADHD-specific transient declines in verbal memory function. Ten headings also blunted learning effects in visual memory function in the ADHD group while the non-ADHD counterparts improved both verbal and visual memory functions even after ten headings. Blood biomarker levels of the ADHD group were sensitive to the stress induced by ten headings, where plasma GFAP and UCH-L1 levels acutely increased after 10 headings. Variance in ADHD-specific verbal memory decline was correlated with increased levels of plasma GFAP in the ADHD group.

CONCLUSIONS: These data suggest that ADHD may reduce brain tolerance to repetitive subconcussive head impacts

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J Atten Disord. 2022 Jan;26:25-33.

PSYCHOMETRIC PROPERTIES OF THE SLUGGISH COGNITIVE TEMPO SCALE IN A TURKISH SAMPLE OF CHILDREN AND ADOLESCENTS.

Gozpinar N, Cakiroglu S, Gormez V.

Sluggish Cognitive Tempo (SCT) has been proposed as a serious problem of attention, however there no validated psychometric measures for its evaluation in Turkish in a community sample. The present study aimed to examine the psychometric characteristics of the first SCT scale in Turkish in children and adolescents. A total of 418 children and adolescents between the ages of 6-18 years (9.83±2.8) were recruited. The data was obtained from parents using Sluggish Cognitive Tempo Scale and Strengths and Difficulties Questionnaire. The SCT scale-Turkish form demonstrated very good internal homogeneity (Cronbach's ± = .90), good test-retest reliability (r = .98), good concurrent validity (r range = .35- .65) and good construct validity. Goodness of fit indices were found to be acceptable and statistically significant associations were found between SDQ and SCT scales. The SCT scale is a valid and reliable instrument in Turkish children and adolescents

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J Atten Disord. 2022 Apr;26:902-14.

DISTANCE LEARNING IN CHILDREN WITH AND WITHOUT ADHD: A CASE-CONTROL STUDY DURING THE COVID-19 PANDEMIC.

Tessarollo V, Scarpellini F, Costantino I, et al.

OBJECTIVE: This research involved the parents of ADHD students to explore how their children coped with online distance learning during COVID-19 pandemic and what implications this schooling method had on their emotional and behavioral well-being.

METHOD: Data were collected during lockdown using an online questionnaire addressed to 100 mothers and were compared with 184 matched controls from a national survey launched in the same period.

RESULTS: Attention span, spontaneous commitment, and autonomy in distance learning was found to be more limited in ADHD group. Compared to controls, 21.7% of ADHD students were not assessed and 40.9% did not receive grades. Behavioral changes were reported in both groups (64.2%), represented mainly by restlessness, aggressiveness, and anxiety.

CONCLUSION: Distance education increases academic difficulties, especially in ADHD pupils. The effects of lockdown should be adequately evaluated upon school reopening and appropriate recovery interventions should be planned

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J Atten Disord. 2022 Jan;26:307-18.

ADHD, RELIGIOSITY, AND PSYCHIATRIC COMORBIDITY IN ADOLESCENCE AND ADULTHOOD.

Dew RE, Kollins SH, Koenig HG.

OBJECTIVE: Religiosity has been repeatedly proposed as protective in the development of depression, sociopathy and addictions. ADHD frequently co-occurs with these same conditions. Although ADHD symptoms may affect religious practice, religiosity in ADHD remains unexplored.

METHOD: Analyses examined data from >8000 subjects aged 12 to 34 in four waves of the Add Health Study. Relationships of religious variables with childhood ADHD symptoms were statistically evaluated. Observed correlations of ADHD symptoms to depression, delinquency, and substance use were tested for mediation and moderation by religiosity.

RESULTS: ADHD symptoms correlated with lower levels of all religious variables at nearly all waves. In some analyses at Wave IV, prayer and attendance interacted with ADHD to predict worsened psychopathology.

CONCLUSION: ADHD symptoms predicted lower engagement in religious life. In adulthood, some aspects of religiosity interacted with ADHD symptoms to predict worse outcomes. Further research should explore whether lower religiosity partially explains prevalent comorbidities in ADHD

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J Atten Disord. 2022 Jan;26:143-48.

THE COURSE OF ADHD DURING PREGNANCY.

Baker AS, Wales R, Noe O, et al.

OBJECTIVE: The aim of this study was to characterize the course of ADHD during pregnancy.

METHOD: Women ages 18 to 45 were followed prospectively at <20weeks, 24weeks, and 36weeks pregnant. Three groups emerged: women who discontinued, maintained, or adjusted their ADHD medications. ADHD symptoms were recorded using the AISRS. Anxiety, depression, stress, and functional impairment were monitored.

RESULTS: A total of 25 women with ADHD were eligible for analysis. No significant difference observed between three groups in AISRS scores. Significant differences found between medication discontinuers vs adjusters for both mood and family functioning (EPDS, 5.3, $p < .0001$; WFIRS, 3.3, $p = .0309$). Significant differences also found between discontinuers vs maintainers for mood and family functioning (EPDS, 4.98, $p = .0009$; WFIRS, 3.09, $p = .0197$).

CONCLUSION: This preliminary study provides novel insight into the course of ADHD during pregnancy, underscoring mood and family functioning as critical domains that may contribute to growing use of psychostimulants during pregnancy

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J Atten Disord. 2022 Jan;26:119-24.

IMPACT OF MEDICATION ON PERFORMANCE OF HOUSEHOLD CHORES BY CHILDREN WITH ADHD .

Park F, Rapoport E, Soled D, et al.

OBJECTIVE: To investigate associations between ADHD medication and household chore performance by children with ADHD.

METHODS: A parent questionnaire collected information about the adequacy and quality of their child's performance of two self-care and six family-care chores. Parent perceptions of ADHD medication effect duration were used to identify children with after-school medication benefits (ASMB). Mann-Whitney U tests compared children with and without ASMB across measures of chore performance.

RESULTS: A total of 565 parents of children with ADHD that regularly take medication completed the questionnaire. Children with ASMB were more likely to meet parental expectations for five of eight household chores and were more likely to be able to independently complete both self-care and family-care chores than those without ASMB. No differences were noted regarding their need for reminders or assistance with chores.

CONCLUSION: Improvement in chore performance may be an additional consideration with respect to medication selection for children with ADHD

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J Atten Disord. 2022 Jan;26:296-306.

BIRDS OF A FEATHER: AN EXAMINATION OF ADHD SYMPTOMS AND ASSOCIATED CONCERNS IN PARTNERS OF ADULTS WITH ADHD.

Steele CM, Wymbs BT, Capps RE.

OBJECTIVE: Adults often select romantic partners who behave like they do (i.e. assortative mating). However, little is known about whether assortative mating is common among adults with attention-deficit/hyperactivity disorder (ADHD) and whether it is related to associated problems.

METHOD: About 94 adults without ADHD, 43 adults with childhood ADHD histories but without current symptoms or impairment (ADHD-Desist), 27 adults with childhood ADHD histories and elevated current symptoms and impairment (ADHD-Persist) rated their partners' ADHD symptoms and their own associated problems (e.g., intimate partner violence, financial difficulties).

RESULTS: The ADHD-Persist group reported that their partners exhibited more ADHD symptoms than the ADHD-Desist group and those without ADHD. Adults in the ADHD-Persist group who had partners with elevated ADHD symptoms endorsed high intimate partner violence and financial difficulties.

CONCLUSION: Assortative mating appears to be common among adults with ADHD, especially those with persistent symptoms, and to increase risk of additional problems

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J Atten Disord. 2022 Jan;26:15-24.

RECALLED EXPERIENCES OF BULLYING AND VICTIMIZATION IN A LONGITUDINAL, POPULATION-BASED BIRTH COHORT: THE INFLUENCE OF ADHD AND CO-OCCURRING PSYCHIATRIC DISORDER.

Fogler JM, Weaver AL, Katusic S, et al.

OBJECTIVE: To describe bullying experiences throughout childhood of people with and without childhood ADHD and co-occurring learning and psychiatric disorders from a population-based birth cohort.

METHODS: In a secondary data analysis of 199 childhood ADHD cases and 287 non-ADHD referents (N = 486), reported experiences of peer interactions during elementary, middle, or high school were classified as "bully," "victim," "neither," or "both." Associations were assessed with multinomial logistic regression.

RESULTS: Adjusted for male sex, the odds of classification as victim-only, victim/bully, or bully- only (vs. neither) were 3.70 (2.36-5.81), 17.71, and 8.17 times higher for childhood ADHD cases compared to non-ADHD referents. Victim-bullies (62.5%) and bullies (64.3%) had both childhood ADHD and other psychiatric disorders versus 38.4% of victims-only and 17.3% of those classified as "neither."

CONCLUSION: The list of serious lifetime consequences of having ADHD also includes bullying. We offer future research directions for determining potential causal pathways

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J Atten Disord. 2022 Jan;26:319-27.

OVERPROTECTIVE PARENTING MEDIATES THE RELATIONSHIP BETWEEN EARLY CHILDHOOD ADHD AND ANXIETY SYMPTOMS: EVIDENCE FROM A CROSS-SECTIONAL AND LONGITUDINAL STUDY.

Meyer A, Kegley M, Klein DN.

Attention Deficit/Hyperactivity Disorder (ADHD) is often comorbid with anxiety disorders in children. Both ADHD and anxiety in childhood has been linked to overprotective parenting styles. In the current study we examine a model wherein early ADHD symptoms predict overprotective parenting, which in turn predicts anxiety symptoms later in childhood. In Study 1 we utilize cross-sectional data in 102 child/parent dyads between the ages of 5 and 7â€‰years old and Study 2 extends these findings by examining this same mediation model longitudinally in 376 child/parent dyads who were assessed when children were 3, 6, and 9â€‰years old. Results from both studies supported a mediation model wherein the relationship between child ADHD symptoms and child anxiety symptoms was mediated by parental overprotection. This is the first study, to our knowledge, to examine overprotective parenting as a mechanism underlying the heterotypic continuity or sequential comorbidity of ADHD to anxiety symptoms

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J Atten Disord. 2022 Jan;26:88-100.

EFFECTS OF THE SNAP25 ON INTEGRATION ABILITY OF BRAIN FUNCTIONS IN CHILDREN WITH ADHD.

Yang Y, Peng G, Zeng H, et al.

OBJECTIVE: The present study aimed to examine the effects of SNAP25 on the integration ability of intrinsic brain functions in children with ADHD, and whether the integration ability was associated with working memory (WM).

METHODS: A sliding time window method was used to calculate the spatial and temporal concordance among five rs-fMRI regional indices in 55 children with ADHD and 20 healthy controls.

RESULTS: The SNAP25 exhibited significant interaction effects with ADHD diagnosis on the voxel-wise concordance in the right posterior central gyrus, fusiform gyrus and lingual gyrus. Specifically, for children with ADHD, G-carriers showed increased voxel-wise concordance in comparison to TT homozygotes in the right precentral gyrus, superior frontal gyrus, postcentral gyrus, and middle frontal gyrus. The voxel-wise concordance was also found to be related to WM.

CONCLUSION: Our findings provided a new insight into the neural mechanisms of the brain function of ADHD children

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J Atten Disord. 2022 Jan;26:109-18.

RECIPROCAL DEVELOPMENTAL RELATIONS BETWEEN ADHD AND ANXIETY IN ADOLESCENCE: A WITHIN-PERSON LONGITUDINAL ANALYSIS OF COMMONLY CO-OCCURRING SYMPTOMS.

Murray AL, Caye A, McKenzie K, et al.

Objective: Significant anxiety often occurs in the presence of ADHD symptoms; however, the reasons are not well understood. We aimed to establish whether the relations between ADHD symptons and anxiety are bidirectional or unidirectional.

METHOD: Weexamined the developmental relations between ADHD and anxiety symptoms across adolescence (ages 13, 15, and 17) in a community-ascertained, normative longitudinal sample of 1,483 youth (52% male). We used an autoregressive latent trajectory model with structured residuals (ALT-SR) to examine within-person developmental relations between ADHD and anxiety symptoms to determine whether it is ADHD symptoms that lead to anxiety symptoms and/or the reverse.

RESULTS: Results suggested that there are reciprocal within-person developmental relations between ADHD and anxiety symptoms.

CONCLUSIONS: Our findings support the recommendation that targeting ADHD symptoms can be fruitful for addressing anxiety symptoms; however, they suggest that targeting anxiety symptoms may also benefit ADHD symptoms. Results also underline the importance of careful assessment for underlying ADHD symptoms among adolescents presenting with anxiety

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J Atten Disord. 2022 Jan;26:267-81.

TIME PERCEPTION DEFICITS IN CHILDREN AND ADOLESCENTS WITH ADHD: A META-ANALYSIS.

Zheng Q, Wang X, Chiu KY, et al.

OBJECTIVE: Prior studies have reported time perception impairment in children and adolescents with ADHD but the results were inconsistent.

METHOD: The current meta-analysis reviews 27 empirical studies published in English after year 2000 that compared time perception competence among children and adolescents with and without ADHD.

RESULTS: Results from 1620 participants with ADHD and 1249 healthy controls showed significant timing deficits in ADHD. Children/adolescents with ADHD perceived time less accurately (Hedges' g>0.40), less precisely (Hedges' g=0.66) and had higher tendency to overestimate time than their healthy counterparts. Moderator analyses indicated that the discrepancy of time perception between groups was not affected by the type of timing tasks nor the modality of stimuli used in the tasks. Nonetheless, results were moderated by age and gender.

CONCLUSION: These findings may update current understanding of the underlying neuropsychological deficits in ADHD and provide insight for future research in clinical assessments and treatments for ADHD

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J Atten Disord. 2022 Jan;26:3-14.

CHILDREN WITH ADHD ARE AT RISK FOR A BROAD ARRAY OF ADVERSE ADULT OUTCOMES THAT CROSS FUNCTIONAL DOMAINS: RESULTS FROM A POPULATION-BASED BIRTH COHORT STUDY.

Harstad EB, Katusic S, Sideridis G, et al.

OBJECTIVE: To identify patterns ("classes") of outcomes for adults with and without childhood ADHD.
METHOD: Subjects were 232 childhood ADHD cases and 335 non-ADHD referents from a 1976 to 1982 birth cohort. We used latent class analyses to identify classes based on a broad array of adult psychosocial outcomes and determined the proportion of subjects with childhood ADHD within each class.
RESULTS: A three class solution provided optimal model fit; classes were termed "good," "intermediate," and "poor" functioning. Subjects with childhood ADHD comprised 62.8% of the "poor," 53.5% of the "intermediate," and 24.9% of the "good" functioning class. The "poor" functioning class was distinguished by increased likelihood of legal trouble and substance use disorders and included more individuals with childhood ADHD and psychiatric disorder than the "intermediate" class (45.5% vs. 30.6%).
CONCLUSION: Children with ADHD are at risk for adverse adult outcomes in multiple domains and co-morbid childhood psychiatric disorders increase risk

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J Atten Disord. 2022 Jan;26:149-224.

A SYSTEMATIC REVIEW OF SLEEP AND CIRCADIAN RHYTHMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Bondopadhyay U, Diaz-Orueta U, Coogan AN.

OBJECTIVE: Children and adults with ADHD often report sleep disturbances that may form part of the etiology and/or symptomatology of ADHD. We review the evidence for sleep changes in children with ADHD.
METHODS: Systematic review with narrative synthesis assessing sleep and circadian function in children aged 5 to 13years old with a diagnosis of ADHD.
RESULTS: 148 studies were included for review, incorporating data from 42,353 children. We found that sleep disturbances in ADHD are common and that they may worsen behavioral outcomes; moreover, sleep interventions may improve ADHD symptoms, and pharmacotherapy for ADHD may impact sleep.
CONCLUSION: Sleep disturbance may represent a clinically important feature of ADHD in children, which might be therapeutically targeted in a useful way. There are a number of important gaps in the literature. We set out a manifesto for future research in the area of sleep, circadian rhythms, and ADHD

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J Atten Disord. 2022 Jan;26:282-95.

EXAMINING THE EDUCATIONAL GAP FOR CHILDREN WITH ADHD AND SUBTHRESHOLD ADHD.

Zendarski N, Guo S, Sciberras E, et al.

OBJECTIVE: The present study examined the impact of Attention Deficit Hyperactivity Disorder (ADHD) on core educational outcomes in two large community cohorts of Australian school children.
METHOD: Academic (reading and numeracy) and non-academic (school engagement, attendance, peer victimization, and parental expectations) outcomes were compared between children with ADHD, subthreshold ADHD, and controls when children were in grade 5 (M age=10.5). Data were drawn from the Longitudinal Study of Australian Children birth cohort (LSAC; N=3,540) and the Children's Attention Project (CAP; N=356).
RESULTS: Both subthreshold ADHD and ADHD groups had poorer outcomes on all measures, with medium effects sizes. Differences were not evident between subthreshold ADHD and ADHD groups.
CONCLUSIONS: Educational outcomes examined in this study highlight the educational risk for upperprimary school children with ADHD or subthreshold ADHD, in comparison to their peers. Monitoring these outcomes is necessary to inform policy, practice, and intervention

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J Autism Dev Disord. 2022 Mar;52:1189-99.

THE RELATIONSHIP BETWEEN MOTOR SKILLS AND INTELLIGENCE IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Ramos-Sanchez CP, Kortekaas D, Van BD, et al.

This study explored the association between intelligence and motor skills in children with ASD after controlling for Attention Deficit and Hyperactivity Disorder (ADHD) and the associations between motor impairment and intellectual disability (ID) in this population. In total, 120 children with ASD (3-16 years; 81.7% boys) completed a standardized intelligence test, the Movement Assessment Battery for Children and Beery-Buktenica Developmental Test of Visual-Motor Integration. Variance in performance IQ was associated with 20.8% of the variance in motor skills while significant associations were found between comorbid ID and motor impairment (É¸=0.304). Manual Dexterity and Balance are moderately influenced by performance IQ in children with ASD. Furthermore, presence of ID is also moderately associated with motor impairment in this population

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J Child Adolesc Psychopharmacol. 2021 Dec;31:653-58.

PSYCHOTROPIC MEDICATION PRESCRIBING FOR YOUTH AT A REGIONAL AUTISM CENTER.

Gannon S, Abdelrazek A, Keller K, et al.

Objectives: The Seattle Children's Autism Center (SCAC) serves youth throughout Washington state (WA). The authors examined (1) whether the ethnicity and race of patients seen at the SCAC aligned with the demographics reported in the WA census, and (2) whether psychotropic medication prescriptions were associated with patient factors, including age, sex, ethnicity, race, insurance, visit number, and diagnoses.

Methods: The authors extracted demographic and prescription data from electronic medical records for all patients (3-21 years) seen at the SCAC in 2018 for psychiatric medication evaluation in the context of autism spectrum disorder (ASD) and/or other related neurodevelopmental disorder (n=1112), and used binary logistic regression to ascertain the effects of patient factors on psychotropic prescriptions.

Results: The SCAC study sample appeared to align well with the WA census. Older age and higher visit number were among the most significant factors associated with psychotropic prescriptions. Psychotropic prescriptions increased with age, across all categories, except attention-deficit/hyperactivity disorder medications. There were no sex differences in prescribing rates. There were differences in prescribing rates by ethnicity and race. There were also increased prescription rates among those with Medicaid insurance.

Conclusion: These demographic differences in prescribing for youth with ASD provide more specificity than prior studies about sex, ethnic, racial, and insurance-related differences, and can serve as an impetus to examine the reasons for variance

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J Child Adolesc Psychopharmacol. 2021 Dec;31:659-69.

PSYCHOTROPIC DRUG TREATMENT PATTERNS IN PERSONS WITH FRAGILE X SYNDROME.

Dominick KC, Andrews HF, Kaufmann WE, et al.

Objective: Psychiatric comorbidity is common in fragile X syndrome (FXS) and often addressed through pharmacological management. Here we examine data in the Fragile X Online Registry With Accessible Research Database (FORWARD) to characterize specific symptoms being treated with psychotropic medication, patterns of medication use, as well as the influence of gender, intellectual disability (ID), age, and autism spectrum disorder (ASD) diagnosis.

Methods: Data were drawn from the 975 participants who have a completed clinician form. We explored the frequency of psychotropic medication use for the following symptom clusters: attention, hyperactivity, anxiety, hypersensitivity, obsessive-compulsive disorder (OCD), mood swings, irritability/agitation, aggression, and self-injury (IAAS).

Results: A majority of participants (617 or 63.3%) were taking a psychotropic medication, including investigational drugs. Medications were often targeting multiple symptoms. Psychotropic medication use was more common in males, adolescents, and those with comorbid ID and ASD. Anxiety was the most frequently targeted symptom, followed by attention-deficit/hyperactivity disorder symptoms and IAAS. Selective serotonin reuptake inhibitors (SSRIs) were the most frequently prescribed medication class among all patients (n=266, 43%), followed by stimulants (n=235, 38%), each with no gender difference. Antipsychotics

were the third most frequently prescribed medication class (n=205, 33%), and were more frequently prescribed to males and those with ID and ASD.
Conclusions: Anxiety, attention and hyperactivity were the most common symptom targets for psychopharmacologic intervention in FXS. Our results support clinical knowledge that males with comorbid ASD and ID have a more severe presentation requiring more intervention including medications. These results highlight the need for examination of symptom overlap and interaction

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J Child Neurol. 2021 Sep;36:875-82.
DIFFERENTIAL CLINICAL FEATURES IN COLOMBIAN PATIENTS WITH ROLANDIC EPILEPSY AND SUGGESTION OF UNLIKELY ASSOCIATION WITH GRIN2A, RBFOX1, OR RBFOX3 GENE VARIANTS.
Tascan-Arcila J, et al.
PURPOSE: Our purpose was to describe the phenotypic features and test for association of genes GRIN2A, RBFOX1 and RBFOX3 with rolandic epilepsy in patients from Colombia.
METHODS: Thirty patients were enrolled. A structured interview was applied. In addition, saliva samples were collected from the patients and their parents. One polymorphism in each of GRIN2A, RBFOX1 and RBFOX3 genes was tested.
RESULTS: The average age at onset was 5.3 years. Almost half the sample presented prolonged seizures (>5 minutes); although the majority of the patients presented their seizures only while asleep, over a quarter presented them only while awake. The most frequent comorbidity was the presence of symptoms compatible with attention-deficit hyperactivity disorder (ADHD). Personal history of febrile seizures and parasomnias were equally frequent (20%). Family history of any type of epilepsy was reported in 80% of the patients, followed by migraine (73.3%) and poor academic performance (63.3%). About half the sample reported sleepwalking in parents or sibs. Most patients had received pharmacologic treatment. We found no association of rolandic epilepsy with the single nucleotide polymorphisms tested.
CONCLUSIONS: Our rolandic epilepsy cohort presents clinical features clearly different from other cohorts. For instance, age at onset is much earlier in our set of patients, and personal and family history of febrile seizures as well as parasomnias are highly prevalent in our sample. No association of rolandic epilepsy with variants at the 3 genes tested was found. This lack of association may reflect the high genetic heterogeneity of the epilepsies

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J Child Psychol Psychiatry. 2022 Jan;63:34-46.
PREVALENCE OF MENTAL DISORDERS IN SCHOOL CHILDREN AND ADOLESCENTS IN CHINA: DIAGNOSTIC DATA FROM DETAILED CLINICAL ASSESSMENTS OF 17,524 INDIVIDUALS.
Li F, Cui Y, Li Y, et al.
Background: To date, no national-scale psychiatric epidemiological survey for children and adolescents has been conducted in China. In order to inform government officials and policymakers and to develop a comprehensive plan for service providers, there was a clear need to conduct an up-to-date systematic nationwide psychiatric epidemiological survey.
Methods: We conducted a two-stage large-scale psychiatric point prevalence survey. Multistage cluster stratified random sampling was used as the sampling strategy. Five provinces were selected by comprehensively considering geographical partition, economic development, and rural/urban factors. In Stage 1, the Child Behavior Checklist was used as the screening tool. In Stage 2, Mini-International Neuropsychiatric Interview for Children and Adolescents and a diagnostic process based on the Diagnostic and Statistical Manual were used to make the diagnoses. Sampling weights and poststratification weights were employed to match the population distributions. Exploratory analyses were also performed using socio-demographic factors. Prevalence in socio-demographic factor subgroups and overall were estimated. Rao-Scott adjusted chi-square tests were utilized to determine if between-group differences were present. Factor interactions were checked by logistic regression analyses.
Results: A total of 73,992 participants aged 6-16 years of age were selected in Stage 1. In Stage 2, 17,524 individuals were screened and diagnosed. The weighted prevalence of any disorder was 17.5% (95% CI: 17.2-18.0). Statistically significant differences in prevalence of any psychiatric disorder were observed

between sexes [χ2 (1, N = 71,929) = 223.0, p < .001], age groups [χ2 (1, N = 71,929) = 18.6, p < .001] and developed vs. developing areas [χ2 (1, N = 71,929) = 2,129.6, p < .001], while no difference was found between rural and urban areas [χ2 (1, N = 71,929) = 1.4, p = .239]. Male, younger individuals, children, and adolescents from developed areas had higher prevalence of any psychiatric disorder. The prevalence of any psychiatric disorder was found to decrease with the age in the male group, while the female group increased with the age. Individuals diagnosed with attention-deficit hyperactivity disorder, oppositional defiant disorder, a tic disorder, conduct disorder, and major depression disorder had the highest rates of comorbidity.
Conclusions: The prevalence of any psychiatric disorder we found is the highest ever reported in China. These results urgently need to be addressed by public mental health service providers and policymakers in order to provide access to the necessary treatments and to reduce the long-term negative impact of these conditions on families and the society as a whole

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J Child Psychol Psychiatry. 2022 Feb;63:143-51.

ADHD AND AUTISM SYMPTOMS IN YOUTH: A NETWORK ANALYSIS.

Farhat LC, Brentani H, de Toledo VHC, et al.

BACKGROUND: Previous research investigating the overlap between attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (henceforth, autism) symptoms in population samples have relied on latent variable modeling in which averaged scores representing dimensions were derived from observed symptoms. There are no studies evaluating how ADHD and autism symptoms interact at the level of individual symptom items.
METHODS: We aimed to address this gap by performing a network analysis on data from a school survey of children aged 6-17 years old (N=7,405). ADHD and autism symptoms were measured via parent-report on the Swanson, Nolan, Pelham-IV questionnaire and the Childhood Autism Spectrum test, respectively.
RESULTS: A relatively low interconnectivity between ADHD and autism symptoms was found with only 10.06% of possible connections (edges) between one ADHD and one autism symptoms different than zero. Associations between ADHD and autism symptoms were significantly weaker than those between two symptoms pertaining to the same construct. Select ADHD symptoms, particularly those presenting in social contexts (e.g. 'talks excessively', 'does not wait turn'), showed moderate-to-strong associations with autism symptoms, but some were considered redundant to autism symptoms.
CONCLUSIONS: The present findings indicate that individual ADHD and autism symptoms are largely segregated in accordance with diagnostic boundaries corresponding to these conditions in children and adolescents from the community. These findings could improve our clinical conceptualization of ADHD and autism and guide advancements in diagnosis and treatment

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J Child Psychol Psychiatry. 2022 Feb;63:187-98.

PERSONALIZED AT-HOME NEUROFEEDBACK COMPARED TO LONG-ACTING METHYLPHENIDATE IN CHILDREN WITH ADHD: NEWROFEED, A EUROPEAN RANDOMIZED NONINFERIORITY TRIAL.

Purper-Ouakil D, Blasco-Fontecilla H, Ros T, et al.

BACKGROUND: Neurofeedback is considered a promising intervention for the treatment of attention-deficit hyperactivity disorder (ADHD). NEWROFEED is a prospective, multicentre, randomized (3:2), reference drug-controlled trial in children with ADHD aged between 7 and 13years. The main objective of NEWROFEED was to demonstrate the noninferiority of personalized at-home neurofeedback (NF) training versus methylphenidate in the treatment of children with ADHD.
METHODS: The NF group (n=111) underwent eight visits and two treatment phases of 16 to 20 at-home sessions with down-training of the theta/beta ratio (TBR) for children with high TBR and enhancing the sensorimotor rhythm (SMR) for the others. The control group (n=67) received optimally titrated long-acting methylphenidate. The primary endpoint was the change between baseline and endpoint in the Clinician ADHD-RS-IV total score in the per-protocol population (90 NF/59 controls).
TRIAL REGISTRATION: US National Institute of Health, ClinicalTrials.gov #NCT02778360.
RESULTS: Our study failed to demonstrate noninferiority of NF versus methylphenidate (mean between-group difference 8.09 90% CI [8.09; 10.56]). However, both treatment groups showed significant pre-post

improvements in core ADHD symptoms and in a broader range of problems. Reduction in the Clinician ADHD-RS-IV total score between baseline and final visit (D90) was 26.7% (SMD=0.89) in the NF and 46.9% (SMD=2.03) in the control group. NF effects increased whereas those of methylphenidate were stable between intermediate and final visit.
CONCLUSIONS: Based on clinicians' reports, the effects of at-home NF were inferior to those of methylphenidate as a stand-alone treatment

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J Child Psychol Psychiatry. 2022 Jan;63:19-33.
INDIVIDUAL DIFFERENCES IN WHITE MATTER OF THE UNCINATE FASCICULUS AND INFERIOR FRONTO-OCCIPITAL FASCICULUS: POSSIBLE EARLY BIOMARKERS FOR CALLOUS-UNEMOTIONAL BEHAVIORS IN YOUNG CHILDREN WITH DISRUPTIVE BEHAVIOR PROBLEMS.
Graziano PA, Garic D, Dick AS.
BACKGROUND: Callous-unemotional (CU) behaviors are important for identifying severe patterns of conduct problems (CP). One major fiber tract implicated in the development of CP is the uncinate fasciculus (UF), which connects amygdala and orbitofrontal cortex (OFC). The goals of the current study were to (a) explore differences in the white matter microstructure in the UF and other major fiber tracks between young typically developing (TD) children and those with a disruptive behavior disorder (DBD) and (b) explore, within the DBD group, whether individual differences in these white matter tracts relate to co-occurring CP and CU behaviors.
METHODS: Participants included 198 young children (69% boys, M(age) =5.66 years; 80% Latinx; 48.5% TD). CU behaviors and CP were measured via a combination of teacher/parent ratings. Non-invasive diffusion-weighted imaging (DWI) was used to measure fractional anisotropy (FA), an indirect indicator of white matter properties.
RESULTS: Relative to TD children, children in the DBD group had reduced FA on four out of the five fiber tracks we examined (except for cingulum and right ILF), even after accounting for whole brain FA, sex, movement, parental income, and IQ. Within the DBD group, no associations were found between CP and reduced white matter integrity across any of the fiber tracks examined. However, we found that even after accounting for CP, ADHD symptomology, and a host of covariates (whole brain FA, sex, movement, parental income, and IQ), CU behaviors were independently related to reduced FA in bilateral UF and left inferior fronto-occipital fasciculus (IFOF) in the DBD group, but this was not the case for TD children.
CONCLUSIONS: Alterations in the white matter microstructure within bilateral UF and left IFOF may be biomarkers of CU behaviors, even in very young children

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J Child Psychol Psychiatry. 2022 Mar;63:305-14.
CLINICAL PRECURSORS OF TICS: AN EMTICS STUDY.
Openneer TJC, Huyser C, Martino D, et al.
Background Children with Tourette syndrome (TS) often have comorbid disorders, particularly attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). While subtle premorbid symptoms have been described in various psychiatric disorders, the presence of clinical precursors that may exist before the onset of tics is unknown. This longitudinal study aimed to find clinical precursors of tics by assessing a range of clinical characteristics prior to tic onset in comparison with children without onset of tics.
Methods A sample of 187 3- to 10-year-old first-degree unaffected relatives of children with TS were followed up to 7 years in the European Multicentre Tics in Children Study (EMTICS). We investigated whether clinical characteristics assessed at baseline predicted tic onset, comparing 126 children without tic onset to 61 children who developed tics. We used the least absolute shrinkage and selection operator (LASSO) method, a penalised logistic regression approach. We also explored sex differences and repeated our analyses in an age- and sex-matched subsample.
Results Children with tic onset were more frequently male (β = −0.36), had higher baseline severity of conduct problems (β = 0.23), autism spectrum disorder symptoms (ASD; β = 0.08), compulsions (β = 0.02) and emotional problems (β = 0.03) compared to children without tic onset. Conduct and ASD problems were

male-specific predictors, whereas severity of compulsions and oppositional (β = 0.39) and emotional problems were female-specific predictors.
Conclusion This study supports the presence of clinical precursors prior to tic onset and highlights the need of sex-specific monitoring of children at risk of developing tics. This may aid in the earlier detection of tics, particularly in females. We moreover found that tics most often persisted one year after tic onset, in contrast to the common belief that tics are mostly transient.

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J Child Psychol Psychiatry. 2022 Feb;63:165-77.

A RANDOMISED CONTROLLED TRIAL (MINDCHAMP) OF A MINDFULNESS-BASED INTERVENTION FOR CHILDREN WITH ADHD AND THEIR PARENTS.

Siebelink NM, et al.

BACKGROUND: Family mindfulness-based intervention (MBI) for child attention-deficit/hyperactivity disorder (ADHD) targets child self-control, parenting and parental mental health, but its effectiveness is still unclear.
METHODS: MindChamp is a pre-registered randomised controlled trial comparing an 8-week family MBI (called 'MYmind') in addition to care-as-usual (CAU) (n=55) with CAU-only (n=48). Children aged 8-16years with remaining ADHD symptoms after CAU were enrolled together with a parent. Primary outcome was post-treatment parent-rated child self-control deficits (BRIEF); post hoc, Reliable Change Indexes were explored. Secondary child outcomes included ADHD symptoms (parent/teacher-rated Conners' and SWAN; teacher-rated BRIEF), other psychological symptoms (parent/teacher-rated), well-being (parent-rated) and mindfulness (self-rated). Secondary parent outcomes included self-ratings of ADHD symptoms, other psychological symptoms, well-being, self-compassion and mindful parenting. Assessments were conducted at post-treatment, 2- and 6-month follow-up.
RESULTS: Relative to CAU-only, MBI+CAU resulted in a small, statistically non-significant post-treatment improvement on the BRIEF (intention-to-treat: d=0.27, p=.18; per protocol: d=0.33, p=.11). Significantly more children showed reliable post-treatment improvement following MBI+CAU versus CAU-only (32% versus 11%, p<.05, Number-Needed-to-Treat=4.7). ADHD symptoms significantly reduced post-treatment according to parent (Conners' and SWAN) and teacher ratings (BRIEF) per protocol. Only parent-rated hyperactivity impulsivity (SWAN) remained significantly reduced at 6-month follow-up. Post-treatment group differences on other secondary child outcomes were consistently favour of MBI+CAU, but mostly non-significant; no significant differences were found at follow-ups. Regarding parent outcomes, significant post-treatment improvements were found for their own ADHD symptoms, well-being and mindful parenting. At follow-ups, some significant effects remained (ADHD symptoms, mindful parenting), some additional significant effects appeared (other psychological symptoms, self-compassion) and others disappeared/remained non-significant.
CONCLUSIONS: Family MBI+CAU did not outperform CAU-only in reducing child self-control deficits on a group level but more children reliably improved. Effects on parents were larger and more durable. When CAU for ADHD is insufficient, family MBI could be a valuable addition

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J Child Psychol Psychiatry. 2022 Feb;63:218-28.

SEX DIFFERENCES IN PSYCHIATRIC COMORBIDITY AND CLINICAL PRESENTATION IN YOUTHS WITH CONDUCT DISORDER.

Konrad K, Kohls G, Baumann S, et al.

BACKGROUND: Conduct disorder (CD) rarely occurs alone but is typically accompanied by comorbid psychiatric disorders, which complicates the clinical presentation and treatment of affected youths. The aim of this study was to investigate sex differences in comorbidity pattern in CD and to systematically explore the 'gender paradox' and 'delayed-onset pathway' hypotheses of female CD.
METHODS: As part of the FemNAT-CD multisite study, semistructured clinical interviews and rating scales were used to perform a comprehensive phenotypic characterization of 454 girls and 295 boys with CD (9-18years), compared to 864 sex- and age-matched typically developing controls.

RESULTS: Girls with CD exhibited higher rates of current major depression, anxiety disorders, post-traumatic stress disorder and borderline personality disorder, whereas boys with CD had higher rates of current attention-deficit/hyperactivity disorder. In line with the 'gender paradox' hypothesis, relative to boys, girls with CD showed significantly more lifetime psychiatric comorbidities (incl. Alcohol Use Disorder), which were accompanied by more severe CD symptoms. Female and male youths with CD also differed significantly in their CD symptom profiles and distribution of age-of-onset subtypes of CD (i.e. fewer girls with childhood-onset CD). In line with the 'delayed-onset pathway' hypothesis, girls with adolescent-onset CD showed similar levels of dimensional psychopathology like boys with childhood-onset CD, while boys with adolescent-onset CD had the lowest levels of internalizing psychopathology.
CONCLUSIONS: Within the largest study of CD in girls performed to date, we found compelling evidence for sex differences in comorbidity patterns and clinical presentation of CD. Our findings further support aspects of the 'gender paradox' and 'delayed-onset pathway' hypotheses by showing that girls with CD had higher rates of comorbid lifetime mental disorders and functional impairments, and they usually developed CD during adolescence. These novel data on sex-specific clinical profiles of CD will be critical in informing intervention and prevention programmes

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J Clin Pharm Ther. 2022 Jan;47:6-23.

"REAL-WORLD" EFFECTIVENESS OF METHYLPHENIDATE IN IMPROVING THE ACADEMIC ACHIEVEMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER DIAGNOSED STUDENTS-A SYSTEMATIC REVIEW.

de Faria JCM, Duarte LJR, Ferreira LA, et al.

WHAT IS KNOWN AND OBJECTIVE: Attention-deficit hyperactivity disorder (ADHD) symptoms usually impairs academic achievement and can trigger the onset of medication. Methylphenidate is a drug widely prescribed to treat ADHD. However, systematic reviews of randomized clinical trials suggest that it does not lead to great improvements in academic performance. Thus, we aimed to evaluate the evidence on the "real-world" effectiveness of methylphenidate in improving the academic achievement of ADHD students. METHODS: We conducted a systematic review of observational studies retrieved from five electronic databases, besides a manual search and search in grey literature. Studies evaluating treatment with methylphenidate compared to no treatment or other pharmacological/non-pharmacological alternatives used in ADHD were included. The risk of bias of the selected studies was assessed using adapted versions of the Newcastle-Ottawa Scale. RESULTS AND DISCUSSION: Nine studies (from ten reports) were included in the review: four cohorts, two before-and-after designs and three cross-sectional studies. They involved 12,269 children and adolescents aged 6-18 years. The doses of methylphenidate ranged from 10 to 72 mg/day, and the duration of the treatment from 2.6 months to 4.25 years. Five of these studies concluded that methylphenidate improves academic performance. However, three of the four lowest-bias risk studies concluded that the drug is ineffective. Five studies assessed the long-term use of methylphenidate, and four of them concluded that it does not result in better outcomes in the school setting. Most included studies had considerable limitations and significant heterogeneity regarding methodological design and academic performance measurement criteria. WHAT IS NEW AND CONCLUSION: Although some studies indicate that the short-term use of methylphenidate may improve outcomes in the school environment, the available evidence does not support the establishment of adequate conclusions about the real benefits of methylphenidate in the academic improvement of ADHD students

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J Commun Disord. 2022 Jan;95:106165.

AWARENESS OF DEVELOPMENTAL LANGUAGE DISORDER AMONGST WORKPLACE MANAGERS.

Lemos C, Kranios A, Beauchamp-Whitworth R, et al.

BACKGROUND: Developmental Language Disorder (DLD) is one of the most prevalent developmental disorders and affects expressive and receptive language with no clear cause (Bishop et al., 2017). Awareness of DLD is currently much lower than other (sometimes less prevalent) disorders such as Autism or Attention Deficit Hyperactivity Disorder (ADHD) (Bishop, 2010). Despite this, it has now been established that the implications of DLD reach well into adulthood (Botting, 2020; Botting et al., 2016; Clegg et al., 2005; Johnson et al., 2010). Thus, DLD may affect not only school progress but also employment. Whilst recent

research indicates that the rate of employment in this group was similar to peers (Conti-Ramsden etÂ al., 2018), it also reported lower levels of employment in terms of hours, contracts and employment type. However, there is virtually no research examining why this might be the case. In contrast there is already a growing evidence base surrounding Autism Spectrum Disorder (ASD) and Dyslexia in the workplace. Systematic reviews of factors affecting employment in ASD and Dyslexia (de Beer etÂ al., 2014; Scott etÂ al., 2019) have revealed barriers including the job application process itself.
AIMS & METHODS: In this study we aimed to explore managers' awareness of DLD and their views on training, adjustments and feasibility when considering employing an individual with DLD. Specifically, we asked: 1) What awareness do managers have of DLD and how does this compare to awareness of ASD and other developmental disorders? 2) What is the extent of training on DLD and other developmental disorders in the workplace? 3) What barriers to employment are perceived to be most significant by managers? 4) What strategies do managers report as currently in place to help support people with DLD? 5) What are perceived strengths of people with DLD according to managers?
RESULTS: In total, 77 managers completed an anonymous online survey which was accessed via a social media link. Managers came from a wide variety of backgrounds with an equal split between public and private organisations, and across gender. The number of managers who had heard of DLD was lower than for the other disorders (ADHD, ASD, Dyslexia). This pattern was partly mirrored in the proportion of managers who felt they had received adequate training on communication difficulties. However, training on developmental disorders generally was reported as very scarce. A qualitative examination of barriers identified by managers included interviewing and CV submission, reading and following instructions, lack of clear guidelines around support needed, and financial restrictions in providing support.
CONCLUSIONS: These findings support existing literature and have implications for policy and practice - namely that young people with DLD may need to be proactive about disclosing their language needs, and that workplaces need increased basic training in DLD

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J Dev Behav Pediatr. 2022 Feb;43:80-86.
EFFECT OF IRON SUPPLEMENTATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND IRON DEFICIENCY: A RANDOMIZED CONTROLLED TRIAL.
Pongpitakdamrong A, Chirdkiatgumchai V, Ruangdaraganon N, et al.
OBJECTIVES: To determine the effectiveness of combined iron supplementation and methylphenidate treatment on attention-deficit/hyperactivity disorder (ADHD) symptoms in children/adolescents with ADHD and iron deficiency compared with methylphenidate alone.
METHODS: In total, 116 children/adolescents with ADHD were screened for iron deficiency. Participants who exhibited iron deficiency were randomized into 2 groups (ferrous supplementation vs placebo). Vanderbilt ADHD rating scales were completed by parents and teachers at prestudy and poststudy periods. Student's t tests were used to determine improvements of Vanderbilt scores between the groups.
RESULTS: Among 116 children who participated in this study, 44.8% (52/116) met the criteria for iron deficiency. Of the total 52 participants with iron deficiency, 26 were randomized to the ferrous group and 26 to the placebo group. Most participants in each group had been prescribed short-acting methylphenidate twice daily in the morning and at noon. After a 12-week study period, total parents' Vanderbilt ADHD symptom scores showed a significant improvement between the groups (mean decrement = -3.96 ± 6.79 vs 0 ± 6.54, p = 0.037). However, teachers' Vanderbilt ADHD symptom scores showed no difference between the groups.
CONCLUSION: Children with ADHD and iron deficiency being on methylphenidate and iron supplementation had shown improvement of ADHD symptoms that were reported by parents

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J Dev Behav Pediatr. 2022 Feb;43:e87-e93.
PSYCHOPATHOLOGY AND ADAPTIVE FUNCTIONING IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH NOONAN SYNDROME.
Davico C, Borgogno M, Campagna F, et al.

OBJECTIVE: The objective of this study was to examine psychopathology and its impact on adaptive functioning in a sample of patients affected by Noonan syndrome (NS), a genetically heterogeneous condition with systemic manifestations.
METHOD: Forty-two subjects affected by NS (23 males and 19 females), aged 5 to 21 years (mean 12.6 Â± SD 5.1), were assessed for nonverbal cognitive abilities, with dimensional measures of psychopathology, adaptive functioning, and family quality of life.
RESULTS: The nonverbal intelligence quotient (IQ) mean was 99.4 ± SD 22.2, with 3 subjects (8%, 95% confidence interval [CI], 1.6%-20.9%) showing cognitive impairment (IQ<70). The Parent Child Behavior Checklist (CBCL) total psychopathology score was in the clinical range in 10% of sample and borderline in another 10%. On the Conners' Parent Rating Scales, scores suggestive of attention-deficit/hyperactivity disorder (ADHD) were in the clinical range in 20%. On the autism quotient, autism spectrum disorder symptoms were reported in 10%. Higher scores on the Adaptive Behavioral Assessment System-Second Edition and on the World Health Organization Quality of Life (26 items) were associated with lower problems on the CBCL (r = -0.63, 95% CI, -0.78 to -0.40 and r = -0.48, 95% CI, -0.69 to -0.20, respectively).
CONCLUSION: Psychopathology was common in patients with NS and negatively correlated with global functioning and family quality of life. Treatable psychopathology, such as ADHD, may constitute a treatment target for improving adaptive functioning

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J Dev Orig Health Dis. 2021 Oct;12:694-703.
ASSOCIATION BETWEEN GESTATIONAL CANNABIS EXPOSURE AND MATERNAL, PERINATAL, PLACENTAL, AND CHILDHOOD OUTCOMES.
Ayonrinde OT, Ayonrinde OA, Van RD, et al.
Globally, the availability and formulations for the administration of cannabis are changing with decriminalization or legalization of recreational use in some jurisdictions, and the prescription of cannabis also occurring. These changes are likely to affect the prevalence of use, including by women of childbearing age. The effects of in utero and infant alcohol and tobacco exposure are well-documented, but the outcomes of cannabis exposure are less certain. The content of delta-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis has progressively increased over several decades. This review explores the limited knowledge surrounding the epidemiology of gestational and postnatal cannabis exposure and implications for the mother-placenta-fetus/neonate triad. We examine cannabis' effects from antenatal and lactation exposure on (a) pregnancy and perinatal outcomes, (b) placental health, and (c) longer term cardiometabolic and neurodevelopmental risks and outcomes. Though definitive outcomes are lacking, gestational cannabis has been associated with increased risk of other substance use during pregnancy; impaired placental blood flow; increased risk of small for gestational age births; and associated complications. Childhood and adolescent outcomes are sparsely assessed, with suggested outcomes including increased risk of depression and attention-deficit hyperactivity disorder. Cardiometabolic implications of gestational cannabis use may include maternal fatty liver, obesity, insulin resistance, and increased risk of gestational diabetes mellitus (GDM), with potential consequences for the fetus. Clinical implications for pediatric practice were explored in a bid to understand any potential risk or impact on child health and development

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J Gastroenterol Hepatol. 2021 Aug;36:2165-70.
EPIDEMIOLOGY AND RISK OF PSYCHIATRIC DISORDERS AMONG PATIENTS WITH CELIAC DISEASE: A POPULATION-BASED NATIONAL STUDY.
Alkhayyat M, Qapaja T, Aggarwal M, et al.
BACKGROUND AND AIM: Celiac disease (CD) is a chronic disorder resulting from an immune reaction to gluten in genetically predisposed individuals. Although several studies have linked CD to psychiatric diseases, there are limited data on this topic. Using a large database, we sought to describe the epidemiology of several psychiatric disorders in CD.
METHODS: We queried a multicenter database (Explorys Inc), an aggregate of electronic health record data from 26 major integrated healthcare systems from 2016 to 2020 consisting of 360 hospitals in the USA. A

cohort of patients with a Systematized Nomenclature Of Medicine - Clinical Terms diagnosis of CD was identified. Multivariate analysis was performed using Statistical Package for Social Sciences version 25.
RESULTS: Of the 37 465 810 patients in the database between 2016 and 2020, there were 112Â 340 (0.30%) individuals with CD. When compared with patients with no history of CD, patients with CD were more likely to have a history of anxiety (odds ratio [OR]: 1.385; 95% confidence interval [CI]: 1.364-1.407), depression (OR: 1.918; 95% CI: 1.888-1.947), bipolar (OR: 1.321; 95% CI: 1.289-1.354), attention-deficit hyperactivity disorder (OR: 1.753; 95% CI: 1.714-1.792), eating disorder (OR: 15.84; 95% CI: 15.533-16.154), and childhood autistic disorder (OR: 4.858; 95% CI: 3.626-6.508). Patients with CD and psychiatric conditions were more likely to be smokers, with history of alcohol and substance abuse as well as a history of personality disorder.
CONCLUSIONS: In this large database, patients with CD are at increased risk of having multiple psychiatric diseases including anxiety, depression, bipolar, attention-deficit hyperactivity disorder, eating disorder, and childhood autism. Individual care and referral to psychiatry when appropriate are warranted while taking care of this group of patients

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J Health Psychol. 2022 Jan;27:36-46.

ACCEPTABILITY OF TRANSCRANIAL DIRECT CURRENT STIMULATION IN CHILDREN AND ADOLESCENTS WITH ADHD: THE POINT OF VIEW OF PARENTS.

Buchanan DM, D'Angiulli A, Samson A, et al.

Transcranial direct current stimulation (tDCS) is a novel treatment option for attention deficit hyperactivity disorder. To facilitate translation into clinical practice, we interviewed parents of children who have experienced experimental tDCS. A grounded theory approach using open, axial, and selective coding provided seven emergent themes for acceptability: tDCS provides hope for parents, safety tolerability and side effects of tDCS versus medication, burden of treatment, education and trust with care providers, cost and coverage, unestablished tDCS efficacy versus established medication effectiveness, perceived compliance of tDCS versus medication. Results suggest tDCS is acceptable but depends on evidence of effectiveness and regular availability

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J Korean Med Sci. 2021 Oct;36:e260.

COGNITIVE AND BEHAVIORAL OUTCOMES OF SCHOOL-AGED CHILDREN BORN EXTREMELY PRETERM: A KOREAN SINGLE-CENTER STUDY WITH LONG-TERM FOLLOW-UP.

Kim ES, Kim EK, Kim SY, et al.

BACKGROUND: School-aged children born very preterm have been suggested to have worse cognitive and behavioral outcomes than children born full-term. Executive function (EF) is a higher level of cognitive function related to academic achievement. The present study aimed to evaluate the cognitive (including EF) and behavioral outcomes of Korean children born extremely preterm (EP) and to analyze any biological or socioeconomic risk factors for poor cognitive outcomes in this population.
METHODS: A total of 71 infants weighing < 1,000 g at birth or born before 30 weeks of gestation (EP group) who were admitted to the neonatal intensive care unit from 2008 to 2009 were included in this study and compared with 40 term-birth controls. The Korean Wechsler Intelligence Scale for Children-Fourth Edition, Advanced Test of Attention (ATA), Stroop test, Children's Color Trails Test (CCTT), and Wisconsin Card Sorting Test (WCST) were used. Additionally, the Korean Child Behavior Checklist (K-CBCL) and Korean ADHD Rating Scale (K-ARS) were completed. Perinatal and demographic data were collected and analyzed.
RESULTS: The mean full-scale intelligence quotient (FSIQ) score in the EP group was significantly lower than that of the term control group (89.1 ± 18.3 vs. 107.1 ± 12.7; P < 0.001). In the EP group, 26 (37%) children had an FSIQ score below 85, compared to only one child (3%) in the control group. Furthermore, the EP group showed significantly worse EF test results (ATA, Stroop test, CCTT, WCST). Except for the higher social immaturity subscore in the EP group, the K-CBCL and K-ARS scores were not different between the two groups. EP children who received laser treatment for retinopathy of prematurity (ROP) had an 8.8-fold increased risk of a low FSIQ score, and a 1-point increase in the discharge weight Z-score decreased the risk of a low FSIQ score by approximately half in this EP cohort.

CONCLUSION: This is the first Korean study to investigate the cognitive and behavioral outcomes of school-aged children born EP. In the study cohort, EP children exhibited significantly lower FSIQ scores and EF than their full-term peers, and 37% of them had cognitive problems. Nonetheless, except for social immaturity, the behavioral problems were not different in EP children. Severe ROP and low discharge weight Z-score were identified as independent risk factors for low FSIQ score after adjusting for birth weight

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J Neural Eng. 2022 Feb;19.

NEUROLOGICAL STATE CHANGES INDICATIVE OF ADHD IN CHILDREN LEARNED VIA EEG-BASED LSTM NETWORKS.

Chang Y, Stevenson C, Chen IC, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that pervasively interferes with the lives of individuals starting in childhood.

Objective. To address the subjectivity of current diagnostic approaches, many studies have been dedicated to efforts to identify the differences between ADHD and neurotypical (NT) individuals using electroencephalography (EEG) and continuous performance tests (CPT).

Approach. In this study, we proposed EEG-based long short-term memory (LSTM) networks that utilize deep learning techniques with learning the cognitive state transition to discriminate between ADHD and NT children via EEG signal processing. A total of 30 neurotypical children and 30 ADHD children participated in CPT tests while being monitored with EEG. Several architectures of deep and machine learning were applied to three EEG data segments including resting state, cognitive execution, and a period containing a fusion of those.

Main results. The experimental results indicated that EEG-based LSTM networks produced the best performance with an average accuracy of 90.50 Â± 0.81% in comparison with the deep neural networks, the convolutional neural networks, and the support vector machines with learning the cognitive state transition of EEG data. Novel observations of individual neural markers showed that the beta power activity of the O1 and O2 sites contributed the most to the classifications, subjects exhibited decreased beta power in the ADHD group, and had larger decreases during cognitive execution.

Significance. These findings showed that the proposed EEG-based LSTM networks are capable of extracting the varied temporal characteristics of high-resolution electrophysiological signals to differentiate between ADHD and NT children, and brought a new insight to facilitate the diagnosis of ADHD. The registration numbers of the institutional review boards are 16MMHIS021 and EC1070401-F

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J Nutr. 2021 Oct;151:3045-52.

NEURODEVELOPMENTAL OUTCOMES IN INFANTS FED WITH SOY FORMULA: A RETROSPECTIVE, NATIONAL POPULATION-BASED OBSERVATIONAL COHORT STUDY.

Ha EK, Lee SW, Kim JH, et al.

BACKGROUND: Soy-based infant formulas are increasingly popular, but data regarding their effects on neurodevelopmental outcomes during early childhood is scanty.

OBJECTIVE: This study investigated the effect of consuming soy-based infant formula at 9-12 mo after birth on the subsequent development of epilepsy, neurodevelopmental disorders, and developmental status.

METHODS: This nationwide retrospective administrative study used health screening examinations and linked insurance claims data of children born in Korea during 2008 and 2009. Infants who received soy formula were compared with those who received cow's milk formula using propensity score matching that considered birth history, economic status, clinical conditions, and drug prescription records. Exposure was defined as soy formula feeding determined from questionnaires completed by the parents when children were 9-12 mo old. Outcomes were epilepsy, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and developmental status. Children were followed until 31 December, 2017.

RESULTS: A total of 153,841 eligible participants were enrolled; 11,535 (7.5%) children received soy formula, while 142,864 (92.5%) received cow's milk formula. The incidence rate of epilepsy during the follow-up period was 29.8 per 100,000 person-years (95% CI: 19.48, 41.65) in the soy formula group and 22.6 per 100,000 person-years (95% CI: 31.97, 59.07) in the cow's milk formula group, with no significant difference (aHR: 1.318; 95% CI: 0.825, 2.106). The 2 groups also had no difference based on prespecified analysis

using different definitions of epilepsy. Likewise, no significant associations of soy formula with ADHD (aHR: 1.26; 95% CI: 1.00, 1.60) or ASD (aHR: 0.99; 95% CI: 0.54, 1.83), or delays of developmental stages were observed.
CONCLUSIONS: Feeding with soy formula rather than cow's milk formula had no apparent association with increased risks of epilepsy, ADHD, ASD, and developmental status, according to this cohort composed of a general pediatric population

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J Nutr. 2021 Nov;151:3483-94.
OMEGA-3 FATTY ACID DIETARY SUPPLEMENTS CONSUMED DURING PREGNANCY AND LACTATION AND CHILD NEURODEVELOPMENT: A SYSTEMATIC REVIEW.
Nevins JEH, Donovan SM, Snetselaar L, et al.
BACKGROUND: Maternal nutrition during pregnancy and lactation has profound effects on the development and lifelong health of the child. Long-chain PUFAs are particularly important for myelination and the development of vision during the perinatal period.
OBJECTIVES: We conducted a systematic review to examine the relationship between supplementation with omega-3 fatty acids during pregnancy and/or lactation and neurodevelopment in children, to inform the Scientific Report of the 2020 Dietary Guidelines Advisory Committee.
METHODS: We identified articles on omega-3 fatty acid supplementation in pregnant and lactating women that included measures of neurodevelopment in their children (0-18 y) by searching PubMed, CENTRAL, Embase, and CINAHL Plus. After dual screening articles for inclusion, we qualitatively synthesized and graded the strength of evidence using pre-established criteria for assessing risk of bias, consistency, directness, precision, and generalizability.
RESULTS: We included 33 articles from 15 randomized controlled trials (RCTs) and 1 prospective cohort study. Of the 8 RCTs that delivered omega-3 fatty acid dietary supplements during pregnancy alone (200-2200 mg/d DHA and 0-1100 mg/d EPA for approximately 20 wk), 5 studies reported 1 finding that supplementation improved measures of cognitive development in the infant or child by 6%-11% ($P < 0.05$), but all 8 studies also reported 1 nonsignificant ($P > 0.05$) result. There was inconsistent or insufficient evidence for other outcomes (language, social-emotional, physical, motor, or visual development; academic performance; risks of attention deficit disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, or depression) and for supplementation during lactation or both pregnancy and lactation. Populations with a lower socioeconomic status and adolescents were underrepresented and studies lacked racial and ethnic diversity.
CONCLUSIONS: Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. There was insufficient evidence to evaluate the effects of omega-3 fatty acid supplementation during pregnancy and/or lactation on other developmental outcomes

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J Nutr. 2022 Feb;152:484-91.
CHILDREN'S DIET AT 2 YEARS AND TRAJECTORIES OF HYPERACTIVITY-INATTENTION SYMPTOMS AND CONDUCT PROBLEMS BETWEEN 3 AND 8 YEARS: THE EDEN COHORT.
Iv N, Herbein M, Heude B, et al.
BACKGROUND: Although the role of diet is increasingly acknowledged in psychiatry, data are still scarce regarding its early impact on the most significant behavioral disorders of childhood (i.e., hyperactivity-inattention and conduct problems).
OBJECTIVES: The objective of this study was to explore the relation between children's dietary patterns at 2 years and developmental trajectories of hyperactivity-inattention and conduct problems between 3 and 8 years.
METHODS: We recruited 1432 mother-child dyads from the French EDEN (etude sur les d©terminants pr©- et postnatals du d©veloppement et de la sant© de l'enfant) mother-child cohort to conduct the analyses. Three dietary patterns, labeled guidelines, processed and fast foods, and baby foods, were identified using an FFQ in children aged 2 years in a previous study. The Strengths and Difficulties Questionnaire was used to assess hyperactivity-inattention and conduct problems at 3, 5, and 8 years of age and build related

trajectories from 3 to 8 years. The relation between children's dietary patterns at 2 years and the worst developmental trajectories of hyperactivity-inattention and conduct problems were determined with multivariable logistic regressions adjusted for potential socioeconomic, maternal, and child confounders.
RESULTS: The score on the guidelines dietary pattern was negatively associated with the risk of hyperactivity-inattention problems (OR: 0.75; 95% CI: 0.60-0.94), contrary to adherence to the baby foods dietary pattern (OR: 1.41; 95% CI: 1.16-1.71).
CONCLUSIONS: Distinct patterns of children's diet at 2 years were predictive of developmental trajectories of hyperactivity-inattention problems between 3 and 8 years. These results highlight the relevance of conducting further studies to clarify the mechanisms involved

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J Pediatr. 2022 Feb;241:147-53.
BEHAVIORAL HEALTH DIAGNOSES IN YOUTH WITH GENDER DYSPHORIA COMPARED WITH CONTROLS: A PEDSNET STUDY.
Nunes-Moreno M, Buchanan C, Cole FS, et al.
OBJECTIVE: To assess the odds of a psychiatric or neurodevelopmental diagnosis among youth with a diagnosis of gender dysphoria compared with matched controls in a large electronic health record dataset from 6 pediatric health systems, PEDSnet. We hypothesized that youth with gender dysphoria would have higher odds of having psychiatric and neurodevelopmental diagnoses than controls.
STUDY DESIGN: All youth with a diagnosis of gender dysphoria (n = 4173 age at last visit 16.2 ± 3.4) and at least 1 outpatient encounter were extracted from the PEDSnet database and propensity-score matched on 8 variables to controls without gender dysphoria (n = 16 648, age at last visit 16.2 ± 4.8) using multivariable logistic regression. TheÂ odds of having psychiatric and neurodevelopmental diagnoses were examined using generalized estimating equations.
RESULTS: Youth with gender dysphoria had higher odds of psychiatric (OR 4.0 [95% CI 3.8, 4.3] P < .0001) and neurodevelopmental diagnoses (1.9 [1.7, 2.0], P < .0001). Youth with gender dysphoria were more likely to have a diagnosis across all psychiatric disorder subcategories, with particularly high odds of mood disorder (7.3 [6.8, 7.9], P < .0001) and anxiety (5.5 [5.1, 5.9], P < .0001). Youth with gender dysphoria had a greater odds of autism spectrum disorder (2.6, [2.2, 3.0], P < .0001).
CONCLUSIONS: Youth with gender dysphoria at large pediatric health systems have greater odds of psychiatric and several neurodevelopmental diagnoses compared with youth without gender dysphoria. Further studies are needed to evaluate changes in mental health over time with access to gender affirming care

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J Psychiatr Pract. 2021 Nov;27:439-47.
HOW ARE ATTENTION-DEFICIT HYPERACTIVITY AND INTERNET GAMING DISORDERS RELATED IN CHILDREN AND YOUTH?
Muzwagi AB, Motiwala FB, Manikkara G, et al.
OBJECTIVES: This review addresses important practical questions facing clinicians regarding internet gaming disorder (IGD) and attention-deficit/hyperactivity disorder (ADHD) in children and youth (C-Y). The authors investigated data concerning the risk that C-Y who have ADHD will develop IGD, whether effective treatment of ADHD positively influences the course of IGD in C-Y who have both, and other findings that might be of benefit to clinicians who treat C-Y with these conditions.
METHODS: We conducted a literature review using 4 databases: PubMed, Scopus, PsychInfo, and Embase.
RESULTS: C-Y with ADHD are at greater risk for developing IGD than those without ADHD. A close association exists between the severity of ADHD symptoms and the severity of IGD. It is unknown what proportion of C-Y with ADHD will develop IGD during their developmental trajectory; however, C-Y with IGD are at risk for developing ADHD, and ADHD can also increase the vulnerability of C-Y to IGD. Adolescents with ADHD and IGD have greater deficits in social skills than those with ADHD but no IGD. Lower parental occupational and socioeconomic status and poor family relationships are associated with more severe IGD symptoms. Atomoxetine and methylphenidate are equally effective in alleviating IGD symptoms comorbid with ADHD.

CONCLUSIONS: C-Y with ADHD are at increased risk for developing IGD compared with C-Y without ADHD, but it has not been determined at what developmental stage IGD is likely to emerge. Since IGD and ADHD are strongly associated, it is imperative to consider ADHD as a significant risk factor for IGD and vice versa, which can help psychiatrists be alert for early signs of IGD and manage them accordingly

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J Psychiatr Res. 2022 Mar;147:313-23.

MEDIA USE AND EMOTIONAL DISTRESS UNDER COVID-19 LOCKDOWN IN A CLINICAL SAMPLE REFERRED FOR INTERNALIZING DISORDERS: A SWISS ADOLESCENTS' PERSPECTIVE.

Werling AM, Walitza S, Gerstenberg M, et al.

The COVID-19 outbreak has profoundly affected adolescents' life. Adolescents with pre-existing psychiatric disorders have been at particular risk of increased mental health problems and problematic media use. 178 patients, aged 12-18 years, referred before the COVID-19 outbreak to child and adolescent psychiatry, participated in an anonymous online survey on the impact of the lockdown on media use and mental well-being. The survey was conducted approximately one month after the first easing of restrictions following a six-week lockdown in Switzerland. Based on self-report, half of the patients had been diagnosed with internalizing disorders (ID; depression or anxiety disorder) and the other half with other disorders (non-ID, e.g. ADHD, autistic spectrum disorder). Patients with ID reported higher emotional distress during the lockdown, and a larger number of patients with ID indicated a deterioration of pre-existing symptoms compared to non-ID patients. Although more patients with ID than with non-ID indicated spending a large amount of time on social media, social media time per day in hours was not significantly higher in ID. Patients with ID indicated a higher impact of media use on well-being and mood in everyday life during the lockdown. Social media time was higher in worsened than in improved non-ID patients, while the opposite was found in ID patients, indicating a possible protective effect of media use at least for some ID patients. The results confirm positive as well as negative associations between mental health, emotional well-being and media use for adolescents with ID during the lockdown

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JAMA Netw Open. 2022 Jan;5:e2143947.

ANALYSIS OF NEURODEVELOPMENTAL DISORDERS IN OFFSPRING OF MOTHERS WITH EATING DISORDERS IN SWEDEN.

Mantel A, et al.

IMPORTANCE: Despite indices of impaired neurodevelopment in children of mothers with eating disorders, it remains unclear whether these children are at increased risk of developing neuropsychiatric diseases.

OBJECTIVE: To evaluate the association between maternal eating disorders, whether preexisting or ongoing during pregnancy, and offspring neuropsychiatric disease risk.

DESIGN, SETTING AND PARTICIPANTS: This population-based prospective cohort study used the Swedish Medical Birth Registry and identified singleton births registered between from January 1, 1990, and December 31, 2012. Children of exposed mothers with eating disorders were matched with comparator children of mothers without diagnoses of eating disorders. To adjust for unmeasured shared familial factors, a cluster of exposed children with full maternal cousin comparators was identified. Follow-up was completed on December 31, 2017. Data were analyzed from August 31, 2020, to April 30, 2021.

EXPOSURES: Maternal eating disorder diagnosis.

MAIN OUTCOMES AND MEASURES: All children were followed up from 1 year of age for autism spectrum disorder (ASD) and from 3 years of age for attention-deficit/hyperactivity disorder (ADHD). The relative risk of ASD and ADHD was assessed among exposed children, stratified by eating disorder subtype and ongoing vs previous disease, adjusted for potential confounders, including parental socioeconomic status and comorbidities. RESULTS: Among the 52 878 children included in the analysis, maternal eating disorder exposure (n = 8813) was associated with an increased risk of ADHD (hazard ratio [HR] for anorexia nervosa, 1.42 [95% CI, 1.23-1.63]; HR for bulimia nervosa, 1.91 [95% CI, 1.43-2.54]; and HR for unspecified eating disorder, 2.00 [95% CI, 1.72-2.32]) and ASD (HR for anorexia nervosa, 2.04 [95% CI, 1.58-2.63]; HR for bulimia nervosa, 2.70 [95% CI, 1.68-4.32]; and HR for unspecified eating disorder, 1.95 [95% CI, 1.49-2.54]). After adjustment for parental confounders, the risk of ADHD remained significantly increased, whereas the

risk of ASD in children to mothers with bulimia nervosa was no longer significant. Ongoing anorexia nervosa was associated with a significantly higher risk of ADHD (HR, 2.52 [95% CI, 1.86-3.42]) and ASD (HR, 3.98 [95% CI, 2.49-6.27]) compared with previous disease (HRs, 1.26 [95% CI, 1.06-1.48] and 1.81 [95% CI, 1.38-2.38], respectively). Results based on the family cluster were similar to those of the main analysis for maternal exposure to anorexia nervosa and bulimia nervosa.
CONCLUSIONS AND RELEVANCE: These findings suggest that children born to mothers with eating disorders, in particular disorders that were active during pregnancy, were at increased risk of developing ADHD and ASD. The association could not be fully explained by parental psychiatric comorbidities, and among children of mothers with anorexia nervosa and bulimia nervosa, it could not be explained by unmeasured familial confounding

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JAMA Netw Open. 2022 Jan;5:e2145719.
ASSOCIATION OF PREECLAMPSIA AND PERINATAL COMPLICATIONS WITH OFFSPRING NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS.
Kong L, Chen X, Liang Y, et al.
IMPORTANCE: Maternal preeclampsia has been reported to increase the risk of autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability in offspring. However, the association between maternal preeclampsia combined with perinatal complications and neurodevelopmental and psychiatric disorders in offspring is less well documented.
OBJECTIVE: To examine the association of maternal preeclampsia, separately and together with perinatal complications, with neurodevelopmental and psychiatric disorders in offspring.
DESIGN, SETTING, AND PARTICIPANTS: This population-based cohort study used data from nationwide registries in Finland to assess all singleton live births (N=1 012 723) between January 1, 1996, and December 31, 2014. Offspring were followed up until December 31, 2018 (when the oldest reached age 22 years). Exclusion criteria were maternal inpatient psychiatric diagnoses and pregestational diabetes. The study and data analysis were conducted from May 1, 2020, to June 1, 2021.
EXPOSURES: Preeclampsia and perinatal complications (delivery earlier than 34 weeks' gestation and/or small for gestational age).
MAIN OUTCOMES AND MEASURES: The primary outcomes were neurodevelopmental and psychiatric diagnoses and dispensation of psychotropic drugs among offspring until December 31, 2018. Cox proportional hazards regression analyses were performed to assess the associations.
RESULTS: Of 1 012 723 singleton live births (51.1% boys; mean [SD] maternal age at birth, 30.0 [5.4] years; specific data on race and ethnicity were not available in the data set), 21 010 children (2.1%) were exposed to preeclampsia alone, 33 625 children (3.3%) were exposed to perinatal complications alone, and 4891 children (0.5%) were exposed to both preeclampsia and perinatal complications. A total of 93 281 children (9.2%) were diagnosed with a neurodevelopmental or psychiatric disorder. Offspring exposed to both preeclampsia and perinatal complications had an increased risk of any neurodevelopmental or psychiatric disorder after adjusting for potential confounding (adjusted hazard ratio [aHR], 2.11; 95% CI, 1.96-2.26) compared with those not exposed to either preeclampsia or perinatal complications; this risk was higher than exposure to either preeclampsia alone (aHR, 1.18; 95% CI, 1.12-1.23) or perinatal complications alone (aHR, 1.77; 95% CI, 1.72-1.82). Sibling pair analyses did not detect any increase in the risk of neurodevelopmental or psychiatric disorders after exposure to preeclampsia alone, but offspring exposed to both preeclampsia and perinatal complications had increased risks of intellectual disabilities (aHR, 3.24; 95% CI, 1.05-10.06), specific developmental disorders (aHR, 3.56; 95% CI, 2.35-5.41), ADHD and conduct disorders (aHR, 2.42; 95% CI, 1.09-5.39), and other behavioral and emotional disorders (aHR, 2.45; 95% CI, 1.17-5.13). The risk estimates for specific developmental disorders (aHR, 2.82; 95% CI, 2.60-3.05) and ADHD and conduct disorders (aHR, 1.88; 95% CI, 1.65-2.14) were higher among offspring exposed to both preeclampsia and perinatal complications compared with those exposed to perinatal complications alone (aHR, 2.26 [95% CI, 2.18-2.33] and 1.60 [95% CI, 1.52-1.68], respectively).
CONCLUSIONS AND RELEVANCE: In this study, exposure to both maternal preeclampsia and perinatal complications was associated with intellectual disabilities, specific developmental disorders, ADHD and conduct disorders, and other behavioral and emotional disorders in offspring. For specific developmental

disorders and ADHD and conduct disorders, the risk estimates were higher among offspring exposed to both preeclampsia and perinatal complications compared with those exposed to perinatal complications only

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JAMA Netw Open. 2022 Feb;5:e2144934.

PREVALENCE OF MENTAL HEALTH DISORDERS AMONG IMMIGRANT, REFUGEE, AND NONIMMIGRANT CHILDREN AND YOUTH IN BRITISH COLUMBIA, CANADA.

Gadermann AM, et al.

IMPORTANCE: There remains limited understanding of population-level patterns of mental disorder prevalence for first- and second-generation immigrant and refugee children and youth and how such patterns may vary across mental disorders.

OBJECTIVE: To examine the diagnostic prevalence of conduct, attention-deficit/hyperactivity disorder (ADHD), and mood/anxiety disorders in immigrant, refugee, and nonimmigrant children and youth in British Columbia, Canada.

DESIGN, SETTING, AND PARTICIPANTS: This retrospective, population-level cohort study examined linked health administrative records of children and youth in British Columbia (birth to age 19 years) spanning 2 decades (1996-2016). Physician billings, hospitalizations, and drug dispensations were linked to immigration records to estimate time-in-British Columbia-adjusted prevalence of mental disorder diagnosis among children and youth from immigrant or refugee backgrounds compared with those from nonimmigrant backgrounds. Analyses were conducted from August 2020 to November 2021.

MAIN OUTCOMES AND MEASURES: The diagnostic prevalence of conduct, ADHD, and mood/anxiety disorders were the main outcomes. Results were stratified by migration category (immigrant, refugee, nonimmigrant), generation status (first- and second-generation), age, and sex. RESULTS: A total of 470-464 children and youth in British Columbia were included in the study (227-217 [48.3%] female). Nonimmigrant children and youth represented 65.5% of the total study population (307-902 individuals). Among those who migrated, 142-011 (87.8%) were first- or second-generation immigrants, and 19-686 (12.2%) were first- or second-generation refugees. Diagnostic prevalence of mental disorders varied by migration category, generation status, age, and sex. Children and youth from immigrant and refugee backgrounds (both first- and second-generation), compared with nonimmigrant youth, generally had a lower prevalence of conduct disorder (eg, age 6-12 years: first-generation immigrant, 2.72% [95% CI, 2.56%-2.90%] vs nonimmigrant, 7.03% [95% CI, 6.93%-7.13%]), ADHD (eg, age 6-12 years: first-generation immigrant, 4.30% [95% CI, 4.10%-4.51%] vs nonimmigrant, 9.20% [95% CI, 9.08%-9.31%]), and mood/anxiety disorders (eg, age 13-19 years: first-generation immigrant, 11.07% [95% CI, 10.80%-11.36%] vs nonimmigrant, 24.54% [95% CI, 24.34%-24.76%]). Among immigrant children and youth, second-generation children and youth generally showed higher prevalence of conduct, ADHD, and mood/anxiety disorders than first-generation children and youth (eg, ADHD among second-generation immigrants aged 6-12 years, 5.94% [95% CI, 5.75%-6.14%]; among first-generation immigrants aged 6-12 years, 4.30% [95% CI, 4.10%-4.51%]). Second-generation refugee children had the highest diagnostic prevalence estimates for mood/anxiety in the 3-to-5-year age range relative to first- and second-generation immigrant and nonimmigrant children (eg, second-generation refugee, 2.58% [95% CI, 2.27%-2.94%] vs second-generation immigrant, 1.78% [95% CI, 1.67%-1.89%]). Mental disorder diagnoses also varied by age and sex within immigrant, refugee, and nonimmigrant groups.

CONCLUSIONS AND RELEVANCE: These findings show differences in diagnostic mental disorder prevalence among first- and second-generation immigrant and refugee children and youth relative to nonimmigrant children and youth. Further investigation is required into how cultural differences and barriers in accessing health services may be contributing to these differences

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JAMA Netw Open. 2022 Feb;5:e2148585.

ASSOCIATION OF GENOME-WIDE POLYGENIC SCORES FOR MULTIPLE PSYCHIATRIC AND COMMON TRAITS IN PREADOLESCENT YOUTHS AT RISK OF SUICIDE.

Joo YY, Moon SY, Wang HH, et al.

IMPORTANCE: Suicide is the second leading cause of death among youths worldwide, but no available means exist to identify the risk of suicide in this population.

OBJECTIVE: To assess whether genome-wide polygenic scores for psychiatric and common traits are associated with the risk of suicide among preadolescent children and to investigate whether and to what extent the interaction between early life stress (a major environmental risk factor) and polygenic factors is associated with suicidal thoughts and behaviors among youths.

DESIGN, SETTING, AND PARTICIPANTS: This cohort study analyzed the genotype-phenotype data of 11 869 preadolescent children aged 9 to 10 years from the Adolescent Brain and Cognitive Development study. Data were collected from September 1, 2016, to October 21, 2018, and analyzed from August 1, 2020, to January 3, 2021. Using machine learning approaches, genome-wide polygenic scores of 24 complex traits were estimated to investigate their phenome-wide associations and utility for assessing risk of suicidal thoughts and behaviors (suicidal ideation [active, passive, and overall] and suicide attempt).

MAIN OUTCOMES AND MEASURES: Genome-wide polygenic scores were used to measure 24 traits, including psychiatric disorders, cognitive capacity, and personality and psychological characteristics. The Child Behavior Checklist was used to measure early life stress, and the Family Environment Scale was used to assess family environment. Suicidal ideation and suicide attempts were derived from the computerized version of the Kiddie Schedule for Affective Disorders and Schizophrenia.

RESULTS: Among 11 869 preadolescent children in the US, complete data for phenotypic outcomes, genotypes, and covariates were available for 7140 participants in the multiethnic cohort (mean [SD] age, 9.9 [0.6] years; 3588 girls [50.3%]), including 925 participants with suicidal ideation and 63 participants with suicide attempts. Among those 7140 participants, 729 had African ancestry (self-reported race or ethnicity: 569 Black, 71 Hispanic, and 89 other), 276 had admixed American ancestry (self-reported race or ethnicity: 265 Hispanic, 3 White, and 8 other), 150 had East Asian ancestry (self-reported race or ethnicity: 67 Asian, 18 Hispanic, and 65 other), 5718 had European ancestry (self-reported race or ethnicity: 7 Asian, 39 Black, 1142 Hispanic, 3934 White, and 596 other), and 267 had other ancestries (self-reported race or ethnicity: 70 Asian, 13 Black, 126 Hispanic, 48 White, and 10 other). Three genome-wide polygenic scores were significantly associated (false discovery rate P<.05) with suicidal thoughts and behaviors among all participants: attention-deficit/hyperactivity disorder (odds ratio [OR], 1.12; 95% CI, 1.05-1.21; P=.001), schizophrenia (OR, 1.50; 95% CI, 1.17-1.93; P=.002), and general happiness (OR, 0.89; 95% CI, 0.83-0.96; P=.002). In the analysis including only children with European ancestry, 3 additional genome-wide polygenic scores with false discovery rate significance were associated with suicidal thoughts and behaviors: autism spectrum disorder (OR, 1.18; 95% CI, 1.06-1.31; P=.002), major depressive disorder (OR, 1.12; 95% CI, 1.04-1.21; P=.003), and posttraumatic stress disorder (OR, 1.12; 95% CI, 1.04-1.21; P=.004). A significant interaction between genome-wide polygenic scores and environment was found, with genetic risk factors for autism spectrum disorder and the level of early life stress associated with increases in the risk of overall suicidal ideation and overall suicidal thoughts and behaviors (OR, 1.20; 95% CI, 1.07-1.35; P=.002). A machine learning model using multitrait genome-wide polygenic scores and additional self-reported questionnaire data (Child Behavior Checklist and Family Environment Scale) produced a moderately accurate estimate of overall suicidal thoughts and behaviors (area under the receiver operating characteristic curve [AUROC], 0.77; 95% CI, 0.73-0.81; accuracy, 0.67) and suicidal ideation (AUROC, 0.76; 95% CI, 0.72-0.80; accuracy, 0.66) among children with European ancestry only. Among all children in the multiethnic cohort, the integrated model also outperformed the baseline model in estimating the risk of overall suicidal thoughts and behaviors (AUROC, 0.71; 95% CI, 0.67-0.75; accuracy, 0.68) and suicidal ideation (AUROC, 0.75; 95% CI, 0.71-0.78; accuracy, 0.67).

CONCLUSIONS AND RELEVANCE: In this cohort study of preadolescent youths in the US, higher genome-wide polygenic scores for psychiatric disorders, such as attention-deficit/hyperactivity disorder, autism spectrum disorder, posttraumatic stress disorder, and schizophrenia, were significantly associated with a greater risk of suicidal ideation and suicide attempt. The findings and quantitative models from this study may help to identify children with a high risk of suicide, potentially assisting with early screening, intervention, and prevention

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JAMA Pediatr. 2022;176:92-94.
RATE OF PEDIATRICIAN RECOMMENDATIONS FOR BEHAVIORAL TREATMENT FOR PRESCHOOLERS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DIAGNOSIS OR RELATED SYMPTOMS.
Bannett Y, Gardner RM, Posada J, et al.

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JAMA Psychiatry. 2022 Jan;79:59-69.
COMPARING COPY NUMBER VARIATIONS IN A DANISH CASE COHORT OF INDIVIDUALS WITH PSYCHIATRIC DISORDERS.
Calle Sn, X, Helenius D, Bybjerg-Grauholm J, et al.
IMPORTANCE: Although the association between several recurrent genomic copy number variants (CNVs) and mental disorders has been studied for more than a decade, unbiased, population-based estimates of the prevalence, disease risks and trajectories, fertility, and mortality to contrast chromosomal abnormalities and advance precision health care are lacking.
OBJECTIVE: To generate unbiased, population-based estimates of prevalence, disease risks and trajectories, fertility, and mortality of CNVs implicated in neuropsychiatric disorders.
DESIGN, SETTING, AND PARTICIPANTS: In a population-based case-cohort study, using the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) 2012 database, individuals born between May 1, 1981, and December 31, 2005, and followed up until December 31, 2012, were analyzed. All individuals (n=57-377) with attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), schizophrenia (SCZ), autism spectrum disorder (ASD), or bipolar disorder (BPD) were included, as well as 30â€¯000 individuals randomly drawn from the database. Data analysis was conducted from July 1, 2017, to September 7, 2021.
EXPOSURES: Copy number variants at 6 genomic loci (1q21.1, 15q11.2, 15q13.3, 16p11.2, 17p12, and 17q12).
MAIN OUTCOMES AND MEASURES: Population-unbiased hazard ratio (HR) and survival estimates of CNV associations with the 5 ascertained psychiatric disorders, epilepsy, intellectual disability, selected somatic disorders, fertility, and mortality. RESULTS: Participants' age ranged from 1 to 32 years (mean, 12.0 [IQR, 6.9] years) during follow-up, and 38 662 were male (52.3%). Copy number variants broadly associated with an increased risk of autism spectrum disorder and ADHD, whereas risk estimates of SCZ for most CNVs were lower than previously reported. Comparison with previous studies suggests that the lower risk estimates are associated with a higher CNV prevalence in the general population than in control samples of most case-control studies. Significant risk of major depressive disorder (HR, 5.8; 95% CI, 1.5-22.2) and sex-specific risk of bipolar disorder (HR, 17; 95% CI, 1.5-189.3, in men only) were noted for the 1q21.1 deletion. Although CNVs at 1q21.1 and 15q13.3 were associated with increased risk across most diagnoses, the 17p12 deletion consistently conferred less risk of psychiatric disorders (HR 0.4-0.8), although none of the estimates differed significantly from the general population. Trajectory analyses noted that, although diagnostic risk profiles differed across loci, they were similar for deletions and duplications within each locus. Sex-stratified analyses suggest that pathogenicity of many CNVs may be modulated by sex.
CONCLUSIONS AND RELEVANCE: The findings of this study suggest that the iPSYCH population case cohort reveals broad disease risk for some of the studied CNVs and narrower risk for others, in addition to sex differential liability. This finding on genomic risk variants at the level of a population may be important for health care planning and clinical decision making, and thus the advancement of precision health care

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JAMA Psychiatry. 2022 Feb;79:160-68.
ROLE OF POLYGENIC RISK SCORE IN THE FAMILIAL TRANSMISSION OF BIPOLAR DISORDER IN YOUTH.
Birmaher B, Hafeman D, Merranko J, et al.
IMPORTANCE: Establishing genetic contributions to the transmission of bipolar disorder (BD) from parents to offspring may inform the risk of developing this disorder and further serve to validate BD in youth.
OBJECTIVE: To evaluate the specific association of BD polygenic risk scores (PRSs) on the familial transmission and validity of pediatric BD.

DESIGN, SETTING, AND PARTICIPANTS: This community-based case-control longitudinal study (Pittsburgh Biological Offspring Study) included parents with BD I/II and their offspring and parents without BD (healthy or non-BD psychopathology) and their offspring. Participants were recruited between March 2001 and May 2007, and analysis took place from December 2020 to September 2021.
EXPOSURES: PRSs for BD, major depressive disorder, schizophrenia, and attention-deficit/hyperactivity disorder.
MAIN OUTCOMES AND MEASURES: Participants were prospectively evaluated using standardized interviews blind to parental diagnosis. DNA was extracted from saliva and genotyped. PRSs were constructed based on independent large-scale genome-wide association studies. RESULTS: A total of 156 parents with BD I/II and 180 parents without BD (mean [SD] age, 39.6 [7.9] years; 241 female [72%]) as well as 251 offspring of parents with BD and 158 offspring of parents without BD (mean [SD] age,10.4[4.7] years; 213 female [52%]) of European ancestry were analyzed. Participants were assessed a mean of 6.7 times during a mean (SD) of 13(3.4) years of follow-up (84% retention). More offspring of parents with BD developed BD (58 [23.1%] vs 8 [5.1%]; P<.001) and depression (126 [50.2%] vs 52 [32.9%]; P<.001) compared with offspring of parents without BD. BD PRS was higher in both parents and offspring with BD than parents and offspring without BD (parents: odds ratio,1.50; 95% CI, 1.19-1.89; P<.001; explained 4.8% of the phenotypic variance vs offspring: hazard ratio,1.34; 95% CI, 1.03-1.7; P=.02; explained 5.0% of the phenotypic variance). BD PRS did not differ across BD subtypes. In a model combining parental and offspring BD PRS, the parental BD PRS association with offspring BD was fully mediated by offspring BD PRS (hazard ratio,1.40; 95% CI, 1.05-1.86; P=.02). Parental BD had a stronger direct association than parental or offspring BD PRS with offspring BD risk (hazard ratio, 5.21; 95% CI, 1.86-14.62; P=.002), explaining 30% of the variance. Parental and offspring BD PRS explained 6% of the BD onset variance beyond parental diagnosis. There were no significant between-group differences in PRSs for major depressive disorder, schizophrenia, and attention-deficit/hyperactivity disorder in parents or offspring and they were not significantly associated with BD onset.
CONCLUSIONS AND RELEVANCE: The findings of this study add to the extant clinical validation of BD in youth. Parental BD and offspring BD PRS independently associated with the risk of BD in offspring. Although this is promising, the association of BD PRS was relatively small and cannot be used alone to determine BD risk until further developments occur

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Japanese Journal of Radiology. 2022.

BRAIN ABNORMALITIES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ASSESSED BY MULTI-DELAY ARTERIAL SPIN LABELING PERFUSION AND VOXEL-BASED MORPHOMETRY.

Gonchigsuren O, Harada M, Hisaoka S, et al.

Purpose: To obtain an understanding of the correlation between hemodynamic differences and morphological changes as well as potential sex differences in children with ADHD using multi-delay pseudo-continuous arterial spin labeling (pCASL) imaging and voxel-based morphometry (VBM), especially given that previous findings are limited for girls.
Materials and methods: We recruited 23 children with ADHD (mean age, 8.3 years; 19 boys; 4 girls) and 24 children without ADHD (mean age, 9.1 years; 13 boys; 11 girls) as controls. All participants underwent 3D multi-delay pCASL and T1-weighted imaging. The voxel-based statistical parameter mapping (SPM) method was used for group-wise comparisons.
Results: Compared with controls, children with ADHD exhibited decreased regional cerebral blood flow (rCBF) and gray matter volume (GMV) in the left middle frontal gyrus and left postcentral gyrus. Analysis by sex revealed reduced rCBF and GMV in the left lingual gyrus and left inferior occipital gyrus in boys with ADHD versus controls and increased rCBF and GMV in the left superior frontal gyrus in girls with ADHD.
Conclusion: Although our results are preliminary because of small sample sizes, several brain regions exhibit changes in both cerebral perfusion and GMV in the same direction in patients with ADHD, with boys with ADHD showing decreased activity and girls with ADHD displaying increased activity in the fronto-parietal cortices

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J Allergy Clin Immunol. 2022;149:AB121.

ALLERGY IN EARLY CHILDHOOD IS A RISK FACTOR FOR THE DEVELOPMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Nemet S, Asher I, Yoles I, et al.

Rationale: Previous studies reported controversial results regarding the association between allergic disorders and ADHD. We, therefore, investigated whether allergic disorders are risk factor for development of ADHD, in a large cohort of pediatric patients.

Methods: A retrospective study using the pediatric (0-18 years) database of Clalit Health services during the years (2000-2018). Diagnosis of all disorders was made by specialist physicians.

Results: 117,022 consecutive non-selective allergic children diagnosed with one or more allergic disorder (asthma, rhinitis,conjunctivitis, skin, food or drug allergy) and 116,968 non-allergic children were enrolled to our study. The mean follow-up period was 11-¦6 years. ADHD was diagnosed in 33008 children (14 % of the entire cohort) at a mean age of 8.5 -¦3.4 years. The presence of one or more allergic disorders in early childhood (mean age at allergic diagnosis 4.5-¦4.3 years) in boys as well as in girls, significantly increased the risk to develop ADHD (O.R 2.45, CI 2.39-2.51; P<0.0001). Significant high risk was observed for each allergic disorder which was studied separately. The risk increased significantly in children with several allergic comorbidities (up to O.R of 5 for children with 4 or more allergic disorders). In a multivariable analysis (adjusted for age at study entry, number of yearly visits and gender) the risk of allergic children to develop ADHD remained significantly higher.

Conclusions: Allergic disorders in early childhood significantly increase the risk to develop ADHD in later life. Caregivers should be aware of this risk in order to provide an early diagnosis and treatment

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J Autism Dev Disord. 2022.

EFFECTS OF PARENTAL INVOLVEMENT IN ROBOT-ASSISTED AUTISM THERAPY.

Amirova A, Rakhymbayeva N, Zhanatkyzy A, et al.

Parental involvement in traditional autism therapy is key to the effective treatment of children with ASD. Little is known about parental involvement in robot-assisted autism therapy (RAAT)ΓÇönovel therapeutic support for children with ASD. Our study investigates the effect of parental presence on multiple-session RAAT conducted with 16 children with ASD. They interacted with the social robot in the presence or absence of their parents. We measured children's socio-behavioral outcomes and conducted semi-structured interviews with parents. Parents did not necessarily affect the children's outcomes during the interventions. However, childrenΓ ÇÖs autism-related symptoms resulted in different socio-behavioral outcomes between sessions with and without parents. Most parents have reported positive changes in their children's behaviors when interacting with the robot

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Journal of Intellectual Disabilities. 2022.

EXPLORING NEEDS, BARRIERS, AND FACILITATORS FOR PROMOTING PHYSICAL ACTIVITY FOR CHILDREN WITH INTELLECTUAL DEVELOPMENTAL DISORDERS: A QUALITATIVE FOCUS GROUP STUDY.

Boman C, Bernhardsson S.

Background: Many children with intellectual developmental disorders are insufficiently physically active and do not reach recommendations for physical activity. Pediatric healthcare providers play a key role in addressing these children’s needs, including promoting interventions for physical activity.

Aim: To explore pediatric healthcare providers perceived needs, barriers, and facilitators for promoting physical activity for children with intellectual developmental disorders.

Methods: Semi-structured focus groups, analyzed using qualitative content analysis. Sixteen healthcare providers participated.

Results: Main findings are the importance of parental support and engagement, need for structure, and stakeholder collaboration to bridge the gap between pediatric organizations and external stakeholders.

Conclusion: The study highlights the need for developing and implementing strategies to promote physical activity for children with intellectual developmental disorders in pediatric health care, and for producing guidelines regarding physical activity interventions for this vulnerable group

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J Invest Med. 2022;70:651-52.

EFFECTS OF ONLINE DISTANCE LEARNING IN THE SETTING OF COVID-19 ON ACADEMIC PERFORMANCE AND BEHAVIORAL SYMPTOMS IN PEDIATRIC PATIENTS WITH ADHD.

Andrews C, Oliver K, Barratt M, et al.

Purpose of Study As COVID-19 cases rose in spring of 2020, schools faced the unprecedented challenge of providing safe and effective education during a global pandemic. With most institutions transitioning to remote instruction, teachers, students, and parents had to cope with changes that came with online distance learning (ODL). Children with learning or behavioral disabilities, such as ADHD, may have faced setbacks. The aim of the study was to examine parents' observations of their children with ADHD transitioning from in-person classroom instruction to ODL in regards to their academic performance and ADHD symptoms during the COVID-19 pandemic.

Methods Used The study utilized a cross-sectional design and recruited patients from a pediatric clinic in Houston, TX. Participants included parents of school-age children with an ADHD diagnosis. Parents were emailed a novel survey that utilized questions from the Vanderbilt Assessment Scale via Qualtrics in February 2021, and again in May 2021. Responses were anonymously collected until August 2021. Children using ODL during some or all of fall 2020 were included in the study. Parents reported semester grades for fall 2019 and fall 2020, and Vanderbilt Survey responses from the same time frame. Grades were measured on a 0-100 sliding scale, and behavioral responses were weighted (1-symptom decreased, 2-symptom did not change, 3-symptom increased). The study was IRB-approved.

Summary of Results Eighty-one parents of children in grades 1-12 with ADHD were identified and contacted to take part in the survey via email. Sixty of these parents received followup phone calls. Twenty-four started surveys. Twenty-one parent-child dyads met the study criteria, completed surveys, and were enrolled in the study. Semester averages in math, science, language arts/reading, and social studies appeared to all decrease from fall 2019 to fall 2020 (-3.5,-5.3,-2.8,-1.6), with the most prominent decrease in science (p=0.08). Overall, ADHD symptoms varied from fall 2019 to fall 2020. Parents reported increases in the following: lack of follow through with directions and failure to finish activities(62%), forgetfulness in daily activities(57%), and lack of attention to detail and making careless mistakes(57%). Most parents reported no change in relationships. Two-thirds of parents reported that their child did not benefit at all from ODL; however, 10% of parents said their child benefitted from less distraction, and 10% said their child preferred computer-based learning. Parents reported the following challenges with ODL: staying focused/organized and boredom(43%), lack of 1-on-1 instruction and ability to ask questions(33%), and social isolation(14%).

Conclusions During the COVID-19 pandemic, pediatric patients with ADHD seemed to perform worse academically in a virtual school setting compared to an in-person classroom. In this same population and time frame, ADHD behavioral symptoms appeared to either increase, especially those that were task-oriented, or remain unchanged

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J Neural Transm. 2022;129:353-60.

INCREASED HAIR CORTISOL IN MOTHERS OF CHILDREN WITH ADHD SYMPTOMS AND PSYCHOSOCIAL ADVERSITY BACKGROUND.

Cosan AS, et al.

Parents of children with attention deficit hyperactivity disorder (ADHD) have shown high perceived parenting stress. Hence, physiological adjustment processes, involving the hypothalamicΓÇôpituitaryΓÇôadrenal axis, seem possible. We hypothesized that (1) ADHD symptoms of the child predict an increase of maternal hair cortisol concentration (HCC), and (2) presence of psychosocial adversity amplifies the prediction. We analyzed a preschool-aged sample using a longitudinal design (T1, at the children's age of 4years; T2, 12 months later). 128 mothers and their children participated in the study. To determine HCC of the previous 3-ámonths, the first scalp-near 3-ácm hair segment was used. ADHD symptoms of the child were measured

using teacher- and parent-report questionnaires and a clinical interview with the mother. The T1 teacher-reported ADHD symptoms score of the child was significantly positively associated with the mother`s T1 and T2 HCC score. In families with high psychosocial adversity, the prediction of an increase in maternal HCC by the teacher-reported ADHD symptoms of child was significantly stronger than in low-adversity families. In presence of psychosocial family adversity, ADHD symptoms of the child predicted an increase in the mother's HCC. As a continuously high cortisol level implicates health risks and might in turn affect parenting resources, the identifying of caregivers at risk through biological markers of stress could be helpful for planning targeted interventions. As our study is the first on this issue, cross-validation is needed

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J Psychopathol Behav Assess. 2022.

SLUGGISH COGNITIVE TEMPO AS A TRANSDIAGNOSTIC LINK BETWEEN ADULT ADHD AND INTERNALIZING SYMPTOMS.

Kamradt JM, Eadeh HM, Nikolas MA.

Although absent from traditional diagnostic nosologies, Sluggish Cognitive Tempo (SCT) may have transdiagnostic utility given its robust associations with ADHD and internalizing symptoms as well as with cognitive impairments common to these conditions. Within-person variation in SCT symptoms may also serve to link ADHD, cognitive deficits, and internalizing psychopathology, however, few studies have utilized intensive longitudinal designs to probe within-person variation in SCT and its links to cognitive deficits and psychopathology. Ecological Momentary Assessment was used to measure between and within-person variance in SCT 4 times per day across 7-ádays (28 time-points) in 158 college students (approximately 51% with elevated ADHD and/or internalizing symptoms). Participants also completed ratings of current and childhood ADHD symptoms, cognitive function and internalizing psychopathology. Parameters derived from longitudinal multilevel models indexing between and within person variation in SCT were examined as mediators of the associations between (1) ADHD and internalizing symptoms and (2) self-reported cognitive functioning and internalizing symptoms. Results indicated that between-person differences in SCT, but not within-person variability, linked current and childhood ADHD and internalizing symptoms. Similarly, problems in time-management and organization influenced internalizing psychopathology via between-person differences in SCT. Results found that SCT may be a transdiagnostic link bridging mental health comorbidities, cognitive dysfunction, and internalizing psychopathology

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J Psychopathol Behav Assess. 2022.

ADHD BEHAVIORS AND SOCIAL FUNCTIONING IN PRESCHOOL CHILDREN: THE MODERATING ROLE OF EMOTION RECOGNITION.

Krasner A, Dennis M, Shoulberg EK, et al.

This study examined the moderating role of emotion recognition on the association between preschoolers ADHD behaviors and social functioning outcomes. Sixty preschoolers (48.3% female; Mage = 3.94, SDage =.56) were recruited from Head Start-affiliated classrooms. Teacher-rated ADHD behaviors and an objective measure of childrenΓÇÖs emotion recognition were assessed at the beginning of the school year. Teacher ratings of social functioning outcomes were obtained approximately three months after the start of school. Hierarchical regressions examined the unique and interactive effects of ADHD behaviors and emotion recognition on preschoolers social functioning outcomes (i.e., oppositional behaviors, peer behavior problems, and social-emotional school readiness). The interaction between ADHD behaviors and emotion recognition predicted oppositional behaviors, peer behavior problems and social-emotional school readiness such that higher levels of emotion recognition appear to buffer the negative association between ADHD behaviors and adaptive social functioning. Preliminary considerations for interventions aimed at promoting preschoolers social functioning are discussed

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J Am Acad Child Adolesc Psychiatry. 2022 Jan;61:80-92.

LONG-TERM TREATMENT WITH EXTENDED-RELEASE METHYLPHENIDATE TREATMENT IN CHILDREN AGED 4 TO <6 YEARS.

Childress AC, Foehl HC, Newcorn JH, et al.

Objective: To investigate long-term (12-month) safety and symptom control of extended-release methylphenidate (MPH-MLR) in children aged 4 to <6 years after treatment optimization.

Method: A total of 90 children aged 4 to <6 years with attention-deficit/hyperactivity disorder (ADHD) were enrolled from 2 MPH-MLR studies. Treatment-emergent adverse events (TEAEs) and ADHD symptom control were assessed in the safety population (n = 89) and modeled with mixed model analyses.

Results: Most TEAEs (89.9%) were rated by investigators as of mild or moderate severity. One serious AE was reported (unrelated to study drug). Ten children discontinued because of TEAEs. Two discontinued because of weight loss; no significant increase in the rate of underweight children from baseline to endpoint was observed. Overall, 18% lost weight and 18% reported decreased appetite. Weight and height z scores and obesity rates decreased significantly from baseline to endpoint. Insomnia was reported (9%); none of these children discontinued. Sleep quality did not change significantly. Hypertension was reported (6.7%); none of these children dropped out. Diastolic, but not systolic, blood pressure increased significantly during the follow-up. Control of ADHD symptoms was maintained throughout follow-up.

Conclusion: These data contribute to the understanding of the long-term safety of an extended-release stimulant in children 4 to <6 years of age. The observed risk of a TEAE-related discontinuation was ~11%. TEAEs were not dose related, and most were of mild to moderate severity. Symptom control was maintained through the year-long study

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J Am Acad Child Adolesc Psychiatry. 2022;61:291-97.

THE COMBINED EFFECTS OF YOUNG RELATIVE AGE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON NEGATIVE LONG-TERM OUTCOMES.

Kuntsi J, Larsson H, Deng Q, et al.

Objective: Young relative age (ie, being among the youngest in a school class) and attention-deficit/hyperactivity disorder (ADHD) are both potential risk factors for adverse long-term outcomes. Young relative age also increases the risk of ADHD diagnosis. Using data from Swedish national registers, we investigate the independent and joint long-term effects of young relative age and ADHD on educational achievement, substance use disorder (SUD), criminality, and depression.

Method: We identified a national cohort of individuals with young relative age (born November December) and a comparison group with old relative age (born January February). Of the total sample of 297,840 individuals, 6,528 individuals had a diagnosis of ADHD in childhood. The 4 outcomes were measured at ages 15 to 23 years. We examined main, additive, and interactive effects of young relative age and ADHD on long-term outcomes.

Results: In the individuals without ADHD, young relative age was associated with increased risk of depression (odds ratio [OR] = 1.14 [95% CI =1.09ΓÇô1.20]), SUD (OR = 1.14 [1.09 1.20]), and low educational achievement (OR = 1.17 [1.14ΓÇô1.20]), but not criminality (OR = 1.00 [0.98ΓÇô1.03]). In the individuals with ADHD, young relative age was associated with increased risk of SUD (OR = 1.23 [1.01 1.50]) and low educational achievement (OR = 1.12 [1.00 0.26]; CI included 1), but not depression or criminality (OR = 0.88 [0.73 1.07] and OR = 0.89 [0.79 1.01], respectively). An interaction emerged between young relative age and ADHD for depression (OR = 0.78 [0.64 0.95]).

Conclusion: We observed relative age effects that add to the evidence supporting a more flexible approach to school starting age and that emphasize the importance of careful age-match comparisons during assessment of childhood ADHD symptoms

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J Am Acad Child Adolesc Psychiatry. 2022.

SYSTEMATIC REVIEW AND META-ANALYSIS: SCREENING TOOLS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.

Mulraney M, Arrondo G, Musullulu H, et al.

Objective: This systematic review and meta-analysis aimed to determine the accuracies of a broad range of screening tools for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents, and to compare the diagnostic accuracy of tools between population-based and clinical/high-risk samples, and across reporters.

Method: MEDLINE, PsycINFO, EMBASE, and PubMed were searched up until February 20, 2020, with no language restrictions. Studies reporting diagnostic accuracy of a screening tool against a diagnosis of ADHD in children and adolescents <18 years of age were eligible for inclusion. Meta-analyses were undertaken to provide pooled estimates of the area under the curve (AUC), and sensitivity and specificity of groups of measures.

Results: A total of 75 studies published between 1985 and 2021 reporting on 41 screening tools that were grouped into 4 categories (Achenbach System of Empirically Based Assessment [ASEBA], DSM-IV symptom scales, SDQ, and Other Scales) were retained. The pooled AUC for studies using a combined ADHD symptoms score was 0.82 (95% CI = 0.78Γêæ0.86), although this varied considerably across reporters (0.67-0.92) and populations (CI = 0.60Γêæ0.95). None of the measures met minimal standards for acceptable sensitivity (0.8) and specificity (0.8).

Conclusion: Most tools have excellent overall diagnostic accuracy as indicated by the AUC. However, a single measure completed by a single reporter is unlikely to have sufficient sensitivity and specificity for clinical use or population screening

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J Am Acad Child Adolesc Psychiatry. 2022.

BRAIN SIGNATURES DURING REWARD ANTICIPATION PREDICT PERSISTENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.

Chen D, Jia T, Cheng W, et al.

Objective: Children experiencing attention-deficit/hyperactivity disorder (ADHD) symptoms may retain symptoms into adulthood, but little is known about the underlying mechanism.

Method: To identify biomarkers of persistent ADHD symptom development, we carried out whole-brain analyses of neuroimaging data during the anticipation phase of the Monetary-Incentive-Delay (MID) task in 1,368 adolescents recruited by the IMAGEN Consortium at age 14 years, whose behavioral measurements were followed up longitudinally at age 16. In particular, we focused on comparing individuals with persistent high ADHD symptoms at both ages 14 and 16 years to unaffected control individuals, but also exploring which individuals demonstrating symptom remission (with high ADHD symptoms at age 14 but much reduced at age 16).

Results: We identified reduced activations in the medial frontal cortex and the thalamus during reward anticipation as neuro-biomarkers for persistent ADHD symptoms across time. The genetic relevance of the above findings was further supported by the associations of the polygenic risk scores of ADHD with both the persistent and control status and the activations of both brain regions. Furthermore, in an exploratory analysis, the thalamic activation might also help to distinguish persons with persistent ADHD from those remitted in both an exploratory sample (odds ratio = 9.43, p <.001) and an independent generalization sample (odds ratio = 4.64, p =.003).

Conclusion: Using a well-established and widely applied functional magnetic resonance imaging task, we have identified neural biomarkers that could discriminate ADHD symptoms that persist throughout adolescence from controls and potentially those likely to remit during adolescent development as well

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J Am Acad Child Adolesc Psychiatry. 2022;61:122-24.
EDITORIAL: ARE WE THERE YET? IDENTIFICATION AND INTERVENTION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE FIRST YEARS OF LIFE.
Miller M.

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Lancet Psychiatry. 2022 Mar;9:187-88.
STRUCTURAL NEUROIMAGING IN CHILDREN WITH ADHD.
Halperin JM.

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Medicina (B Aires). 2022 Feb;82 Suppl 1:17-22.
CARE FOR PATIENTS WITH TRAUMATIC BRAIN INJURY.
Torres AR.
Traumatic brain injury (TBI) as well as Attention Deficit Disorder with or without hyperactivity (ADHD) are very common problems that affect children. It is known that patients who suffer a traumatic brain injury may present symptoms of ADHD, which often go unnoticed in the acute period, especially when there are more serious injuries that hide them and are only evident when the patient returns to their regular cognitive activity after discharge. Symptoms can vary depending on the mechanism of injury, the location in the brain where the trauma or its effects occur, complications, and the severity of the injury. Some symptoms of TBI are identical to those of ADHD, making the diagnosis of these patients more difficult to discern either because the patient or their parents report them together or when the patient already had pre-existing ADHD. We describe some clinical scenarios in this article in which there is an interaction between these two processes that are explained in part because both can affect similar nerve conduction pathways and neurotransmitters. The clinician must recognize attention problems in patients with TBI and other presentations and offer appropriate and timely treatment when symptoms interfere with the patient's functioning. Treatment of ADHD in patients with TBI uses accommodations and medications similar to those used in patients who only have ADHD, but depending on the severity, they can vary in duration

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Medicina (B Aires). 2022 Feb;82 Suppl 1:28-32.
SKEPTICAL REVIEW OF THE STATE OF NEUROIMAGING IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Castellanos FX.
Attention-deficit/hyperactivity disorder (ADHD) has been the focus of magnetic resonance imaging studies for more than 30 years, with more than 2200 articles listed in PubMed. Nevertheless, the brain substrates of ADHD remain poorly understood. This reflects the crisis of replicability across nearly all scientific endeavors, deriving from factors such as small sample sizes combined with a proliferation in analytical approaches, yielding high rates of false positive results. The field of molecular genetics confronted this by adopting open and immediate sharing of raw data and insistence on rigorous corrections for multiple comparisons. These strategies are yielding more robust genetic findings, albeit with much smaller effect sizes than before. This brief review focuses on two recent consortium efforts, i.e., the international Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA), and the U.S. Adolescent Behavior & Cognitive Developm ent Study (ABCD). Both embrace the culture of open science, and are beginning to yield credible findings, despite being limited initially to cross-sectional analyses. As the field continues to mature, these and other ongoing longitudinal large-scale studies are poised to transform our understanding of the pathophysiology of ADHD to bring closer the day when neuroimaging can contribute to clinical utility

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Medicina (B Aires). 2022 Feb;82 Suppl 1:23-27.

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

Albert J, et al.

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

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Medicine. 2021;100.

VAL158MET POLYMORPHISMS OF COMT GENE AND SERUM CONCENTRATIONS OF CATECHOLAMINERGIC NEUROTRANSMITTERS OF ADHD IN CHINESE CHILDREN AND ADOLESCENTS.

Xiong Z, Yan J, Shi S.

This study analyzed the Val158Met polymorphisms of the catechol-O-methyltransferase (COMT) gene and serum concentrations of catecholaminergic neurotransmitters in attention deficit hyperactivity disorder (ADHD) children and adolescents.All the subjects (180 paired ADHD and non-ADHD children and adolescents) were genotyped for the Val158Met polymorphisms of the COMT gene, and determined by the difference of dopamine and noradrenalin from a 1:1 paired case-control study.The frequencies of methionine (A)/A, valine (G)/A, and G/G were 51.67%, 41.11%, and 7.22% in the case group, and 62.22%, 31.11%, and 6.67% in the control group. There was a significant difference in the distribution of all genotypes of the COMT gene between the 2 groups (odds ratio=1.85, 95% confidence interval: 1.62-2.08; $\chi 2=7.80$, $P<.05$). The serum concentrations of dopamine and noradrenalin were 1.42±0.34ng/mL and 177.70±37.92pg/mL in the case group, and 1.94±0.42ng/mL and 206.20±42.45pg/mL in the control group. There were the significant differences in the levels of dopamine and noradrenalin between the 2 groups (dopamine: $t=4.30$, $P<.01$; noradrenalin: $t=2.24$, $P<.05$). Our study suggested that the Val158Met polymorphisms of the COMT gene and serum concentrations of catecholaminergic neurotransmitters were associated with ADHD children and adolescents

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MMWR Morb Mortal Wkly Rep. 2022 Feb;71:319-24.

PEDIATRIC EMERGENCY DEPARTMENT VISITS ASSOCIATED WITH MENTAL HEALTH CONDITIONS BEFORE AND DURING THE COVID-19 PANDEMIC - UNITED STATES, JANUARY 2019-JANUARY 2022.

Radhakrishnan L, Leeb RT, Bitsko RH, et al.

In 2021, a national emergency* for children's mental health was declared by several pediatric health organizations, and the U.S. Surgeon General released an advisory(â€) on mental health among youths. These actions resulted from ongoing concerns about children's mental health in the United States, which was exacerbated by the COVID-19 pandemic (1,2). During March-October 2020, among all emergency department (ED) visits, the proportion of mental health-related visits increased by 24% among U.S. children aged 5-11 years and 31% among adolescents aged 12-17 years, compared with 2019 (2). CDC examined changes in U.S. pediatric ED visits for overall mental health conditions (MHCs) and ED visits associated with specific MHCs (depression; anxiety; disruptive behavioral and impulse-control disorders; attention-deficit/hyperactivity disorder; trauma and stressor-related disorders; bipolar disorders; eating disorders; tic disorders; and obsessive-compulsive disorders [OCD]) during 2019 through January 2022 among children and adolescents aged 0-17 years, overall and by sex and age. After declines in weekly visits associated with MHCs among those aged 0-17 years during 2020, weekly numbers of ED visits for MHCs overall and for specific MHCs varied by age and sex during 2021 and January 2022, when compared with corresponding weeks in 2019. Among adolescent females aged 12-17 years, weekly visits increased for two of nine MHCs

during 2020 (eating disorders and tic disorders), for four of nine MHCs during 2021 (depression, eating disorders, tic disorders, and OCD), and for five of nine MHCs during January 2022 (anxiety, trauma and stressor-related disorders, eating disorders, tic disorders, and OCD), and overall MHC visits during January 2022, compared with 2019. Early identification and expanded evidence-based prevention and intervention strategies are critical to improving children's and adolescents' mental health (1-3), especially among adolescent females, who might have increased need

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MMWR Suppl. 2022 Feb;71:1-42.

MENTAL HEALTH SURVEILLANCE AMONG CHILDREN - UNITED STATES, 2013-2019.

Bitsko RH, Claussen AH, Lichstein J, et al.

Mental health encompasses a range of mental, emotional, social, and behavioral functioning and occurs along a continuum from good to poor. Previous research has documented that mental health among children and adolescents is associated with immediate and long-term physical health and chronic disease, health risk behaviors, social relationships, education, and employment. Public health surveillance of children's mental health can be used to monitor trends in prevalence across populations, increase knowledge about demographic and geographic differences, and support decision-making about prevention and intervention. Numerous federal data systems collect data on various indicators of children's mental health, particularly mental disorders. The 2013-2019 data from these data systems show that mental disorders begin in early childhood and affect children with a range of sociodemographic characteristics. During this period, the most prevalent disorders diagnosed among U.S. children and adolescents aged 3-17 years were attention-deficit/hyperactivity disorder and anxiety, each affecting approximately one in 11 (9.4%-9.8%) children. Among children and adolescents aged 12-17 years, one fifth (20.9%) had ever experienced a major depressive episode. Among high school students in 2019, 36.7% reported persistently feeling sad or hopeless in the past year, and 18.8% had seriously considered attempting suicide. Approximately seven in 100,000 persons aged 10-19 years died by suicide in 2018 and 2019. Among children and adolescents aged 3-17 years, 9.6%-10.1% had received mental health services, and 7.8% of all children and adolescents aged 3-17 years had taken medication for mental health problems during the past year, based on parent report. Approximately one in four children and adolescents aged 12-17 years reported having received mental health services during the past year. In federal data systems, data on positive indicators of mental health (e.g., resilience) are limited. Although no comprehensive surveillance system for children's mental health exists and no single indicator can be used to define the mental health of children or to identify the overall number of children with mental disorders, these data confirm that mental disorders among children continue to be a substantial public health concern. These findings can be used by public health professionals, health care providers, state health officials, policymakers, and educators to understand the prevalence of specific mental disorders and other indicators of mental health and the challenges related to mental health surveillance

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Mod Rheumatol. 2022 Feb;32:422-26.

INCREASED PREVALENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMATOLOGY IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER.

Lavi E, Maree A, Eisenstein EM, et al.

OBJECTIVES: Previous studies suggest that exposure to inflammation in infancy may increase the risk for attention-deficit and hyperactivity disorder (ADHD). We studied the ADHD manifestations among 124 familial Mediterranean fever (FMF) patients and examined the relationship between FMF patient characteristics and ADHD.

METHODS: Clinical, demographic, and genetic data were abstracted from patients' medical records and supplemented by information obtained during clinic visits. ADHD manifestations were assessed using the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) questionnaire.

RESULTS: ADHD was diagnosed in 42 (32.8%) FMF patients, a rate significantly higher than in unselected populations (8%). A majority (n=27, 64.3%) had combined inattentive, hyperactive-impulsive manifestations. Eight (19%) had predominantly hyperactive-impulsive, and seven (16.6%) had predominantly inattentive symptoms. FMF patients with severe manifestations reported more ADHD symptoms. FMF patients with

ADHD symptoms were less adherent to their treatment regimen, with only 61.9% of the patients with ADHD symptoms adhering to colchicine therapy compared to 92.7% of the patients without ADHD symptoms.
CONCLUSION: The high prevalence of ADHD characteristics in children with FMF may support the neuroimmune hypothesis that chronic inflammation increases the risk for ADHD. Children with FMF should be screened for ADHD as its presence may adversely affect adherence to treatment

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Mol Genet Genomic Med. 2021 Aug;9:e1755.

INTERSTITIAL DUPLICATION OF 20Q11.22Q13.11: A CASE REPORT AND REVIEW OF LITERATURE.

Goetzinger L, Starks RD, Dillahunt K, et al.

BACKGROUND: Reports of interstitial duplication of chromosome 20q11 are rare with only nine published patients to date.
METHODS: We performed karyotype and chromosomal microarray analysis on a peripheral blood sample for our patient and reviewed the genes in the region to provide genotype-phenotype correlation.
RESULTS: Clinical features of the patient include minor dysmorphic facial features, shorthands and feet, bilateral conductive hearing loss, global developmental delay, and behavioral issues with attention deficit hyperactivity disorder. Together with previously published cases of 20q11 duplication, we show that patients with overlapping duplications share a similar clinical phenotype of dysmorphic craniofacial features and developmental delay.
CONCLUSION: We report an 8-year-old girl with a 9.1Â Mb interstitial duplication of chromosome 20q11.22q13.11. Our observations suggest that a novel duplication syndrome and documentation of similar cases will further help clarify the phenotype

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Mol Psychiatry. 2021 Nov;26:6655-65.

WHITE MATTER ABNORMALITIES ASSOCIATED WITH ADHD OUTCOMES IN ADULTHOOD.

Versace A, Jones NP, Joseph HM, et al.

It remains unclear if previously reported structural abnormalities in children with ADHD are present in adulthood regardless of clinical outcome. In this study, we examined the extent to which focal-rather than diffuse-abnormalities in fiber collinearity of 18 major white matter tracts could distinguish 126 adults with rigorously diagnosed childhood ADHD (ADHD; mean age [SD]=34.3 [3.6] years; F/M=12/114) from 58 adults without ADHD histories (non-ADHD; mean age [SD]=33.9 [4.1] years; F/M=5/53) and if any of these abnormalities were greater for those with persisting ADHD symptomatology. To this end, a tract profile approach was used. After accounting for age, sex, handedness, and comorbidities, a MANCOVA revealed a main effect of group (ADHD<non-ADHD; F([18,155])=2.1; ‰=0.007) on fractional anisotropy (FA, a measure of fiber collinearity and/or integrity), in focal portions of white matter tracts involved in visuospatial processing and memory (i.e., anterior portion of the left inferior longitudinal fasciculus, and middle portion of the left and right cingulum angular bundle). Only abnormalities in the anterior portion of the left inferior longitudinal fasciculus distinguished probands with persisting versus desisting ADHD symptomatology, suggesting that abnormalities in the cingulum angular bundle might reflect "scarring" effects of childhood ADHD. To our knowledge, this is the first study using a tract profile approach to identify focal or widespread structural abnormalities in adults with ADHD rigorously diagnosed in childhood

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Neurocase. 2022.

IS NEUROFEEDBACK EFFECTIVE IN CHILDREN WITH ADHD? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Rahmani E, Mahvelati A, Alizadeh A, et al.

To evaluate the evidences related to the effectiveness of neurofeedback treatment for children and adolescent with attention-deficit/hyperactivity disorder (ADHD) based on the most-proximal raters. A systematic review of randomized control trials (RCTs) was carried out across multiple databases. the primary outcome measure was the most proximal ratings of ADHD symptoms in subjects. ConnerΓÇÖs Parent Rating Scale (CPRS), ConnerΓÇÖs Teacher Rating Scale (CTRS), and ADHD Rating Scale (ADHD-RS- are considered as primary outcomes. Seventeen trials met inclusion criteria (including 1211 patients). Analysis

showed that there was no significant benefit of neurofeedback treatment compared with other treatments or control conditions [weighted mean difference/CI-=-HI-P: 0.02 (0.26, 0.21), HI-T: 0.01 (0.46, 0.48), weighted mean difference/CI-=-I-P: 0.00 (0.23, 0.23), I-P: 0.12 (0.14, 0.38)]. The results provide preliminary evidence that neurofeedback treatment is no efficacious clinical method for ADHD and suggest that more RTCs are needed to compare common treatment

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Neuroimage Clin. 2022;33:102957.

WHITE MATTER MICROSTRUCTURE IN CHILDREN AND ADOLESCENTS WITH ADHD.

Connaughton M, Whelan R, O'Hanlon E, et al.

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. Advances in diffusion magnetic resonance imaging (MRI) acquisition sequences and analytic techniques have led to growing body of evidence that abnormal white matter microstructure is a core pathophysiological feature of ADHD. This systematic review provides a qualitative assessment of research investigating microstructural organisation of white matter amongst children and adolescents with ADHD. This review included 46 studies in total, encompassing multiple diffusion MRI imaging techniques and analytic approaches, including whole-brain, region of interest and connectomic analyses. Whole-brain and region of interest analyses described atypical organisation of white matter microstructure in several white matter tracts: most notably in frontostriatal tracts, corpus callosum, superior longitudinal fasciculus, cingulum bundle, thalamic radiations, internal capsule and corona radiata. Connectomic analyses, including graph theory approaches, demonstrated global underconnectivity in connections between functionally specialised networks. Although some studies reported significant correlations between atypical white matter microstructure and ADHD symptoms or other behavioural measures there was no clear pattern of results. Interestingly however, many of the findings of disrupted white matter microstructure were in neural networks associated with key neuropsychological functions that are atypical in ADHD. Limitations to the extant research are outlined in this review and future studies in this area should carefully consider factors such as sample size, sex balance, head motion and medication status

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Neurol Neurochir Pol. 2022;56:28-38.

CANNABIS-BASED MEDICINE IN TREATMENT OF PATIENTS WITH GILLES DE LA TOURETTE SYNDROME.

Szejko N, Saramak K, Lombroso A, et al .

INTRODUCTION: Gilles de la Tourette syndrome (GTS) is a childhood onset disorder characterised by the presence of motor and vocal tics. The guidelines of both the American Academy of Neurology (AAN) as well as the European Society for the Study of Tourette Syndrome (ESSTS) recommend behavioural therapy and pharmacotherapy, mainly with antipsychotics, as first line treatments for tics. In spite of these well-established therapeutic approaches, a significant number of patients are dissatisfied because of insufficient tic reduction or intolerable side effects. Previous studies have suggested that cannabis-based medicine (CBM) might be an alternative treatment in these patients.

MATERIAL AND METHODS: Two reviewers (KS, NS) searched the electronic database of PubMed on 1 July, 2021 for relevant studies using the search terms: ('Tourette syndrome' [MeSH Terms] OR 'Gilles de la Tourette syndrome' [MeSH Terms] OR 'tic disorders' [MeSH Terms] OR 'tics' [MeSH Terms] OR 'tic disorders'[Title/Abstract]) AND ('cannabis-based medicine' [Title/Abstract] OR 'cannabis' [Title/Abstract] OR 'dronabinol' [Title/Abstract] OR 'nabiximols' [Title/Abstract] OR 'tetrahydrocannabinol' [Title/Abstract] OR 'THC' [Title/Abstract] OR 'cannabidiol' [Title/Abstract], limit: 'humans'. These studies were further reviewed for additional relevant citations. The titles and abstracts of the studies obtained through this search were examined by two reviewers (KS, NS) in order to determine article inclusion. Discrepancies were addressed by the reviewers through discussion and eventually conversation with the senior reviewer (KMV).

RESULTS: Although the amount of evidence supporting the use of CBM in GTS is growing, the majority of studies are still limited to case reports, case series, and open uncontrolled studies. To date, only two small randomised controlled trials (RCTs) using tetrahydrocannabinol (THC, dronabinol) have been published demonstrating the safety and efficacy of this intervention in the treatment of tics in patients with GTS. On the other hand, another RCT with Lu AG06466 (formerly known as ABX-1431), a modulator of endocannabinoid

neurotransmission, has failed to prove effective in the therapy of GTS. Accordingly, under the guidelines of both the ESSTS and the AAN, treatment with CBM is categorised as an experimental intervention that should be applied to patients who are otherwise treatment-resistant.
CONCLUSIONS: Increasing evidence suggests that CBM is efficacious in the treatment of tics and psychiatric comorbidities in patients with GTS. The results of ongoing larger RCTs, such as CANNA-TICS (ClinicalTrials.gov Identifier: NCT03087201), will further clarify the role of CBM in the treatment of patients with GTS

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Neuropsychiatr Enfance Adolesc. 2022.
PRESCRIPTION OF METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS IN FRANCE: CHARACTERISTICS AND EVOLUTION BETWEEN 2010 AND 2019.
Ponnou S, Haliday H, Thom+® B, et al.
Context: Psychotropic drugs are often prescribed to alleviate the symptoms of Attention Deficit/Hyperactivity Disorder (ADHD) in children and adolescents. However, the governmental regulations of this prescription, its prevalence and its time evolution during the last two decades have greatly varied among developed countries. In France, methylphenidate is the only drug authorized for pediatric ADHD. Here, we describe the pattern of methylphenidate prescription in France from 2010 to 2019 and several clinical, demographic, institutional and social parameters associated with this prescription.
Methods: We analyzed the pattern of methylphenidate prescription through the French Social Security database that includes 87% of the French population. Our retrospective cohort included 144,509 patients aged 0 to 17 years who received at least one methylphenidate prescription between 2010 and 2019.
Results: Between 2010 and 2019, methylphenidate prescription increased by +56% for incidence and +116% for prevalence. The prevalence of methylphenidate prescription among 3-17-year-olds reached in 2019 between 0.61% and 0.75% of the pediatric population. Boys are predominantly medicated (82.5% to 80.8% of prescriptions over the period). The median duration of treatment among 6-year-olds in 2011 was 5.5 years. The youngest children received the longest treatment duration. The number of deliveries per patient and per year increased over the period, suggesting that treatment durations increased from 2010 to 2019. Diagnoses associated with methylphenidate prescription did not always correspond to the therapeutic indication or the marketing authorization. Among children receiving a first prescription of methylphenidate, 22.8% also received one or more other psychotropic drugs during the same year. Most of these co-prescriptions were outside approved indications. A quarter of initiations and half of renewals were made outside governmental recommendations. The prescription distribution suggests that a minority of practitioners and of hospital services were involved in most of the methylphenidate prescriptions. Among young patients treated with methylphenidate, educational and psychotherapeutic follow-up decreased from 4.1 in 2010 to 0.8% in 2019. French children and adolescents, who were the youngest in their class (born in December rather than January), were more likely to be prescribed methylphenidate (+54% average over the period). Children from disadvantaged families had an increased risk of ADHD medication.
Discussion: In European and North American countries, the prevalence of ADHD medication has stabilized or showed a clear trend toward stabilization since 2008. In contrast, in France, the prevalence of methylphenidate prescription has steadily increased from 2003 to now (2019) so much so that the 2019 French prevalence exceeds that observed in UK. The reasons that might explain such an increase are discussed

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Neuropsychiatr Enfance Adolesc. 2022.
MEMORY ABILITIES IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: AN OVERVIEW.
Martin P, Speranza M, Colombel F.
Attention deficit/hyperactivity disorder is a neurodevelopmental disorder marked by a strong heterogeneity of the cognitive and behavioral profiles of affected children. They can be diverse and have various repercussions in the child's daily life. An alteration of the working memory capacities is very often found. This impairment affects the central executive in a privileged way and could be consecutive to the symptoms of the disorder or constitutive of the disorder. The study of episodic memory performance gives less consensual

results. Although secondary weakness can sometimes be observed, episodic impairment does not seem to be systematic. However, some authors believe that episodic impairment may be constitutive of attention deficit/hyperactivity disorder. The memory evaluation of attention deficit/hyperactivity disorder remains interesting from a functional point of view to propose personalized learning techniques. It is also important to look into the quality of memory of these children. Attentional and executive impairments could both falsify memory accuracy, while reinforcing the memory trace due to the processing of many contextual elements during encoding

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Neurosci Lett. 2022 Jan;766:136349.

MANUAL DEXTERITY AND STRENGTH AND IN YOUNG ADULTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Fietsam AC, Tucker JR, Kamath MS, et al.

Manual motor deficits are common in children with attention deficit/hyperactivity disorder (ADHD); however, it is unclear whether these impairments persist into adulthood. The aim of this study was to examine manual dexterity and strength in young adults with ADHD aged 18-25 years. Sixty-one individuals with confirmed ADHD and 56 adults without ADHD completed Purdue Pegboard tasks for manual dexterity and maximal hand- and pinch-grip tests for strength. In the Purdue Pegboard task, participants placed pins using the right, left, and both-hands, respectively. In addition, participants built assemblies using pins, washers, and collars with alternating hand movements. The results demonstrated that women without ADHD out-performed the other three groups in the right-hand, bimanual, and assembly PPB tasks. Both maximal hand strength tests demonstrated that men were stronger than women, but no differences were observed between adults with and without ADHD. The current findings suggest that adults with ADHD may have deficits in manual dexterity and tasks requiring bimanual coordination

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Nord J Psychiatry. 2022.

DRIVING RISKS OF YOUNG DRIVERS WITH SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: ASSOCIATION WITH THE DOPAMINE TRANSPORTER GENE VNTR POLYMORPHISM.

Tokko T, et al.

Background: Road traffic injuries are a leading cause of death for young adults, and young drivers with higher expression of symptoms of attention deficit-hyperactivity disorder (ADHD) could pose an even greater risk in traffic. Dopaminergic dysfunction has been found to occur in ADHD, with the dopamine transporter (DAT) gene VNTR polymorphism (DAT1 VNTR; rs28363170) being one of the most consistent genetic markers. Thus, we aimed at clarifying how the ADHD symptoms and the DAT1 VNTR relate to risk-taking behaviour in traffic, impulsivity and driving anger in young drivers.

Method: We used data of two traffic behaviour study samples (n = 741, mean age = 23.3 -¦ 7.2-áyears; n = 995, mean age = 22.9 -¦ 8.1-áyears) and the Estonian Children Personality Behaviour and Health Study (ECPBHS; traffic behaviour data n = 1,016, mean age = 25.2 -¦ 2.1-áyears). ADHD symptoms were assessed by self-report with the Adult ADHD Self-Report Scale (ASRS v1.1) and impulsivity with the Adaptive and Maladaptive Impulsivity Scale. Traffic behavioural measures were either self-reported (Driver Behaviour Questionnaire, Driving Anger Scale) or obtained from databases (registered accidents and violations).

Results: Drivers with more self-reported ADHD symptoms also reported more risk-taking in traffic and had more of recorded traffic accidents and violations. DAT1 9 R carriers had a higher probability of high traffic risk behaviour only if they also had ADHD symptoms.

Conclusion: Higher level of ADHD symptoms is a significant risk factor in traffic, and carrying of the DAT1 9 R allele appears to aggravate these risks

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Ophthalmologica. 2021;244.

STRUCTURAL CHANGES OF CHOROID VIA BINARIZATION METHOD IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yeter DY, Ozec AV, Aslan H.

Purpose To compare the structural changes of the choroid and the choroidal vascularity index (CVI) alterations in the eyes of the children with attention deficit hyperactivity disorder (ADHD) receiving methylphenidate, children with newly diagnosed ADHD not receiving any medication and with the healthy controls.

Methods This study consisted of 33 right eyes of 33 children who received methylphenidate treatment for at least 6 months, 25 right eyes of 25 patients who were diagnosed with ADHD but not receiving methylphenidate treatment, and 25 right eyes of 25 healthy controls. Demographic data of the patients were evaluated. Subfoveal choroidal thickness was measured in all groups via the images obtained by optical coherence tomography in choroidal mode. Also, calculations of the luminal area (LA) and total choroidal area (TCA) and choroidal vascularity index (CVI) using the binarization method in the ImageJ image analysis software were compared between three groups.

Results The mean age of 83 patients was 10.1-¦2.5 (6-17) of whom 59 (71%) were male; 24 (29%) were female. No statistically significant difference was found between groups in terms of age and gender (p=0.08 for age, p=0.8 for gender). The mean duration of methylphenidate use was 10.4-¦3.3 (6-19) months in the methylphenidate group. The subfoveal choroidal thickness was 301.3-¦26.9 ++m in the ADHD group not receiving medication, 295.6-¦30.7 ++m in the methylphenidate group and 297.9-¦27.3 ++m in the control group. There was no statistically significant difference between the groups regarding subfoveal choroidal thickness (p=0.7). LA and TCA were 0.43-¦0.07 mm2 and 0.65-¦1.0 mm2 in the group not receiving medication; 0.37-¦0.08 mm2 and 0.53-¦0.11 mm2 in the methylphenidate group; and 0.4-¦0.06 mm2 and 0.58-¦0.1 mm2 in the control group respectively. CVI was 0.66-¦0.02 in the group not receiving medication; 0.68-¦0.02 in the methylphenidate group, and 0.68-¦0.02 in the control group. Although LA and TCA were statistically higher in the ADHD group not receiving medication (p=0.002 for LA and p=0.001 for TCA), CVI was found to be statistically lower (p=0.001).

Conclusions TCA and LA were higher in the eyes of children with ADHD not receiving medication compared to healthy controls. The use of methylphenidate may cause decrease in both LA and TCA. However, the lower CVI in the group not receiving medication can be explained by the fact that methylphenidate use causes a greater reduction in the total choroid area compared to the luminal area. It would be beneficial to design future studies with the correlation of premedication, post-medication measurements in the same patient group diagnosed with ADHD and duration of medication use

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Paediatr Perinat Epidemiol. 2022.

PRESCRIBED MEDICINE USE AND EXTENT OF OFF-LABEL USE ACCORDING TO AGE IN A NATIONWIDE SAMPLE OF AUSTRALIAN CHILDREN.

Schaffer AL, Bruno C, Buckley NA, et al.

Background: Medicine prescribing for children is impacted by a lack of paediatric-specific dosing, efficacy and safety data for many medicines. Objectives: To estimate the prevalence of medicine use among children and the rate of off-label prescribing according to age at dispensing.

Methods: We used population-wide primarily outpatient dispensing claims data for 15% of Australian children (0-17-áyears), 2013-2017 (n-=-840,190). We estimated prescribed medicine use and off-label medicine use according to the child's age (<1-year, 15-years, 6-11-years, 12-17-years) defined as medicines without age-appropriate dose recommendations in regulator-approved product information. Within off-label medicines, we also identified medicines with and without age-specific dose recommendations in a national prescribing guide, the Australian Medicines Handbook Children's Dosing Companion (AMH CDC).

Results: The overall dispensing rate was 2.0 dispensings per child per year. The medicines with the highest average yearly prevalence were systemic antibiotics (435.3 per 1000 children), greatest in children 1-5-áyears (546.9 per 1000). Other common medicine classes were systemic corticosteroids (92.7 per 1000), respiratory medicines (91.2 per 1000), acid-suppressing medicines in children <1-year (47.2 per 1000), antidepressants in children 12-17-áyears (40.3 per 1000) and psychostimulants in children 6-11-years (27.0 per 1000). We identified 12.2% of dispensings as off-label based on age, but 66.3% of these had age-specific

dosing recommendations in the AMH CDC. Among children <1-year, off-label dispensings were commonly acid-suppressing medicines (35.5%) and topical hydrocortisone (33.1%); in children 6-11years, off-label prescribing of clonidine (16.0%) and risperidone (13.1%) was common. Off-label dispensings were more likely to be prescribed by a specialist (21.7%) than on-label dispensings (7.5%).
Conclusions: Prescribed medicine use is common in children, with off-label dispensings for medicines without paediatric-specific dosing guidelines concentrated in classes such as acid-suppressing medicines and psychotropics. Our findings highlight a need for better evidence to support best-practice prescribing

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Pediatr Neurol. 2022 Jan;126:20-25.
RISK BEHAVIORS IN YOUTH WITH AND WITHOUT TOURETTE SYNDROME.
Vermilion J, Augustine EF, Adams HR, et al.
BACKGROUND: Specific health-risk behaviors are present in older adolescents and young adults wtih Tourette syndrome (TS), but little is known about health-risk behaviors in youth with TS.
METHODS: We compared responses on the Youth Risk Behavior Surveillance System (YRBS) in youth with TS with those in a concurrent community control group. The YRBS evaluates risk behaviors most closely associated with morbidity and mortality in young people. Tic severity, presence of comorbid attention-deficit/hyperactivity disorder (ADHD), measures of ADHD symptom severity, and whether or not the individual had been bullied in school were also compared between the groups.
RESULTS: Data from 52 youth with TS and 48 control youth were included. We did not detect any differences between control youth and youth with TS in the reporting of risky behaviors. Tic severity was not significantly associated with high-risk behavior. However, ADHD was significantly more common in youth with TS (PÂ <Â 0.0002), and youth with TS who identified themselves as victims of bullying had significantly higher ADHD symptom severity scores (P = 0.04) compared with those who were not bullied.
CONCLUSIONS: Risk behaviors are not reliably or clinically different in youth with TS compared with control youth. ADHD severity, but not tic severity, was associated with being bullied in youth with TS

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Pediatr Neurol. 2022 Feb;127:28-31.
DELAYED SLEEP-WAKE PHASE DISORDER: CAN POLYSOMNOGRAPHY BE USEFUL?
Pa-hodova I, et al.
BACKGROUND: Delayed sleep-wake phase disorder (DSWPD) is a chronic condition with a multifactorial etiology that primarily affects adolescents, significantly influencing their quality of life. In clinical practice, the contribution of intrinsic and behavioral factors is difficult to determine. The aim of our study was to compare data from clinical interviews, sleep diaries, actigraphy, and nocturnal polysomnography (PSG) in a cohort of adolescents with DSWPD and to assess psychiatric/neurodevelopmental comorbidity.
METHODS: Thirty-one patients (22 male; mean age 15.4 ± 2.2 years, range 12 to 19 years) with a diagnosis of DSWPD based on detailed history, sleep diary, and actigraphy underwent nocturnal polysomnography (PSG) and neurological, psychological, and psychiatric examination.
RESULTS: Attention-deficit/hyperactivity disorder (ADHD) was present in 14 cases (45%), specific learning difficulties in nine (29%), and mood disorder (anxiety/depression) in 16 patients (52%). PSG revealed sleep-onset delay in only 12 (38%) cases. No differences in clinical data or psychiatric comorbidity between the group with sleep delay and the group with normal sleep onset were detected. Decreased total sleep time, sleep efficiency, rapid eye movement (REM) sleep, and prolonged REM sleep latency were observed in patients with delayed sleep onset.
CONCLUSIONS: PSG showed delayed sleep timing in only 38% of patients with a diagnosis of DSWPD based on diagnostic criteria of the International Classification of Sleep Disorders. We suggest that PSG can provide useful information regarding the prevailing etiology (biological versus behavioral) if dim light melatonin onset testing is not available

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Pediatr Drugs. 2022.

ACUTE TOLERABILITY OF METHYLPHENIDATE IN TREATMENT-NA+»VE CHILDREN WITH ADHD: AN ANALYSIS OF NATURALISTICALLY COLLECTED DATA FROM CLINICAL PRACTICE.

Masi G, Pfanner C, Liboni F, et al.

Objectives: The acute tolerability of methylphenidate (MPH) in children with attention-deficit/hyperactivity disorder (ADHD) has been studied mainly in research samples. Taking advantage of the mandatory test-dose procedure required for starting MPH in Italy, this study aimed to assess the incidence of intolerable adverse events after initial exposure to MPH in routine clinical practice.

Methods: The medical records of 480 consecutively treated, previously drug-naïve children and adolescents with ADHD (90% male, mean age 10.6 ± 3.0 years) were retrospectively analyzed. All children received an initial single dose of MPH immediate release (5 or 10 mg) followed by a 4-hour direct medical observation. Heart rate and blood pressure were measured at dosing and 1, 2, and 3 hours afterwards. If the first dose was well tolerated, the child continued treatment with MPH 5–20 mg daily, and was reassessed a week later.

Results: Eleven patients (2.3%, 95% CI 1.1–4.1) interrupted treatment within a week of initiation because of the following adverse events: irritability (n = 3), tics worsening (n = 3), reduced appetite (n = 1), enuresis (n = 1), hallucinations (n = 1), hyperfocus (n = 1), and 'rebound' behavioral worsening (n = 1). The most common adverse events were reduced appetite (20%), irritability (14.2%), headache (10.6%), sleep problems (9.4%), stomachache (9.4%), and tics (5%). Intellectual disability increased the risk of any adverse event in general and of irritability in particular. No cardiovascular symptom was clinically reported. However, routine assessments of vital signs during the first 3 hours after the first dose of MPH showed that 9% of the children had a 20% increase in heart rate, 8.8% had a 20% increase in diastolic blood pressure and 4.5% had a 20% increase in systolic blood pressure. Of these, 25.2% still had an elevated heart rate 1 week later.

Conclusions: Among stimulant-naïve children in clinical practice, the incidence of acute MPH intolerance can be estimated to be between 1.2 and 4.1%. An asymptomatic elevation in cardiovascular parameters can be observed in about 1 out of 10 children and warrants monitoring during ongoing treatment

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Pediatr Neurol. 2022;128:45-51.

ASSOCIATED FACTORS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DIAGNOSIS AND PSYCHOSTIMULANT USE: A NATIONWIDE REPRESENTATIVE STUDY.

Arruda MA, Arruda R, Guidetti V, et al.

Background: Connections between epidemiological findings and children's and adolescents' mental health policies have not been properly made in Brazil, and such nationwide studies are scarce. This epidemiological study (1) estimated the prevalence and predictors of parent-reported attention-deficit/hyperactivity disorder (ADHD) (ADHD-report), (2) estimated the probable diagnosis and risk of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria (ADHD-probable), and (3) estimated current psychostimulant use (ADHD-pst) in a representative nationwide sample of Brazilian school-aged children and adolescents.

Methods: Data were obtained from 7114 school-aged children (49.9% boys) from 87 cities in 18 Brazilian states. Parents and teachers were interviewed using psychometrically sound questionnaires. Data and codes are available.

Results: The prevalence of ADHD-report, ADHD-probable, and ADHD-pst were 7.1%, 3.9%, and 1.9%, respectively. The agreement was low between ADHD-probable and ADHD-report (22.6%) and between ADHD-report and ADHD-pst (15.6%). Logistic regression revealed that predictors of all three categories were male gender (odds ratio [OR] = 1.71, 2.32, and 1.96, respectively), divorced parents (OR = 1.47, 1.65, and 1.68, respectively), and below-expectation school performance (OR = 3.1, 13.74, and 3.95, respectively). Socioeconomic status was a significant predictor of ADHD-report, and participants from lower classes were less frequently diagnosed with ADHD than their peers from upper classes (OR = 0.57, 95% confidence interval = 0.37-0.88, P = 0.012).

Conclusions: The present findings provide an accurate description of ADHD in Brazil. We suggest disparities in agreement between report, risk, and psychostimulant use among children and adolescents and discrepancies between socioeconomic classes
concerning the prevalence of an ADHD diagnosis

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Pharmacogenomics. 2021 Jun;22:447-50.

THE NEED FOR A REFINED UNDERSTANDING OF CYP2D6 IN SECOND-GENERATION ANTIPSYCHOTIC OUTCOMES IN CHILDREN AND ADOLESCENTS.

Rossow KM, Vaughn SE, Strawn JR, et al.

Tweetable abstract High-quality studies examining the influence of CYP2D6 on the exposure and tolerability of antipsychotics in youth are needed to mitigate the limitations of prior studies

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Pharmacopsychiatry. 2022 Mar;55:95-107.

LIFE-TIME ACTIONABLE PHARMACOGENETIC DRUG USE: A POPULATION-BASED COHORT STUDY IN 86â€‰040 YOUNG PEOPLE WITH AND WITHOUT MENTAL DISORDERS IN DENMARK.

Lunenburg CATC, Ishtiak-Ahmed K, Werge T, et al.

OBJECTIVE: To describe life-time use of current actionable pharmacogenetic (PGx) somatic and psychotropic drugs according to international PGx consortia in people with and without hospital-diagnosed mental disorders in the Danish population.

METHODS: Population- and register-based observational drug utilization study in 56065 individuals with mental disorders, i.e. attention-deficit/hyperactivity disorder, autism, bipolar disorder, depression and schizophrenia, and a random, representative sample of 29975 individuals of the Danish population, born between 1981 and 2005. Individuals were followed from 1995 or birth until 2016 (for a maximum of 22 years). We report prevalence and incidence rates of PGx drug use by age, sex and mental disorders based on redeemed prescriptions between 1995 and 2016.

RESULTS: Of the 69 PGx drugs, prescriptions of 39 drugs had been redeemed by the study population by 35 years of age. The use of at least 1 PGx drug varied between 23.1% in males without mental disorders and 97.2% in females with schizophrenia. Males with ADHD or autism were the youngest first-time PGx drug users at a mean of 11.6 years. The mean number of different PGx drugs used was 1.2 in males without mental disorders and 5.6 in individuals with schizophrenia. The prevalence of different PGx drugs linked to more than one gene was 25.3% in males without mental disorders to 94.1% in females with schizophrenia.

CONCLUSION: PGx drugs are commonly used by younger people, more often by individuals with mental disorders and by females. Panel-based PGx testing could contribute to treatment decisions at a very young age

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Phytother Res. 2022 Feb;36:996-1012.

EFFECTS OF BACOPA MONNIERI (CDRI 08®) IN A POPULATION OF MALES EXHIBITING INATTENTION AND HYPERACTIVITY AGED 6 TO 14 YEARS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.

Kean JD, Downey LA, Sarris J, et al.

The current study investigated the efficacy of extract of Bacopa monnieri (BM; CDRI 08®) in reducing levels of inattention and hyperactivity in young children. BM has demonstrated improvements in cognitive outcomes in adults, yet little research is available on its effects in younger populations. A 14-week randomized, double-blind, placebo-controlled clinical trial, with placebo run-in and run-out phases, investigated the effects of BM on behavioural, cognitive, mood, and sleep effects in male children aged 6 to 14 years against placebo. One-hundred and twelve participants were recruited into the trial, with 93 datasets available for analysis. No significant behavioural differences were noted between treatment groups. Cognitive outcomes indicated decreased error-making in children taking CDRI 08Â® ($p = .04$) and increased speed of reaction time in those taking placebo ($p = .04$) at study end. Improvements in cognitive flexibility ($p = .01$), executive functioning ($p = .04$), interpersonal problems ($p = .02$), and sleep routine ($p = .04$) were noted in those consuming CDRI 08® over placebo. CDRI 08® did not improve behavioural outcomes, but may have cognitive, mood and sleep benefits in children aged 6 to 14 years. Further study is required to support the findings presented here

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PLoS ONE. 2022;17:e0263366.

EXPERIENCES OF CRITICISM IN ADULTS WITH ADHD: A QUALITATIVE STUDY.

Beaton DM, Sirois F, Milne E.

People with ADHD are at high risk of receiving criticism from others, yet criticism has not been well researched in this population. This study aimed to provide a rich understanding of what experiences adults with ADHD traits have with criticism. As part of a larger study, 162 participants with ADHD and high ADHD traits provided a written response to an open question asking about their experiences of criticism from other people. Thematic analysis was used to identify five common themes in the responses. Behaviours associated with inattention were perceived as the most criticised, whilst impulsive behaviours were mostly criticised in social contexts. Criticism was perceived via numerous conducts and was reported to have negative consequences for self-worth and wellbeing. To cope, some participants avoided criticism or changed how they reacted, including trying to accept themselves as they are. The responses indicated that receiving understanding from others played an important role in whether criticism was perceived. Overall, the findings highlight the need for more knowledge, understanding and acceptance towards neurodiversity from the general population

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Prog Neuropsychopharmacol Biol Psychiatry. 2021 Aug;110:110326.

THE PEDIATRIC PSYCHOPHARMACOLOGY OF AUTISM SPECTRUM DISORDER: A SYSTEMATIC REVIEW - PART I: THE PAST AND THE PRESENT.

Persico AM, Ricciardello A, Lamberti M, et al.

Autism Spectrum Disorder (ASD) is a severe and lifelong neurodevelopmental disorder, with high social costs and a dramatic burden on the quality of life of patients and family members. Despite its high prevalence, reaching 1/54 children and 1/45 adults in the United States, no pharmacological treatment is still directed to core symptoms of ASD, encompassing social and communication deficits, repetitive behaviors, restricted interests, and abnormal sensory processing. The purpose of this review is to provide an overview of the state-of-the-art of psychopharmacological therapy available today for ASD in children and adolescents, in order to foster best practices and to organize new strategies for future research. To date, atypical antipsychotics such as risperidone and aripiprazole represent the first line of intervention for hyperactivity, impulsivity, agitation, temper outbursts or aggression towards self or others. Tricyclic antidepressants are less prescribed because of uncertain efficacy and important side effects. SSRIs, especially fluoxetine and sertraline, may be effective in treating repetitive behaviors (anxiety and obsessive-compulsive symptoms) and irritability/agitation, while mirtazapine is more helpful with sleep problems. Low doses of buspirone have shown some efficacy on restrictive and repetitive behaviors in combination with behavioral interventions. Stimulants, and to a lesser extent atomoxetine, are effective in reducing hyperactivity, inattention and impulsivity also in comorbid ASD-ADHD, although with somewhat lower efficacy and greater incidence of side effects compared to idiopathic ADHD. Clonidine and guanfacine display some efficacy on hyperactivity and stereotypic behaviors. For several other drugs, case reports and open-label studies suggest possible efficacy, but no randomized controlled trial has yet been performed. Research in the pediatric psychopharmacology of ASD is still faced with at least two major hurdles: (a) Great interindividual variability in clinical response and side effect sensitivity is observed in the ASD population. This low level of predictability would benefit from symptom-specific treatment algorithms and from biomarkers to support drug choice; (b) To this date, no psychoactive drug appears to directly ameliorate core autism symptoms, although some indirect improvement has been reported with several drugs, once the comorbid target symptom is abated

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Psychopharmakotherapie. 2021;28:223.

ADHD IN CHILDREN AND ADOLESCENTS. NEW METHYLPHENIDATE PREPARATION: STABLE DRUG LEVEL OWING TO SIMPLE APPLICATION.

Eimer M.

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Res Dev Disabil. 2022;123.

VISUAL-MOTOR ATTENTION IN CHILDREN WITH ADHD: THE ROLE OF AUTOMATIC AND CONTROLLED PROCESSES.

Fabio RA, et al.

Background: there are evidence that children with ADHD exhibit a deficit both in automatic and controlled processes. Aims: the present study aimed to examine the visual-motor attention and the influence of cognitive load through a dual task paradigm in children with ADHD compared with typical developing children (TD).

Methods and procedures: 113 children with ADHD: 40 with subtype inattentive (ADHD- I group), 16 with subtype hyperactive (ADHD-H group), 57 with subtype combined (ADHD-C group), and 113 TD children (TD group) were recruited. We used a dual-task paradigm in which the primary task was a figure-tracing test whereas the second task was a digit span test. A figure-tracing test was used to evaluate visual motor attention. Based on the length and intersection of the lines, the figures of the primary task were categorized into simple and complex.

Outcomes and results: the ADHD groups compared to the TD group showed a worse accuracy of performance in both condition with and without cognitive load.

Conclusions and implications: The findings were discussed in light of the relationship between automatic and controlled processes involved in the visual-motor attention

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Rev Neurol. 2021 Nov;73:339-44.

QUALITY OF LIFE AND PSYCHIATRIC COMORBIDITIES IN PEDIATRIC PATIENTS WITH GILLES DE LA TOURETTE SYNDROME.

Solais-Garcia G, et al.

INTRODUCTION: Tourette Syndrome (TS) is a complex neurodevelopmental disorder which is normally associated to psychiatric comorbidity such as attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety or depression. Quality of life (QoL) in these patients can be affected by tic severity and associated comorbidities. AIM: The aim of the study was to describe and analyze QoL and psychiatric comorbidities in a sample of pediatric patients, as well as to develop a Spanish version of the questionnaire CandA-GTS-QoL to measure quality of life in this population.

PATIENTS AND METHODS: Single-center, observational, prospective study. Patients aged 6 to 16 years old with TS were included. Demographic, clinical, diagnostic and treatment data were gathered. Questionnaires regarding tic severity, psychiatric comorbidity and quality of life were used.

RESULTS: Twenty-two patients with DSM-5 diagnosis of TS were included (86.4% male, median age 11 years). Of those, 86.4% had been previously diagnosed of psychiatric comorbidities and 72.7% received psychopharmacologic treatment. The prevalence of an ICD-10 current diagnosis of anxiety was 72.7%, depression 50%, ADHD 40.9% and OCD 7.3%. Median QoL score was 59.5 (RIC: 34.8-71.3) for PedsQL, and 55.5 (RIC: 45-65) for CandA-GTS-QoL, with a correlation between scores of $R2 = 0.83$ ($p < 0.01$). Higher tic severity was associated with poorer QoL (PedsQL R2: -0.732, $p <0.01$, CandA-GTS-QoL R2: -0.501, $p = 0.021$). A higher EDAH score for ADHD was associated with poorer QoL (PedsQL R2: -0.463, $p = 0.03$, CandA-GTS-QoL R2-0.534, $p < 0.01$).

CONCLUSION: Prevalence of psychiatric comorbidities in pediatric TS is high and frequently underdiagnosed. Tics and psychiatric comorbidities affect quality of life. Further studies are needed to validate the Spanish version of CandA-GTS-QoL scale

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Rev Neurol. 2021 Nov;73:403-08.

VARIABILITY OF THE CLINICAL EXPRESSION OF KCNB1 ENCEPHALOPATHY.

Púa-Torrejón R, et al.

INTRODUCTION: The KCNB1 gene encodes a voltage-dependent potassium channel that regulates transmembrane currents in pyramidal neurons. Heterozygous variants have recently been associated with early-onset epileptic encephalopathies and intellectual disability, but their clinical characterisation has not yet been fully defined.

AIM: To describe the clinical spectrum associated with variants of KCNB1 in paediatric patients.

PATIENTS AND METHODS: Retrospective study of four patients from three families with KCNB1 encephalopathy, including an analysis of the clinical and electroencephalographic features of epilepsy, associated neurological manifestations and neurodevelopmental pattern.
RESULTS: In two of them, the mutation in KCNB1 was de novo; the other two, who were sisters, inherited the variant from a parent with germline mosaicism. All had mild-to-moderate intellectual disability, two patients had autistic spectrum disorder and two had attention deficit hyperactivity disorder. Only case 2 displayed alterations in the MRI brain scan: progressive cortical atrophy. Three of them developed epilepsy (cases 1-3). Case 1: onset at 9.5 months with West syndrome that was well controlled with vigabatrine and zonisamide. Case 2: onset at 13 months with West syndrome, evolutionary development of polymorphic seizures (atonic, hypermotor, dysautonomic and tonic) that were refractory to 10 antiepileptic drugs and corticosteroids. Accompanied by a movement disorder characterised by ataxia, dyskinesias and tremor. Case 3: onset at 14.5 years with atonic seizures, multifocal EEG pattern and adequate control with levetiracetam.
CONCLUSIONS: KCNB1 encephalopathy has a heterogeneous natural history, mainly with respect to epilepsy, ranging from patients with refractory epilepsy to patients without any epileptic seizures. All had neurodevelopmental disorders, such as intellectual disability or autism spectrum disorder, independent of epilepsy

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Rev Neurol. 2021 Nov;73:307-14.

PAIN AND ACHILLES TENDON SHORTENING IN PATIENTS WITH IDIOPATHIC TOE WALKING.

López-López J, ulido-Valdeolivas I, artÃn-Gonzalo JA, et al.

INTRODUCTION: Idiopathic toe walking (ITW) is a heterogeneous disorder, which is associated with muscle shortening in lower limbs, pain and neurodevelopmental disorders. We try to study the frequency of clinical features in patients with ITW.
PATIENTS AND METHODS: Out of 100 patients evaluated with toe walking in a pediatric rehabilitation clinic, 77 (24,7% women) patients were diagnosed with ITW by means of TWT questionnaire. Achilles' tendon shortening with Silfverskiold manoeuvre, pain and attention deficit hyperactivity disorder (ADHD) were studied. In the group of patients with pain (n = 30), we studied pain evolution by means of a telephonic interview which assessed intensity, location, school absenteeism and used therapies.
RESULTS: Out of 77 patients, 44.2% had family history of toe walking. 37.7% and 9.1% showed Achilles' tendon shortening and Knee flexor shortening, respectively. Confirmed diagnosed of ADHD was present in 9.1% and was suspected in 20.8%. The older the patient was, the higher frequency of pain and the lower passive ankle dorsiflexion. Pain has a moderate-severe intensity, was related with school absenteeism in 42.3% of the patients with pain. Pain was located mainly on the calf, the ankle and the foot. It was treated with physiotherapy, oral pain relievers, orthosis and botulinum toxin type A (BTxA).
CONCLUSIONS: Pain in ITW is frequent, have a moderate-severe intensity, interferes in normal life and is referred in older children with lower ankle dorsiflexion. We found a common association between ITW and ADHD which points out ITW as alarm sign of learning problems

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Sch Psychol. 2022 Mar;37:147-59.

A PRELIMINARY EXAMINATION OF KEY STRATEGIES, CHALLENGES, AND BENEFITS OF REMOTE LEARNING EXPRESSED BY PARENTS DURING THE COVID-19 PANDEMIC.

Roy AK, Breaux R, Sciberras E, et al.

Among the many impacts of the Coronavirus disease (COVID-19) pandemic, one of the most dramatic was the immediate closure of in-person schooling in March/April 2020 when parents were faced with much greater responsibility in supporting their children's learning. Despite this, few studies have examined parents' own perspectives of this experience. The aims of this preliminary study were to (a) identify challenges, benefits, and useful strategies related to remote learning and (b) examine differences in findings across two countries, between parents of youth with and without attention-deficit/hyperactivity disorder (ADHD), and between parents of children and adolescents. To address these aims, parent responses to open-ended questions on the Home Adjustment to COVID-19 Scale (HACS; Becker, Breaux, et al., 2020) were examined across three

studies conducted in the United States and Australia (N = 606, children: 68.5% male, ages 6-17 years). The challenges most frequently expressed by parents included the child's difficulty staying on task (23.8% of parents), lack of motivation (18.3%), remote learning factors (17.8%), and lack of social interaction (14.4%). The most frequently expressed strategy related to using routines and schedules (58.2%) and the biggest benefit was more family time (20.3%). Findings were largely consistent across countries, ADHD status, and age, with a few notable group differences. Given that the most common challenges involved child- (e.g., difficulties with staying on task and motivation), parent- (e.g., balancing remote learning with work responsibilities), and school- (e.g., remote instruction difficulties) related factors, there is a need for improved support across these systems going forward

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Sch Psychol. 2022 Jan;37:26-36.

INCORPORATING CALLOUS-UNEMOTIONAL BEHAVIORS INTO SCHOOL-BASED RESEARCH.

Willoughby MT, Murray D, Kuhn LJ, et al.

This study investigated the utility of including teacher-reported callous-unemotional (CU) behaviors in the assessment of disruptive behaviors in school-based research. Participants included 138 first- and second-grade children (68% male; 76% eligible for free or reduced-price lunch; 61% Black, 9% Latinx, 23% White, and 7% multiracial) who completed assessments during the baseline assessment of an intervention study. Results indicated that teachers could distinguish CU from traditional indicators of disruptive behavior, including attention deficit hyperactivity disorder (ADHD) behaviors and conduct problems (CP). When considered alone, there was mixed evidence for the utility of CU behaviors. Although higher levels of CU behaviors explained unique variation in teacher-reported social competence and global impairment, CU behaviors did not explain unique variation in disciplinary infractions, classroom behavior, or academic functioning after accounting for ADHD and CP behaviors. A different pattern of results was evident when CU was considered in conjunction with ADHD and CP behaviors. Latent profile analyses identified three subgroups of participants (i.e., a nondisruptive group, an ADHD group, and a comorbid group, who exhibited elevated levels of ADHD, CP, and CU). Compared to the nondisruptive group, the ADHD group exhibited higher rates of off-task classroom behavior and worse academic functioning. The comorbid group exhibited moderate-to-large differences from both groups on teacher-reported and objective outcomes. The implications of these results are discussed with respect to the potential value of incorporating CU behaviors, which are becoming prominent in clinical psychology and psychiatry, into school-based research and for school psychology practice. (PsycInfo Database Record (c) 2022 APA, all rights reserved)

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Sci Rep. 2021 Dec;11:24276.

CONTRIBUTION OF VASCULAR RISK FACTORS TO THE RELATIONSHIP BETWEEN ADHD SYMPTOMS AND COGNITION IN ADULTS AND SENIORS.

Callahan BL, Plamondon A, Gill S, et al.

Symptoms of attention-deficit/hyperactivity disorder (ADHD) in childhood have been found to be predictive of compromised cognitive function, and possibly even dementia, in later adulthood. This study aimed to test vascular risk as a hypothesized moderator or mediator of this association, because individuals with elevated ADHD symptoms frequently have comorbid vascular disease or risk factors which are recognized to contribute to later-life cognitive decline. Data from 1,092 adults aged 18-85 were drawn from the Enhanced Nathan Kline Institute Rockland Sample. Childhood ADHD symptoms (assessed using the Adult ADHD Clinical Diagnostic Scale) were assessed as predictors of cognitive functioning in adulthood (assessed using subtests from the University of Pennsylvania Computerized Neurocognitive Battery, the Delis-Kaplan Executive Functioning System, and the Wechsler Memory Scale). Vascular risk factors (including diabetes, tobacco use, obesity, hypertension, and hypercholesterolemia) were tested as both a moderator and mediator of this relationship. Childhood ADHD symptoms and vascular risk factors were both independently associated with later-life cognition, but vascular risk was not a significant moderator or mediator of relationships between ADHD symptoms and cognition in statistical models. Results from this large

community sample suggest that the relationship between ADHD symptoms and cognition is not accounted for by vascular risk. This question should also be investigated in clinical samples

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Sci Rep. 2021 Nov;11:22628.

LARGE-SCALE GENETIC INVESTIGATION REVEALS GENETIC LIABILITY TO MULTIPLE COMPLEX TRAITS INFLUENCING A HIGHER RISK OF ADHD.

Garcia-Marin LM, Campos AI, et al.

Attention Deficit-Hyperactivity Disorder (ADHD) is a complex psychiatric and neurodevelopmental disorder that develops during childhood and spans into adulthood. ADHD's aetiology is complex, and evidence about its cause and risk factors is limited. We leveraged genetic data from genome-wide association studies (GWAS) and performed latent causal variable analyses using a hypothesis-free approach to infer causal associations between 1387 complex traits and ADHD. We identified 37 inferred potential causal associations with ADHD risk. Our results reveal that genetic variants associated with iron deficiency anemia (ICD10), obesity, type 2 diabetes, synovitis and tenosynovitis (ICD10), polyarthritis (ICD10), neck or shoulder pain, and substance use in adults display partial genetic causality on ADHD risk in children. Genetic variants associated with ADHD have a partial genetic causality increasing the risk for chronic obstructive pulmonary disease and carpal tunnel syndrome. Protective factors for ADHD risk included genetic variants associated with the likelihood of participating in socially supportive and interactive activities. Our results show that genetic liability to multiple complex traits influences a higher risk for ADHD, highlighting the potential role of cardiometabolic phenotypes and physical pain in ADHD's aetiology. These findings have the potential to inform future clinical studies and development of interventions

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Sci Rep. 2022 Feb;12:2080.

ASSOCIATION BETWEEN BIRTH WEIGHT AND NEURODEVELOPMENTAL DISORDERS ASSESSED USING THE KOREAN NATIONAL HEALTH INSURANCE SERVICE CLAIMS DATA.

Song IG, Kim HS, Cho YM, et al.

The risk of neurodevelopmental disorders in low birth weight (LBW) infants has gained recognition but remains debatable. We investigated the risk of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in school-aged children according to their birth weight. We conducted a retrospective cohort study using the Korean National Health Insurance claims data of 2,143,652 children who were born between 2008 and 2012. Gestational age of infants was not available; thus, outcomes were not adjusted with it. Not only infants with birth weights of<1.5 kg, but also 2.0-2.4 kg and 1.5-1.9 kg were associated with having ADHD; odds ratio (OR), 1.41 (95% confidence interval [CI] 1.33-1.50), and 1.49 (95% CI 1.33-1.66), respectively. The OR in infants with birth weights of 2.0-2.4 kg and 1.5-1.9 kg was 1.91 (95% CI 1.79-2.05) and 3.25 (95% CI 2.95-3.59), respectively, indicating increased odds of having ASD. Subgroup analysis for children without perinatal diseases showed similar results. In this national cohort, infants with birth weights of<2.5 kg were associated with ADHD and ASD, regardless of perinatal history. Children born with LBW need detailed clinical follow-up

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Sci Rep. 2022 Feb;12:2073.

DEVELOPMENT OF COORDINATION AND MUSCULAR FITNESS IN CHILDREN AND ADOLESCENTS WITH PARENT-REPORTED ADHD IN THE GERMAN LONGITUDINAL MOMO STUDY.

Opper E, Kunina-Habenicht O, Oriwol D, et al.

This study examined the development of muscular fitness and coordination in children and adolescents with and without attention deficit hyperactivity disorder (ADHD) over a period of 11Â years. Data was collected in three measurement waves as part of the longitudinal, representative Motorik-Modul (MoMo) study in Germany (2003-2006, 2009-2012, 2014-2017). The overall sample comprised 2988 participants (253 with ADHD, 65% males; 2735 non-ADHD, 47% males; mean age 9Â years). Structural equation modeling was conducted, and the estimated models had a good fit. No differences in muscular fitness were observed between participants with and without ADHD. Participants with ADHD had a lower coordinative performance

at first measurement than those without ADHD. The difference in coordinative performance persisted throughout the study period

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Sci Rep. 2022 Jan;12:1352.

AUDITORY TIME THRESHOLDS IN THE RANGE OF MILLISECONDS BUT NOT SECONDS ARE IMPAIRED IN ADHD.

Anobile G, Bartoli M, Pfanner C, et al.

The literature on time perception in individuals with ADHD is extensive but inconsistent, probably reflecting the use of different tasks and performances indexes. A sample of 40 children/adolescents (20 with ADHD, 20 neurotypical) was engaged in two identical psychophysical tasks measuring auditory time thresholds in the milliseconds (0.25–1 s) and seconds (0.75–3 s) ranges. Results showed a severe impairment in ADHD for milliseconds thresholds (Log10BF = 1.9). The deficit remained strong even when non-verbal IQ was regressed out and correlation with age suggests a developmental delay. In the seconds range, thresholds were indistinguishable between the two groups (Log10BF = − 0.5) and not correlated with milliseconds thresholds. Our results largely confirm previous evidence suggesting partially separate mechanisms for time perception in the ranges of milliseconds and seconds. Moreover, since the evidence suggests that time perception of milliseconds stimuli might load relatively less on cognitive control and working memory, compared to longer durations, the current results are consistent with a pure timing deficit in individuals with ADHD

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Sleep Health. 2021 Jun;7:375-83.

LINKS BETWEEN PARENT-REPORTED MEASURES OF POOR SLEEP AND EXECUTIVE FUNCTION IN CHILDHOOD AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Holingue C, Volk H, Crocetti D, et al.

OBJECTIVES: This study sought to assess whether poor sleep is associated with aspects of executive function (EF) among children with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), or typical development (TD), after adjusting for demographic variables, stimulant medications, intelligence, anxiety, inattention, and hyperactivity.

DESIGN: Cross-sectional.

SETTING: Children recruited through ongoing studies at the Kennedy Krieger Institute.

PARTICIPANTS: We studied 735 children (323 TD; 177 ASD; 235 ADHD) aged 8 to 12 years.

MEASUREMENTS: We investigated associations of parent-reported sleep measures from the Children's Sleep Habits Questionnaire (CSHQ) with parent-report measures of EF and performance-based processing speed with each clinical population. EF was measured using 8 clinical T scores that fall under 2 domains (behavioral regulation and metacognition) from the Behavior Rating Inventory of EF (BRIEF) and the processing speed index from the Wechsler Intelligence Scale for Children-IV or -V.

RESULTS: Higher CSHQ scores were associated with poorer EF on all BRIEF scales, across all child groups, after adjustment for demographic factors, stimulant medications, and IQ. Among children with ADHD, these associations largely remained after adjusting for anxiety. Among those ASD, anxiety partially accounted for these associations, especially for behavioral regulation EF outcomes. Co-occurring symptoms of inattention and hyperactivity/impulsivity further accounted for the associations between sleep and EF. Poor sleep was not significantly associated with processing speed.

CONCLUSIONS: Strong links exist between parent-reported poor sleep and executive dysfunction in children with typical development. Targeting anxiety may alleviate executive dysfunction, especially among children with ASD

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S Afr J Psychiatry. 2022;28.

WORKING MEMORY AND SET-SHIFTING IN SCHOOL-AGED CHILDREN CLASSIFIED AS HAVING ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Mphahlele RM, Meyer A, Pillay BJ.

Background: Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric disorder reported in both children and adults; it is often associated with a variety of executive functioning deficits.
Aim: This study investigated the extent to which working memory and set-shifting are impaired in school children with and without ADHD.
Setting: This included primary schools in Lepelle-Nkumpi Municipality in Limpopo province, South Africa.
Methods: A total of 216 children (108 screened positive for ADHD and 108 matched controls without ADHD symptoms), aged between 6 and 15 years, participated in the study. The performance of the two groups was compared on tests of working memory (Forward and Backward Digit Span subtests of the Wechsler Intelligence Scale for Children Fourth Edition) and set-shifting (Trail Making Test Part B). The scores were analysed as a function of gender and age.
Results: The group with possible ADHD performed worse than the neurotypical control group on tasks of working memory and set-shifting. The results did not indicate that gender affected performance. However, the younger age group performed worse than the older children.
Conclusion: Children classified as ADHD showed significantly more impairments in working memory and set-shifting than neurotypical controls. Neither test showed any significant difference between male and female performance, whilst age was shown to affect performance on both tests. Early identification and treatment of children with attention-deficit hyperactivity disorder are crucial to their well-being

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Syst Rev. 2022 Feb;11:28.

SYNTHESISING THE EXISTING EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS TARGETING OUTCOMES RELEVANT TO YOUNG PEOPLE WITH ADHD IN THE SCHOOL SETTING: SYSTEMATIC REVIEW PROTOCOL.

Russell AE, Moore D, Sanders A, et al.

BACKGROUND: Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) have impairing levels of difficulty paying attention, impulsive behaviour and/or hyperactivity. ADHD causes extensive difficulties for young people at school, and as a result these children are at high risk for a wide range of poor outcomes. We ultimately aim to develop a flexible, modular 'toolkit' of evidence-based strategies that can be delivered by primary school staff to improve the school environment and experience for children with ADHD; the purpose of this review is to identify and quantify the evidence-base for potential intervention components. This protocol sets out our plans to systematically identify non-pharmacological interventions that target outcomes that have been reported to be of importance to key stakeholders (ADHD symptoms, organisation skills, executive-global- and classroom-functioning, quality of life, self-esteem and conflict with teachers and peers). We plan to link promising individual intervention components to measured outcomes, and synthesise the evidence of effectiveness for each outcome.
METHODS: A systematic search for studies published from the year 2000 that target the outcomes of interest in children and young people aged 3-12 will be conducted. Titles and abstracts will be screened using prioritisation software, and then full texts of potentially eligible studies will be screened. Systematic reviews, RCTs, non-randomised and case-series studies are eligible designs. Synthesis will vary by the type of evidence available, potentially including a review of reviews, meta-analysis and narrative synthesis. Heterogeneity of studies meta-analysed will be assessed, along with publication bias. Intervention mapping will be applied to understand potential behaviour change mechanisms for promising intervention components.
DISCUSSION: This review will highlight interventions that appear to effectively ameliorate negativeÂ outcomes that are of importance for people with ADHD, parents, school staff and experts. Components of intervention design and features that are associated with effective change in the outcome will be delineated and used to inform the development of a 'toolkit' of non-pharmacological strategies that school staff can use to improve the primary school experience for children with ADHD.
TRIAL REGISTRATION: PROSPERO number CRD42021233924

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Lancet Psychiatry. 2022;9:222-31.

STRUCTURAL BRAIN MEASURES AMONG CHILDREN WITH AND WITHOUT ADHD IN THE ADOLESCENT BRAIN AND COGNITIVE DEVELOPMENT STUDY COHORT: A CROSS-SECTIONAL US POPULATION-BASED STUDY.

Bernanke J, Luna A, Chang L, et al.

Background: Structural neuroimaging research has identified a variety of abnormalities in cortical and subcortical structures in children with ADHD. However, studies to date have not employed large, non-referred samples, complete with data on potential confounding variables. Here, we tested for differences in structural MRI measures among children with and without ADHD using data from the Adolescent Brain and Cognitive Development (ABCD) Study, the largest paediatric brain imaging study in the USA.

Methods: In this cross-sectional study, we used baseline demographic, clinical, and neuroimaging data from the ABCD Study, which recruited children aged 9ΓÇô10 years between Sept 1, 2016, and Aug 31, 2018, representative of the sociodemographic features of the US population. ADHD was diagnosed by parent report of symptoms. Neuroimaging data underwent centralised quality control and processing by the ABCD team. Linear mixed effects models were used to estimate Cohen's d values associated with ADHD for 79 brain measures of cortical thickness, cortical area, and subcortical volume. We used a novel simulation strategy to assess the ability to detect significant effects despite potential diagnostic misclassification.

Findings: Our sample included 10 736 participants (5592 boys, 5139 girls; 5692 White, 2165 Hispanic, 1543 Black, 221 Asian, and 1100 of other race or ethnicity), of whom, 949 met the criteria for ADHD and 9787 did not. In the full model, which included potential confounding variables selected a priori, we found only 11 significant differences across the 79 brain measures after false discovery rate correction, all indicating reductions in brain measures among participants with ADHD. Cohen's d values were small, ranging from 0-11 to 0-06, and were not meaningfully changed by using a more restrictive comparison group or alternative diagnostic methods. Simulations indicated adequate statistical power to detect differences even if there was substantial diagnostic misclassification.

Interpretation: In a sample representative of the general population, children aged 9-10 years with ADHD differed only modestly on structural brain measures from their unaffected peers. Future studies might need to incorporate other MRI modalities, novel statistical approaches, or alternative diagnostic classifications, particularly for research aimed at developing ADHD diagnostic biomarkers.

Funding: Edwin S Webster Foundation and Duke University, NC, USA

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Turkish Journal of Biochemistry. 2021;46:655-60.

COMPARISON OF NITRIC OXIDE AND ADRENOMEDULLIN LEVELS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ANXIETY DISORDER.

Karagaz YS, et al.

Objectives: Many studies show that adrenomedullin (ADM) is associated with nitric oxide (NO) and various mechanisms and is involved in the etiopathogenesis of schizophrenia, bipolar disorder and autism by oxidative stress and HPA axis dsyregulation. The aim of this study comparison of nitric oxide and adrenomedullin levels in children with ADHD, AD and healthy control included in our study, especially due to their effect mechanisms as they may predict anxiety symptom, was to investigate the relationship between nitric oxide and adrenomedullin levels and anxiety symptoms in children with ADHD, AD and healthy control.

Methods: The study included 27 ADHD, 27 AD and 23 healthy children without any previous drug use, without comorbid disease. The semi-structured interview was conducted by the researcher in all the children attending the study. Sociodemographic information form, ConnerΓÇÖs Parent and Teacher Rating scale and State-Trait Anxiety Inventory (STAI) were evaluated. NO level measured by spectrophotometer, ADM levels were measured by ELISA.

Results: There was no statistically significant difference in the serum NO and ADM levels of the children included in the sampling group according to age and sex. There was no statistically significant difference between NO and ADM levels between ADHD, AD and control groups. There was no statistically significant relationship between serum NO and ADM levels and ADHD, AD and control group children of state-trait anxiety scores.

Conclusions: These findings may suggest that NO and ADM levels in children with ADHD, AD do not show these diseases and that these parameters are not associated with anxiety symptoms

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Z Kinder Jugendpsychiatr Psychother. 2021 Mar;50:105-19.

SUBSTANCE USE, RESULTING DISORDERS, AND COLLATERAL MENTAL DISORDERS AMONG ADOLESCENTS IN A SPECIAL OUTPATIENT INSTITUTIONS FOR ADDICTIONS.

Wiedmann M, Atzendorf J, Basedow LA, et al .

Substance Use, Resulting Disorders, and Collateral Mental Disorders Among Adolescents in a Special Outpatient Institutions for Addictions Abstract. Objective: Only few clinics offer the outpatient treatment of substance use disorders (SUDs) among adolescents. Therefore, only limited data describe substance use patterns, SUDs, and co-occurring psychiatric disorders characteristic of adolescents who present in such outpatient clinics specialized in the treatment of SUDs. Method: Via interview we collected data from n = 201 patients between 12 and 19 years concerning their substance use, SUDs, and current co-occurring psychiatric disorders. We created descriptive presentation of data regarding use patterns, SUDs, and co-occurring disorders divided by sex and current age. Results: Tobacco (88 %) and cannabis (86 %) were the most frequently used substances. 67 % of all patients presented with more than one SUD, cannabis use disorder being the most prevalent one (84 %). 72 % presented with at least one co-occurring disorder, with conduct disorders (40 %), attention deficit (hyperactivity) disorders (21 %), and depressive disorders (18 %) being the most frequent ones. Conclusions: Adolescent SUD patients often present with co-occurring psychiatric disorders. Institutions for adolescent SUD treatment should also focus on treating co-occurring conduct disorders, depression, and attention deficit disorders

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Zhonghua Er Ke Za Zhi. 2022 Mar;60:263-66.

TREATMENT ADVANCES IN PEDIATRIC TIC DISORDERS AND ITS COMORBIDITY.

Xin YY, Sun D, Liu ZS.

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genes

MDPI

Article

Brain Anatomical Mediators of *GRIN2B* Gene Association with Attention/Hyperactivity Problems: An Integrated Genetic-Neuroimaging Study

Maria Nobile [1,†], Eleonora Maggioni [2,†], Maddalena Mauri [1,3], Marco Garzitto [4], Sara Piccin [5], Carolina Bonivento [4], Roberto Giorda [6], Rossano Girometti [7], Barbara Tomasino [4], Massimo Molteni [1], Franco Fabbro [4] and Paolo Brambilla [2,8,9,*]

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Abstract: This study aims to investigate the genetic and neural determinants of attention and hyperactivity problems. Using a proof-of-concept imaging genetics mediation design, we explore the relationship between the glutamatergic *GRIN2B* gene variants and inattention/hyperactivity with neuroanatomical measures as intermediates. Fifty-eight children and adolescents were evaluated for behavioral problems at three time points over approximately 7 years. The final assessment included blood drawing for genetic analyses and 3T magnetic resonance imaging. Attention/hyperactivity problems based on the Child Behavior Checklist/6-18, six *GRIN2B* polymorphisms and regional cortical thickness, and surface area and volume were estimated. Using general linear model (GLM) and mediation analyses, we tested whether *GRIN2B* exerted an influence on stable inattention/hyperactivity over development, and to what extent this effect was mediated by brain morphology. GLM results enlightened the relation between *GRIN2B* rs5796555-/A, volume in the left cingulate isthmus and inferior parietal cortices and inattention/hyperactivity. The mediation results showed that rs5796555-/A effect on inattention/hyperactivity was partially mediated by volume in the left isthmus of the cingulate cortex, suggesting a key role of this region in translating glutamatergic *GRIN2B* variations to attention/hyperactivity problems. This evidence can have important implications in the management of neurodevelopmental and psychiatric disorders.

Keywords: imaging genetics; magnetic resonance imaging; neurodevelopment; mediation; gray matter volume; cortical surface area; cortical thickness

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1. Introduction

Attention and hyperactivity problems—which are core symptoms of attention deficit/hyperactivity disorder (ADHD) but are also expressed in other developmental internalizing and externalizing disorders (e.g., anxiety, depression, oppositional defiant, disruptive mood dysregulation disorders)—are complex behavior traits with a multifactorial etiology: genetic, epigenetic, and environmental factors influence their development and persistence [1,2].

Literature evidence suggests high stability for both attention problems and hyperactivity-impulsivity traits, but their phenotypes seem to follow different developmental trajectories. Indeed, gender, pharmacologic, or psychosocial treatment and environment might influence their manifestation over time [3]. Twin studies on developmental aged cohorts found a high heritability of attention problems, between 70 and 75%. This genetic influence is stable from 3 to 12 years of age, with trait correlations estimated between 0.40 and 0.70 [4,5]. Regarding ADHD diagnosis, heritability is estimated at 70% [6,7].

One of the most frequently investigated genes in populations with attention and hyperactivity problems is the glutamatergic *GRIN2B*, a moderately large gene located on chromosome 12p13.1, comprising 13 exons and spanning a genomic region of approximately 400 kb [8].

GRIN2B codes for the Glun2B subunit of N-Methyl-D-Aspartate (NMDA) receptor, which mediates the slow Ca^{+} component of excitatory synaptic transmission in the central nervous system. Glun2B is highly expressed prenatally [9] and plays a central role in brain development, synaptic plasticity, and long-term potentiation [10,11].

These molecular mechanisms are crucial in the development of different cognitive functions, such as memory, learning, and attention [12,13]. In fact, *GRIN2B* variants have been associated not only with ADHD [8], but also with cognitive deficits in heterogeneous neurodevelopmental and psychiatric disorders, including autism spectrum disorders, Alzheimer's and Parkinson's diseases, bipolar disorder, and schizophrenia [14–18].

In recent years, the joint analysis of genomic and neuroimaging data, known as imaging genetics, has provided the opportunity to get a more complete knowledge of how genetic and neurobiological factors interplay to determine behaviors [19]. Imaging genetics research sets its roots on the evidence of a close association of genetics with brain structure and function, in accord with the notion that brain physiology is etiologically closer to molecular biology than behavior [20]. In this line, studies of genetic effects on behavior should account for neuroimaging parameters as intermediate phenotypes, which may influence the link between genetic variants and complex behaviors.

In Imaging genetics literature, there is evidence of an association between variants in glutamate system genes, including *GRIN2B* polymorphisms, and neuroimaging phenotypes in healthy and clinical populations [21,22]. Recent magnetic resonance studies have suggested a link between *GRIN2B* variants and abnormal glutamatergic neurotransmission and brain volume in children and adolescents with obsessive compulsive [23] and alcohol use [24] disorders. Although ADHD has been shown to share symptoms and risk factors with these disorders [25,26], the complex relationships between the *GRIN2B* gene, brain, and inattention/hyperactivity traits remain largely unknown.

In this pilot work, for the first time, we explore the possible link between *GRIN2B* marker variants, changes in brain morphology, and attention/hyperactivity problems in a juvenile sample. Through an exploratory mediation design, we intend to verify whether *GRIN2B* polymorphisms influence attention and hyperactivity phenotypes and, if yes, if such an effect is mediated (and in what proportions) by brain morphology.

2. Materials and Methods

2.1. Longitudinal Study Protocol

The present study is part of the Genesis Project, an imaging genetics longitudinal study conducted to identify and understand developmental trajectories of mental disorders in children and adolescents.

The Genesis Project involved a clinical sample of children and adolescents who were referred for emotional and behavioral problems at the Scientific Institute IRCCS Eugenio Medea (Italy) [27,28]. The research design involved three observations of the recruited cohort. At Wave 0, a demographic and clinical assessment of the subjects was performed, including the administration of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version [29], the Child Behavior Checklist (CBCL/6-18) [30], the Barratt's Simplified Measure of Social Status [31] and the Wechsler Intelligence Scale for Children [32]. At Waves 1 and 2, subjects were re-evaluated for emotional and behavioral problems using the CBCL/6-18. At Wave 2, the assessment included blood drawing for genetic analyses and a magnetic resonance imaging (MRI) session. More details are reported in the following sections.

2.2. Subjects

The participants' sociodemographic, clinical and cognitive characteristics are reported in Table 1. The sample included 58 unrelated patients (42 males and 16 females, aged 8.78 ± 2.43 years) who took part in the three waves of the Genesis Project. In the recruited sample, Waves 1 and 2 were conducted 5.74 ± 1.66 and 7.39 ± 1.65 years after Wave 0, respectively.

Table 1. Sociodemographic, clinical and cognitive characteristics of the sample.

	Males (n = 42)	Females (n = 16)	Total (n = 58)
Wave 0			
Age (years) [1]	8.55 ± 2.51	9.38 ± 2.07	8.78 ± 2.43
SES [1]	49.05 ± 18.59	36.25 ± 21.18	45.52 ± 20.17
CBCL Attention Problems [1]	63.10 ± 9.40	66.56 ± 10.37	64.05 ± 9.80
FSIQ [1]	108.81 ± 16.39	109.38 ± 13.93	108.96 ± 15.65
K-SADS-PL DIAGNOSIS [2]			
ADHD	N = 9 (21.4%)	N = 4 (25.0%)	N = 13 (22.4%)
Any behavioral disorder	N = 10 (23.8%)	N = 0 (0.0%)	N = 10 (17.2%)
Any mood disorder	N = 12 (28.6%)	N = 6 (37.5%)	N = 18 (31.0%)
Any anxiety disorder	N = 19 (45.2%)	N = 9 (56.3%)	N = 28 (48.3%)
Other diagnoses	N = 7 (16.7%)	N = 5 (31.3%)	N = 12 (20.7%)
No current diagnosis	N = 2 (4.8%)	N = 1 (6.3%)	N = 3 (5.2%)
Comorbidities	1 diagnosis: N = 25 (59.5%) 2 diagnoses: N = 13 (31.0%) 3 diagnoses: N = 2 (4.8%)	1 diagnosis: N = 8 (50.0%) 2 diagnoses: N = 5 (31.3%) 3 diagnoses: N = 2 (12.5%)	1 diagnosis: N = 33 (56.9%) 2 diagnoses: N = 18 (31.0%) 3 diagnoses: N = 4 (6.9%)
Wave 1			
Age (years) [1]	14.12 ± 2.09	15.58 ± 2.24	14.52 ± 2.23
CBCL Attention Problems[1]	59.48 ± 7.86	62.06 ± 7.24	60.19 ± 7.78
Wave 2			
Age (years) [1]	15.80 ± 2.30	17.14 ± 2.43	16.17 ± 2.41
CBCL Attention Problems [1]	57.83 ± 6.88	59.00 ± 4.98	58.16 ± 6.43

[1] Mean ± standard deviation; [2] N (%). SES: socioeconomic status; FSIQ: full-scale intelligence quotient; K-SADS-PL: Kiddie schedule for affective disorders and schizophrenia for school-age children-present and lifetime version; ADHD: attention deficits/hyperactivity disorder. CBCL: Child Behavior Checklist.

Exclusion criteria were diagnoses of Autism Spectrum Disorder or Intellectual Disability, neurological diseases (including epilepsy and traumatic brain injuries), severe sensory and linguistic comprehension deficits.

The study protocol was approved by the Research Ethical Committee of our Scientific Institute and performed in accordance with the Declaration of Helsinki. Parents' written informed consent to the study was obtained for all participants.

2.3. Behavioral and Clinical Measures

Child Behavior Checklist (CBCL/6-18)

It is an empirically-based checklist of social competence and behavioral problems filled out by parents of children and adolescents aged 6–18 years. According to the Achenbach System of Empirically Based Assessment (ASEBA) [30], CBCL/6-18 items can be scored to obtain the following eight subscales: anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking, aggressive behavior, social, thought and attention problems. The parent responds along a 3-point scale where 0, 1, and 2 indicate that the behavior is not true, sometimes true or often true for the child, respectively. The psychometric stability of the CBCL/6-18 has been well established [33,34].

In this study, we employed the attention problems (AP) scale T scores (mean = 50; standard deviation = 10) based on the set of multicultural norms "group 2", which applies to the normative sample of the Italian population as suggested by the multicultural supplement to the ASEBA manual. The AP scale consists of 11 items (e.g., cannot concentrate, cannot pay attention for long, is impulsive or acts without thinking) assessing both inattentive and hyperactive-impulsive symptoms. For the AP scale, the ASEBA identifies as normal scores below 65, as borderline scores between 65 and 70, and as clinical scores above 70. In the following analyses, we considered the mean score obtained in the AP scale across the three time points, which represents a stable measurement of this behavioral dimension over development.2.3.2. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL).

K-SADS-PL is a semi-structured diagnostic interview created to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria.

2.4. Genotyping

Participants' DNA was obtained from saliva samples collected and extracted using Oragene OG-500 kits (DNA Genotek, Ottawa, Canada). Amplification and sequencing of *GRIN2B* regions allowed us to type rs2268119 A/T, rs22161128 A/G, rs5796555 -/A, rs1012586 G/C, rs11609779 C/T, rs2192973 G/A Single Nucleotide Polymorphisms (SNPs).

Amplifications were performed in 10-µL reactions using JumpStart REDAccuTaq LA DNA polymerase (Sigma-Aldrich, St. Louis, MO, USA) and the following protocol: 30 s at 96 °C, 35 cycles of 15 s at 94 °C/20 s at 58 °C/30 s at 68 °C, 5 min final elongation time. Sequencing reactions were performed with a Big Dye Terminator Cycle Sequencing kit (Applied Biosystems, Monza, Italy) and run on ABI Prism 3130xl (Applied Biosystems, Monza, Italy) and 3500AV Genetic Analyzers (Applied Biosystems, Monza, Italy).

Table 2 shows allelic frequencies and Hardy-Weinberg equilibrium (HWE) for the considered markers. Genotype distributions did not significantly deviate from HWE. No SNPs were therefore excluded from further analyses. The *GRIN2B* linkage disequilibrium structure (Figure 1) shows a squared correlation coefficient between 0.00 and 0.74. Genotypes were grouped into a two-level variable, each level representing the presence or absence of minor frequency alleles.

Table 2. *GRIN2B* allele frequencies and Hardy-Weinberg equilibrium's *p*-values.

GRIN2B SNP	Allele	Frequency [1]	Hardy-Weinberg Equilibrium
rs5796555	- A	0.71 0.29	0.201
rs1012586	G C	0.66 0.34	0.744
rs2268119	A T	0.73 0.27	0.213
rs2216128	A G	0.74 0.26	0.146
rs11609779	C T	0.84 0.16	0.546
rs2192973	G A	0.78 0.22	0.115

SNP: single nucleotide polymorphism. [1] Fraction of the total. - is marker of the allele.

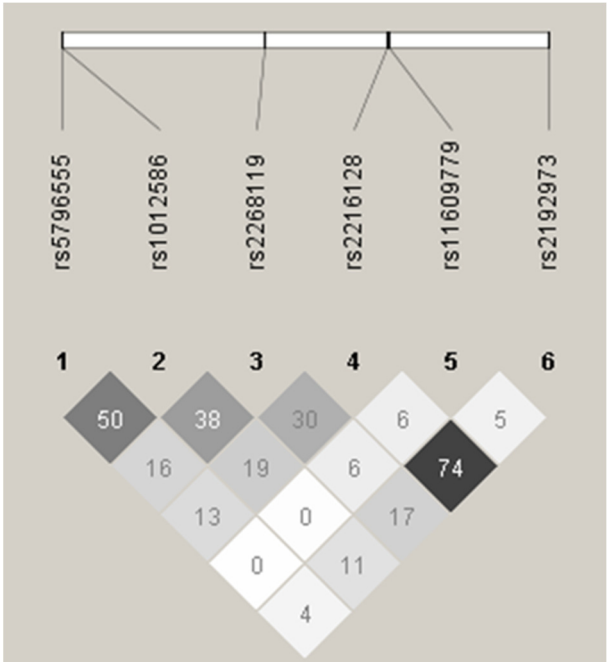

Figure 1. *GRIN2B* linkage disequilibrium. Haploview plot showing pairwise linkage disequilibrium (r^2 values) for 6 SNPs of *GRIN2B* based on the sample's genotypes.

2.5. MRI Data Acquisition

Structural MRI data were acquired in the University Hospital of Udine (Udine, Italy) using a Philips Achieva 3.0 Tesla scanner (Philips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil for radiofrequency transmission and reception. All images were obtained with a T1-weighted MPRAGE 3D TFE sequence, with the following parameters: echo time = 3.7 ms, repetition time = 8.1 ms, in-plane field of view = 240 × 240 mm^2, in-plane matrix size = 240 × 240, 190 axial slices with no gap, voxel size = 1 mm^3.

2.6. MRI Data Processing

The MRI images were processed using the open-source Freesurfer software, v5.3.0 (http://surfer.nmr.mgh.harvard.edu/, downloaded on 8 March 2017) [35], which provides an accurate 3D reconstruction of the cerebral cortex. For each subject, starting from the T1-weighted image, Freesurfer performs a brain tissue segmentation and estimates the gray matter/white matter interface, which is used to model the cortical surfaces. In our

study, the segmentation output and the reconstructed surfaces were visually inspected and corrected, if necessary, by a trained user.

The subject's cortical model was parceled into regions of interest (ROIs) based on the Desikan-Killiany atlas [36] and cortical thickness (CT), cortical surface area (CSA), and gray matter volume (GMV) were estimated at the ROI level and used for the following analyses.

2.7. Statistical Analyses

2.7.1. General Linear Model (GLM) Analyses

In a set of preliminary GLM analyses based on in-house Matlab scripts (R2018b, The Mathworks, Inc. Natick, MA, USA), we investigated the relation among *GRIN2B* markers, brain morphology and inattention/hyperactivity. First, we evaluated the impact of *GRIN2B* SNPs on neuroanatomical parameters (design #1), *GRIN2B* SNPs on inattention/hyperactivity (mean CBCL/6-18 AP score over time) (design #2). We then selected the morphological parameters significantly influenced by the *GRIN2B* SNP/SNPs exerting a significant effect on attention/hyperactivity (intersection of results #1 and #2) and investigated their possible influence on the CBCL/6-18 AP variable (design #3).

GRIN2B SNPs and regional morphological parameters were investigated one by one in separate models, i.e., we performed 1116 GLM analyses for design #1 (combination of 62 ROIs, three surface-based measures for each ROI and 6 *GRIN2B* SNPs) and 6 GLM analyses for design #2. In all GLM designs, age and gender were added as covariates to remove their possible contribution to the results. In designs #1 and #3, the total intracranial volume was used as a normalization factor when focusing on GMV, while the total surface area was used when focusing on CSA.

We made inference using double-sided t-tests, where the significance threshold was set to $p = 0.05$. In the GLM design #1 analyses, in order to limit false positive rates, a correction for multiple comparisons (MC) was applied (N = 37, 31 regions in each hemisphere + 6 *GRIN2B* markers).

The GLM results were examined to detect any joint relationships among *GRIN2B* SNPs, ROI parameters, and CBCL/6-18 AP score. The mutually related variables were used in the following mediation analysis, with the objective to check whether the causal effect of *GRIN2B* marker variants on attention/hyperactivity phenotype was mediated (and, if yes, in what proportions) by brain morphology.

2.7.2. Mediation Analyses

Mediation was assessed using the open-source Bootstrap Regression Analysis of Voxelwise Observations (BRAVO) toolbox (https://sites.google.com/site/bravotoolbox/, downloaded on 5 March 2018) in Matlab. On each triad of selected variables, we designed a simple mediation model, where the *GRIN2B* SNP was the causal variable X, the CBCL/6-18 AP score the outcome Y, and the ROI morphological parameter the mediator M (Figure 2).

Provided that X significantly accounts for variability in both Y (path c) and M (path a), and M accounts for variability in Y when covarying for X (path b), M is the mediator of the X-Y relationship if the effect of X on Y substantially decreases when M is entered simultaneously with X as a predictor of Y (path c'). Further details on mediation models can be found in [37].

In our study, we used a mediation regression model with age and gender as covariates. The mediation significance was assessed through a permutation procedure with 5000 iterations. Before running the analyses, the values of X, Y, and M were normalized using the Z-score standardization. The strength of model path, for both observed data and bootstrap distributions, was assessed through Ordinary Least Square regression. Confidence intervals and *p*-values were then estimated using the bias corrected and accelerated formula described in [38]. For all model coefficients (a, b, ab, c, c'), the significance threshold was set to $p = 0.05$. Multiple comparison corrections were performed if appropriate, based on the number of mediation models applied.

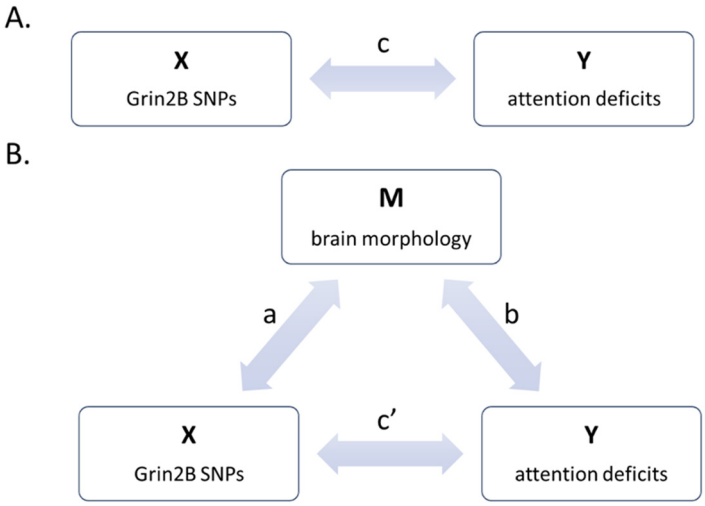

Figure 2. Mediation model design. (**A**) Model of direct effect of X on Y. (**B**) Mediation model, where X has both direct and indirect (through M) effects on Y.

3. Results

3.1. GLM Analyses

3.1.1. Design #1. *GRIN2B* Effects on Neuroanatomy

The GLM statistics concerning *GRIN2B* effects on regional brain morphology are reported in Table 3. We detected significant associations between rs5796555-/A marker and regional GMV, and rs2268119A/T and rs2216128T/C markers and regional CSA ($p < 0.05$, MC corrected). On the contrary, no significant effects of *GRIN2B* markers on CT emerged.

Table 3. General Linear Model results of *GRIN2B* markers effect on brain morphological parameters.

GRIN2B SNP	Allele	FS Feature	Brain Region	T [1]	p	p_{corr} [2]
rs5796555	"-/A" and "A/A"	Volume	Left inferior parietal	3.72	<0.001	<0.05
			Left isthmus cingulate	3.62	<0.001	<0.05
			Left middle temporal	3.90	<0.001	<0.05
			Left pars orbitalis	3.72	<0.001	<0.05
			Left precuneus	3.78	<0.001	<0.05
			Left rostral middle frontal	3.59	<0.001	<0.05
			Right caudal ACC	4.32	<0.0001	<0.01
			Right inferior parietal	4.14	<0.001	<0.01
			Right middle temporal	3.43	0.001	<0.05
			Right pars orbitalis	3.72	<0.001	<0.05
			Right rostral ACC	3.95	<0.001	<0.01
			Right rostral middle frontal	3.49	<0.001	<0.05
			Right transverse temporal	3.40	0.001	<0.05
rs2268119	"A/T" and "T/T"	Area	Left lateral orbitofrontal	3.40	0.001	<0.05
			Right lateral occipital	3.98	<0.001	<0.01
rs2216128	"G/C" and "C/C"		Right isthmus cingulate	3.42	0.001	<0.05

SNP: single nucleotide polymorphism; FS: FreeSurfer software; ACC: anterior cingulate cortex. ROI: region of interest. [1] general linear model design: ROI parameter ~ 1 + Gender + Age + *GRIN2B* SNP. Observations were 58, error degrees of freedom were 54. ROI volumes were normalized using total intracranial volume. ROI surface areas were normalized using total cortical surface area. [2] Level of significance after multiple comparison correction: $p < 0.0016$.

Specifically, the less frequent allele "A" of marker rs5796555-/A was associated with GMV deficits in left isthmus of cingulate cortex, left precuneus, right caudal and rostral anterior cingulate cortex, right transverse temporal gyrus and bilateral rostral middle frontal gyrus, inferior parietal gyrus, middle temporal cortex and pars orbitalis. Notably, this effect was highly significant ($p < 0.01$, MC corrected) in regions of the right hemisphere, that is, the caudal and rostral anterior cingulate cortex and inferior parietal gyrus. As

inferred from Table 3, the peak T statistics was observed in the caudal portion of the right anterior cingulate cortex.

We also found a negative association between the genotype carrying the less frequent allele "T" of marker rs2268119A/T and CSA in left lateral orbitofrontal cortex ($p < 0.05$, MC corrected) and right lateral occipital cortex ($p < 0.01$, MC corrected), and the genotype carrying the minor allele "C" of marker rs2216128G/C and CSA in the right isthmus of the cingulum ($p < 0.05$, MC corrected). None of the above brain features were affected by gender or age ($p > 0.05$).

3.1.2. Design #2. *GRIN2B* Association with Attention/Hyperactivity Problems

The GLM analyses assessing the impact of *GRIN2B* markers on inattention/hyperactivity revealed a significant positive association between the genotype carrying the minor allele 'A' of marker rs5796555-/A and the mean CBCL/6-18 AP score ($T(54) = 2.41$, $p < 0.05$). No influences of gender or age on this score emerged ($p > 0.05$).

3.1.3. Design #3. Neuroanatomy Effects on Attention/Hyperactivity Problems

In view of the results of designs #1 and #2, the neuroanatomy-attention GLM analyses were performed on the only brain morphological parameters influenced by *GRIN2B* marker rs5796555-/A (Table 3). We found that the CBCL/6-18 AP score was inversely proportional to GMV in the left isthmus of the cingulate cortex ($T(54) = 2.67$, $p < 0.05$) and in the right inferior parietal cortex ($T(54) = 2.26$, $p < 0.05$), suggesting a possible role of these regions as mediators of the effect of *GRIN2B* marker rs5796555-/A on inattention/hyperactivity.

3.2. Mediation Analyses

In view of the GLM results, two separate mediation analyses (MA1 and MA2) were performed to investigate the relationship among *GRIN2B* rs5796555-/A genotype (causal variable X), CBCL/6-18 AP score (outcome Y), and (i) GMV in the left isthmus of the cingulate cortex (mediator variable M1), (ii) GMV in the right inferior parietal cortex (mediator variable M2). No mediation analyses were performed on *GRIN2B* genotypes or brain features other than those specified due to the absence of the mediation model prerequisites.

The mediation model parameters, 95% confidence intervals (CI), and p-values are reported in Table 4. In line with preliminary GLM results, both mediation analyses confirmed a significant total effect of rs5796555-/A genotype on CBCL/6-18 AP score ($c = 0.31$, $p < 0.05$).

Table 4. Summary of mediation results.

Mediation Analysis 1				Mediation Analysis 2			
Parameter	**Value**	**95% CI**	***p***	**Parameter**	**Value**	**95% CI**	***p***
a	–0.45	[–0.26 0.26]	<0.001	a	0.48	[–0.26 0.26]	<0.001
b	–0.25	[–0.27 0.26]	0.037	b	−0.18	[–0.25 0.29]	0.08
c	0.31	[–0.27 0.26]	0.011	c	0.31	[–0.27 0.26]	0.011
ab	0.11	[–0.04 0.05]	<0.001	ab	n.e.	n.e.	n.e.
c′	0.20	[–0.27 0.27]	0.09	c′	n.e.	n.e.	n.e.

Causal variable X: GRIN2B marker rs5796555-/A. Outcome variable Y: CBCL/6-18 attention problem score. Mediator variable MA1: left isthmus of cingulate cortex volume. MA2: right inferior parietal cortex. CI: confidence interval. n.e: not evaluated.

As shown in Figure 3, MA1 results confirmed that genotypes carrying the minor allele A of rs5796555-/A were associated with GMV deficits in the left isthmus of the cingulate cortex ($a = -0.45$, $p < 0.001$), and in turn that such deficits (while regressing out rs5796555-/A effect) were linked to CBCL/6-18 AP score ($b = -0.25$, $p < 0.05$). After inclusion of M1 in the model, the direct effect of rs5796555-/A on CBCL/6-18 AP score was not significant ($c' = 0.20$, $p = 0.09$), whereas its indirect effect through GMV in the left

isthmus of cingulate cortex remained significant (ab = 0.11, $p < 0.001$). Specifically, 35.89% of the total rs5796555-/A effect on attention was mediated by GMV in this region.

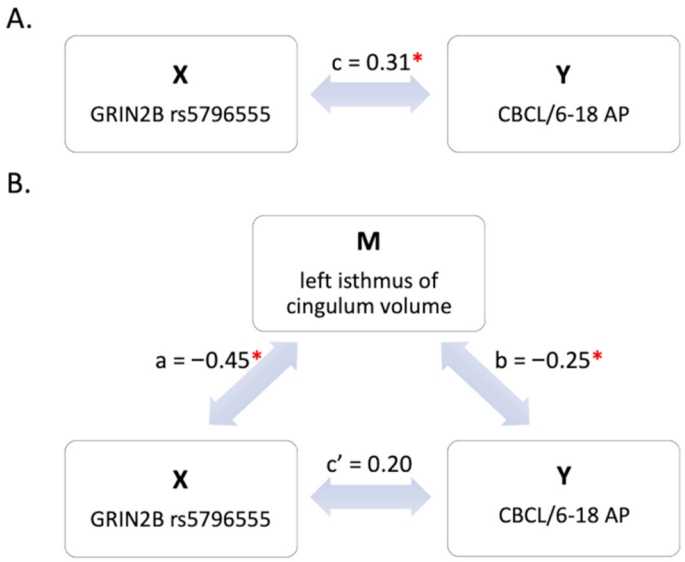

Figure 3. Mediation analysis 1 (MA1) results. (**A**) Model of direct effect of X on Y. (**B**) Mediation model, where X has both direct and indirect (through M) effects on Y. Significant pathways are highlighted with *. CBCL/6-18 AP: Child Behavior Checklist Attention Problems score.

On the contrary, MA2 showed that rs5796555-/A genotypes were linked to GMV in the right inferior parietal gyrus (a = −0.48, $p < 0.001$), but did not confirm a significant influence of the right inferior parietal deficits on attention/hyperactivity problems while controlling for rs5796555-/A contribution (b = −0.18, $p = 0.08$). The absence of a net effect of M2 on Y ruled out the investigation of any mediated effects of this variable. Of note, since only MA1 analysis was successfully conducted, no multiple comparison corrections were performed on MA1 analysis coefficients.

4. Discussion

In this preliminary work, an innovative genetic-neuroimaging-behavioral approach was adopted to investigate the potential causal effects of *GRIN2B* markers on developmental attention/hyperactivity problems through neuroanatomy. To this end, we genotyped 6 *GRIN2B* markers and measured brain morphological parameters and inattention/hyperactivity in a large clinical sample followed from childhood to adolescence.

Our results confirm the presence of a causal chain of relationships among the three variables, showing that *GRIN2B* rs5796555-/A effects on inattention/hyperactivity over time is significantly mediated by volume in the left isthmus of the cingulate cortex. This unprecedented finding supports the hypothesis that *GRIN2B* variants affect the structure of key brain regions for executive functioning, ultimately exerting both direct and indirect impact on these developmental problems. This evidence offers new opportunities and translational pathways in the identification and management of attention/hyperactivity deficits in the delicate phase of neurodevelopment.

4.1. GRIN2B *Effect on Attention Deficits*

To our knowledge, this is the first study on *GRIN2B* that considered multiple time measures of behavioral attention/hyperactivity problems. The use of the mean CBCL/6-18 AP score across three time points allowed us to smooth the variability due to different manifestations of this complex behavior from childhood to adolescence. In fact, the CBCL/6-18 AP scale assesses both inattentive and hyperactive-impulsive symptoms linked to ADHD,

and longitudinal studies suggest that these dimensions may follow separate developmental trajectories and have different manifestations at different ages [3].

In line with previous studies, we found a significant relation between persistent attention deficits and the *GRIN2B* gene. Specifically, subjects carrying the minor allele 'A' of *GRIN2B* rs5796555-/A were characterized by a higher CBCL/6-18 AP score.

Our findings further confirm the crucial role of *GRIN2B* in behavioral functions. Given the importance of the Glun2B subunit of NMDA receptor for maturation and plasticity of the central nervous system, it is not surprising that over 60 variants of *GRIN2B* have been associated with heterogeneous neurodevelopmental and psychiatric disorders [16].

Previous literature reported evidence of the association of *GRIN2B* gene variants with attention deficits in the general population and patient samples. Of note, [39] found an association between *GRIN2B* genotypes and CBCL/6-18 AP score in a general population sample aged 6-11. [8] investigated inattention and impulsive symptoms in a sample of ADHD children and found a positive correlation between both symptom classes and nine *GRIN2B* SNPs. On the same line, a study on attention performance in ADHD patients linked *GRIN2B* and GRIN2A variants to increased susceptibility to attention problems [12]. Our study confirms and strengthens these findings, showing a role of *GRIN2B* rs5796555-/A in the genetic risk for inattention/hyperactivity traits that remains stable during development.

4.2. GRIN2B *Influence on Brain Structure*

Brain imaging features may provide biological endophenotypes for genetic studies on inattention/hyperactivity. Nevertheless, in the growing imaging genetics field, just a few studies explored the link between *GRIN2B* markers and brain morphology.

For the first time, we assessed the influence of six *GRIN2B* SNPs on a set of morphological features. The extraction of regional cortical thickness, volume and surface area has offered a unique opportunity to delineate the structural brain correlates of *GRIN2B* variants with high specificity.

Interestingly, we found selective associations between *GRIN2B* markers and morphological features. The brain feature that resulted in being most widely influenced by *GRIN2B* SNPs was regional GMV. On the contrary, the CT feature showed no influence of the *GRIN2B* markers. The minor allele of marker rs5796555-/A was associated with lower GMV in frontal, parietal and temporal regions. Conversely, the minor allele of marker rs2268119A/T was associated with lower CSA in left frontal and right occipital regions, and rs2216128G/C genotypes carrying the minor allele "C" showed CSA deficits in the right cingulate cortex.

Previous studies already showed an association between glutamatergic genes and regional GMV in children with neurodevelopmental disorders involving, at different levels, attention deficits.

Probably due to different clinical populations and research methods, literature results are mixed. In patients with obsessive compulsive disorder (OCD), [40] reported *GRIN2B* SNPs to be associated with total thalamus volume. In another pediatric OCD study, a significant association between left orbitofrontal and right anterior cingulate volumes and *GRIN2B* SNPs emerged [23]. Of note, *GRIN2B* was linked to left posterior cingulate volume in adolescents with alcohol dependence, one of the disorders most closely related to impulsivity [24]. Since these findings emerged from clinical samples that share only some features with attention deficit syndromes, further investigations are needed to confirm our findings and interpret them in a wider dimensional perspective.

To our knowledge, the only imaging-*GRIN2B* study that has focused on inattention/hyperactivity is a resting state functional MRI (fMRI) study on ADHD children, which showed *GRIN2B* influence on regional homogeneity in left superior parietal cortex, being part of the attention circuit and with a role in inhibition [41].

Overall, these results suggest that *GRIN2B* regulation is not confined to specific brain regions but involves complex brain networks. Indeed, precuneus, cingulate, prefrontal, orbitofrontal, inferior parietal and temporal cortices, which were found to be affected

by *GRIN2B* markers, are included in the default mode network (DMN) [42,43]. The DMN is a spontaneous resting state network that deactivates during task performance, whose activation has been implicated in attention and, specifically, in exteroceptive and interoceptive attentional orientation [44–47]. The DMN failure to deactivate during tasks might result in attentional intrusions and deficits in performance [48].

Moreover, the posterior and rostral cingulate cortex, prefrontal cortex, and inferior parietal lobule are part of the frontoparietal control network [49–52], involved in executive control. During tasks demanding direct attention to external information, activity increases in the frontoparietal control network and decreases in DMN [53].

The above evidence supports the hypothesis that *GRIN2B* effects on brain structure might be interpreted in terms of brain circuitries, especially those that in turn impact on behavioral functions.

4.3. Brain Correlates of Attention/Hyperactivity Problems

In the imaging-behavioral analysis, we deliberately focused on the brain regions that resulted in being affected by *GRIN2B* rs5796555-/A, which may act as intermediate biological phenotypes in *GRIN2B* effect on inattention/hyperactivity. The study of the link between other brain features (e.g., regional CSA or CT) and attention/hyperactivity problems went beyond the scope of our study, but could be the subject of future investigations.

Interestingly, we found a negative association between CBCL/6-18 AP score and GMV in the left isthmus of the cingulum and the right inferior parietal cortex. The involvement of the posterior cingulate cortex and inferior parietal lobule in functional networks of attention control may explain the relation between attention problems and structural abnormalities in these areas and further supports the aforementioned network-based perspective.

4.4. From GRIN2B to Behavior through Neuroanatomy

In recent years, imaging genetics aimed to disentangle the pathways from genes to behavior. Instead of directly measuring the association between complex behavioral phenotypes and genetics, brain functionality and anatomy might be used as reliable intermediate phenotype, with a more direct and interpretable relation with genetics [41].

The results of our preliminary GLM analyses support the hypothesis that regional GMV (in left isthmus of cingulate cortex and right inferior parietal gyrus) might mediate *GRIN2B* effect on inattention/hyperactivity. Hence, two separate mediation analyses were performed to investigate the relationship among *GRIN2B* rs5796555-/A genotype, mean CBCL/6-18 AP score and, as mediator, GMV in left isthmus of cingulate cortex and right inferior parietal cortex.

The failure to verify the second mediation hypothesis suggests that GMV in the right inferior parietal cortex, besides being regulated by *GRIN2B* rs5796555-/A, does not shape genetic susceptibility for inattention/hyperactivity.

On the contrary, our results suggest that GMV in the left isthmus of cingulate cortex may play a key role in this mechanism. Indeed, after inclusion of this parameter in the mediation model, the direct effect of *GRIN2B* rs5796555-/A on CBCL/6-18 AP score became not significant, whereas its indirect effect through GMV in this region emerged to be significant. Specifically, more than 30% of the *GRIN2B* rs5796555-/A genotype effect on CBCL/6-18 AP score was mediated by GMV in left isthmus of cingulate volume.

Therefore, we believe that this region might play a relevant role in translating *GRIN2B* variation to the complex attention phenotype. Until now, the isthmus of cingulate cortex, also known as retrosplenial cortex, has received little attention in studies on attention deficits. Nevertheless, a recent research found that the right cingulate isthmus was thinner in children with comorbid developmental coordination disorder (DCD) and ADHD compared to children with DCD alone. Previous fMRI studies reported an involvement of the retrosplenial cortex in spatial attention [54], episodic memory [55] and emotional processing [56]. Overall, this evidence enhances the need for focused research on structural and functional alterations of this region in attention/hyperactivity disorders.

4.5. Limitations

In the discussion of these results, the following limitations should be considered. First, the sample size was limited by difficulties related to the longitudinal study protocol. Specifically, the MRI acquisitions required high level of patient compliance, which was not always achieved due to the young age and clinical characteristics of our sample. The use of a modest sample has limited the statistical power and the reliability of the emerged imaging-genetic-behavioral associations, which need to be reproduced on larger, independent samples.

The integration of genetic, neuroimaging, and psychopathologic information enhanced the possible sources of error. Larger sample size replications are needed in order to minimize the risk of false positive results.

It is worth mentioning that our research protocol included children and adolescents with emotional and behavioral difficulties but not comparison subjects. Despite this limit, the clinical heterogeneity of the sample has enabled its stratification based on attention and hyperactivity problems and the investigation of the underlying genetic and neuroanatomic mechanisms.

Another important point is the lack of environmental factors in the model, which may have affected the findings' reliability, as gene-environment interactions are implicated in the development of complex psychopathological behaviors [2,57].

Regarding the measurement of attention/hyperactivity problems, we used the CBCL/6-18 "Attention Problems" subscale, fulfilled by the participants' caregivers. This scale evaluates both inattention and impulsivity from a hetero-referred point of view. In the future, it is desirable to integrate the measurement of these traits with neuropsychological tasks or clinical measures from different raters, and to disentangle the contributions of inattention and hyperactivity problems.

A final, intrinsic limitation of our study concerns the focus on a specific gene of the glutamatergic pathway. This choice was driven by growing evidence from genetic studies, suggesting a role of *GRIN2B* in attention deficits/hyperactivity traits. Given the increasing interest in polygenic risk factors, future study extensions should additionally consider the effect of other genes implicated in this behavior. We should investigate the interactions between genes, also known as "epistasis" [58], i.e., the extent to which the effect of one gene upon the phenotype is moderated by other genetic variations at a statistical and, possibly, a biological level [13].

5. Conclusions

Using a proof-of-concept imaging genetics mediation design, we explored the relationship between the glutamatergic *GRIN2B* gene variants and attention deficits and impulsive-hyperactive behaviors by introducing neuroanatomical measures as intermediate factors.

Our findings confirm that brain anatomy, more specifically volumetry, is closely related to *GRIN2B* variations and can act as an intermediate phenotype between genetics and complex behaviors. The mediation results highlight a possible role of the left isthmus of the cingulum in mediating heritable risk for inattention/hyperactivity linked to *GRIN2B* variants. Confirmatory longitudinal studies are required to better delineate the genetic, neuronal and environmental mechanisms contributing to developmental risk pathways, with important implications for effective prevention, identification and treatment of early-onset psychiatric disorders.

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Moderators and Other Predictors of Methylphenidate Response in Children and Adolescents with ADHD

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Abstract: Methylphenidate (MPH) is the treatment of first choice for developmental ADHD. To date, no reliable method to predict how patients will respond to MPH exists and conflicting results are reported on clinical characteristics of responders. The present study aims to give a more precise characterization of the patients who will respond best to MPH to help clinicians in defining the treatment plan. Age, neuropsychological functioning (i.e., attention and working memory), and behavioral/emotional symptoms of 48 drug-naïve children and adolescents with ADHD (42 boys and 6 girls, age-range 6–16 years, mean age 10.5 ± 2.5 years, mean IQ 101.3 ± 11.2) were studied to assess how these different characteristics affected a single-dose MPH response. Four hierarchical linear regression models were used to explore whether age, neuropsychological measures at baseline, and behavioral/emotional symptoms could predict attention and working memory measures after a single-dose MPH administration. We found that improvement in attention and working memory was predicted by age, neuropsychological measures at baseline, and severity of ADHD symptoms. No behavioral and emotional symptoms predicted single-dose MPH response with the exception of conduct symptoms.

Keywords: methylphenidate; ADHD; behavioral and emotional symptoms; executive functions; conduct symptoms

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1. Introduction

Executive functions (EF) are cognitive processes that allow problem-solving behavior geared toward the attainment of a future goal [1]. Several studies [2–4] have documented that a set of EF, including response inhibition and working memory, are deficient in attention-deficit hyperactivity disorder (ADHD). Specifically, working memory deficits are found in 30% to 37% of children with ADHD [4,5] and inhibitory control deficits in 21% to 46% [4,6–8].

Studies have demonstrates that patients with ADHD improve significantly in EF when on methylphenidate (MPH), the first-choice treatment for ADHD in the developmental age [9,10]. In particular, MPH ameliorated inhibitory control [4,11–14], visual-spatial working memory [15], sustained and selective attention [16], and reaction times (RT) [14].

A recent meta-analysis [17] suggests that after a flexible titration, i.e., considering the presence of ADHD symptoms, and tolerated, i.e., considering the presence of dose-limiting adverse effects, higher doses of stimulants were associated with both better efficacy and acceptability.

There is evidence that when MPH dosage was optimized the majority of patients with ADHD achieved a remission of symptoms and demonstrated functional improvement attaining to the level of non-ADHD peers [18]. However, there is also evidence that the severity of ADHD and comorbid symptoms, such as conduct problems, oppositional and defiant behavior, depression, and substance use may interfere with MPH effect [19–22]. A recent study [23] demonstrated that emotional and behavioral-associated symptoms influenced pharmacological response in ADHD. Specifically, children with ADHD and comorbid emotional dysregulation responded worse to a 4-week MPH administration than children with ADHD without associated symptoms.

There has been a growing interest in identifying predictive factors of response to pharmacological treatment in ADHD. Besides comorbid psychopathology that could worsen the MPH response, pre-treatment EF measures have been recently found as predictors of the clinical response to MPH [24]. Age has also been considered as a possible mediator of MPH effect [25]. Neuroimaging studies [12,26] observed that the effect of MPH was stronger in younger children with ADHD than in older ones. Nevertheless, the majority of studies did not take age into account as a possible moderating factor of MPH response, and the few studies that considered age as a possible confounding factor lead to mixed results [19,24].

The aim of the present study is to better understand what factors condition the response to MPH in children and adolescents with ADHD.

In this context, we examine how different aspects of drug-naïve children and adolescents with ADHD, such as age, EF (i.e., attention and working memory) at baseline, and behavioral/emotional symptoms impact on EF changes after a single dose of MPH administration.

We hypothesize that the greater the severity of ADHD, behavioral and emotional symptoms, age of the participants, attention and working memory deficits, the worse the response will be to the MPH administration.

2. Materials and Methods

2.1. Participants

Three hundred and two children and adolescents received a first diagnosis of ADHD at the Child and Adolescent Neuropsychiatric Unit of the Bambino Gesù Children's Hospital in Rome in 2020. Among these patients, 110 were prescribed MPH for the first time and underwent a single MPH dose challenge.

We excluded from the current study 62 patients for the following reasons: (1) they were under psychopharmacological treatment different from MPH at the time of recruitment; (2) they suffered from autistic spectrum disorder; (3) they suffered from genetic syndromes; (4) they suffered from neurological disorders; and (5) they had an IQ below 80.

According to the exclusion criteria, 48 participants with the combined hyperactive/impulsive and inattentive presentation of ADHD were recruited (Table 1). Neurocognitive performance may differ between ADHD presentations [27]. Therefore, including only participants with ADHD combined presentation and not participants with the inattentive or hyperactive/impulsive presentation, might increase homogeneity in neurocognitive functioning [25].

After performing the neuropsychiatric and psychopathological assessment, each participant completed neuropsychological tasks at baseline (t0) and after MPH administration (t1). All participants and parents were informed about assessment instruments and treatment options. Written informed consent was obtained from parents. The study was conformed to Declaration of Helsinki.

Table 1. Demographic information of participants with ADHD.

Demographic Characteristics	*N*	Mean (SD)	% of Total Sample
Gender			
Males	42		
Females	6		
Age		10.5 (2.5)	
IQ		101.3 (11.2)	
Comorbid diagnosis			
Oppositional defiant disorder			43.8
Specific learning disorder			25
Anxiety disorder			8.3
No comorbid diagnosis			22.9

2.2. Psychopathological Assessment

Psychiatric diagnoses were based on developmental history, extensive clinical examination and the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version DSM-5 [28], a semi-structured interview that assesses the presence of psychopathological disorders according to DSM-5 classification.

Behavioral and emotional symptoms were assessed by the child behavior checklist 6–18 (CBCL) and the Achenbach system of empirically based assessment (ASEBA) questionnaire. The CBCL parent questionnaire [29] is a well-known tool to detecting psychopathological symptoms in children and adolescents. The hierarchical structure of the CBCL encompasses several scales. We analyzed the following six DSM-oriented Scales (CBCL affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) because there were no overlapping items across scales. Raw scores were converted in T-scores. According to the cut-off thresholds of Achenbach and Rescorla [29], T-scores > 69 were classified as clinically relevant, T-scores between 65 and 69 were classified as borderline, and T-scores < 65 indicated non-clinical symptoms.

The severity of ADHD symptoms was assessed by Conners' parent rating scales long version revised (CPRS) [30], completed by parents. We analyzed two DSM-IV symptom scales: inattentive (CPRS L) and hyperactive-impulsive (CPRS M). Raw scores were converted in T-scores. According to the cut-off thresholds, T-scores >70 were classified as very elevated and T-scores from 60 to 70 were classified as high average or elevated.

2.3. Executive Functions Assessment

The continuous performance test II (CPT) [31] is composed of 360 letters, presented one at a time for approximately 250 ms each, which are presented in the standard format of 18 sub-blocks of 20 trials each. The blocks differ in the interstimulus intervals (ISI) between letter presentations, which last 1, 2, or 4 s. ISI are randomized between blocks so that all three ISI conditions occur every three blocks. The transition from one block to the next is unannounced and occurs without delay. The participants were instructed to press the spacebar when any letter except the letter "X" appeared on the screen. The percentage of trials when letters other than "X" appear is 90% across all ISI blocks. RT is measured from the point at which any letter other than "X" appears on the screen until the spacebar was pressed (Go trial). No-Go trials occur when an "X" is presented. The task took 14 min to complete. All participants had a 3-min practice session prior to starting the CPT, to reduce the effect of familiarity stemming from repeated tests. Accuracy, reaction times in milliseconds, and the reaction time variability (RTV) in milliseconds were recorded at t0 and t1.

The N-back [32] is one of the most widely used culture free tools applied to evaluate working memory. The visual-spatial condition consists of presenting a series of visual stimuli (blue boxes) in a certain location on the screen. After a training phase, participants were required to indicate whether the location of each box presented was the same as the location of the box presented immediately prior (level: 1-back). When the accuracy

was equal to or greater than 80%, the difficulty of the N-back increased (for example, passing from 1-back to 2-back). The analyses were based on scores in the last N-back span achieved (i.e., percentage accuracy value ≥80%) and the percentage of accuracy in the next unachieved N-back (i.e., percentage accuracy value <80%). For example, when the participant reached the 2-back and its accuracy exceeded only 30%, the score was 2.3.

2.4. Medication

MPH is the first-line medication for children and adolescents with ADHD in line with the National Institute for Health and Care Excellence (NICE) and Agenzia Italiana del Farmaco (AIFA) guidelines. Before the single-dose MPH challenge, all the patients who were eligible to receive MPH treatment underwent an electrocardiogram (ECG) with the calculation of the corrected QT interval, and blood tests to exclude any other medical condition associated with ADHD or potentially mimicking ADHD symptoms (e.g., thyroiditis). All participants underwent CPT and N-back one day before drug administration (t0) and one hour after the administration of 0.3 mg/kg of the short-acting MPH preparation Ritalin© (t1).

2.5. Statistical Analyses

Paired sample *t*-tests were used to compare EF measures at t0 and at t1. To correct for multiple comparisons (4 measures: CPT Accuracy, CPT RT, CPT RTV, and N-back scores), Holm–Bonferroni-corrected alpha values were applied [33].

To determine whether MPH response was predicted by age, EF measures at t0 and behavioral and emotional measures, four different hierarchical regression analyses with 3 steps were computed. Precisely, the dependent variables were EF measures (N-back scores, CPT Accuracy, CPT RT, or CPT RTV) at t1 and the predictors were age at step 1, EF measures at t0, the two DSM-IV symptoms scales of CPRS (inattentive and hyperactive-impulsive) at step 2, and the six DSM-oriented Scales of CBCL (affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) at step 3. Moderation effects were examined using multicollinearity tests for interaction.

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

3. Results

Concerning working memory, results on N-back demonstrated that the scores obtained by children and adolescents with ADHD at t0 were lower than scores obtained at t1 ($t_{47} = -2.35$, $p = 0.023$, Cohen's d = 0.44) as reported in Table 2.

Table 2. Comparisons between t0-t1 on neuropsychological measures.

Measures	t0 Mean (SD)	t1 Mean (SD)
N-back	1.6 (0.4)	1.8 (0.5)
CPT accuracy	92.6 (6.2)	95.5 (5.1)
CPT RT	448.1 (96.1)	435.9 (80.5)
CPT RTV	285.8 (154.3)	206.41 (127.2)

As for CPT, we found that participants improved CPT accuracy ($t_{47} = -4.71$, $p < 0.001$, Cohen's d = 0.51) and reduced CPT RTV ($t_{47} = 0.45$, $p < 0.001$, Cohen's d = 0.56) at t1 compared to t0. CPT RT did not differ between t0 and t1 ($t_{47} = 0.96$, $p = 0.33$, Cohen's d = 0.13).

After the Holm–Bonferroni correction, N-back scores ($p = 0.04$), CPT accuracy ($p = 0.004$), and CPT RTV ($p = 0.004$) were still significant.

In the first model of the forward hierarchical regression to predict N-back scores at t1, age was entered at step 1, N-back scores at t0, the two DSM-IV symptoms scales of CPRS (inattentive and hyperactive-impulsive) were entered at step 2, and the six DSM-oriented scales of CBCL (affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) were entered at step 3 as predictors.

Overall, the regression model accounted for 51.9% of the variance. As reported in Table 3, age accounted for 29.2% of the unique variance (with older children improving more), while the N-back scores at t0 accounted for 7.4% (with higher scores at t1 in participants who demonstrated higher scores at t0).

Table 3. Hierarchical linear regression model predicting N-back at t1 after MPH administration.

Steps	Predictors	R^2	F	*p*	*B*
Step 1	Age	0.292	19.0	0.0001	0.26
Steps	N-back at t0	0.074	5.2	0.027	0.31
	CPRS M	0.055	4.2	0.046	−0.07
Step 3	CBCL ADHD problems	0.098	8.7	0.005	−0.36

Moreover, CPRS M accounted for 5.5% of the unique variance (with lower scores for higher N-back scores at t1) and CBCL ADHD problems accounted for 9.8% of the unique variance (with lower scores for higher N-back scores at t1). No interaction effect was found between any of the predictive variables.

In the second model of forward hierarchical regression to predict CPT accuracy at t1, age was entered at step 1, CPT accuracy at t0, the two DSM-IV symptoms scales of CPRS (inattentive and hyperactive-impulsive) were entered at step 2, and six CBCL DSM-oriented scales (affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) were entered at step 3 as predictors. Overall, the regression model accounted for 51.8% of the variance. As reported in Table 4, the age accounted for 22.4% of variance (with older children improving more), and the CPT accuracy at t0 accounted for 29.5% (with higher scores at t1 in participants who demonstrated higher scores at t0). No significant effect of CBCL DSM-oriented scales or of DSM-IV symptoms scales of CPRS on CPT accuracy at t1 was found.

Table 4. Hierarchical linear regression model predicting CPT accuracy at t1 after MPH administration.

Steps	Predictors	R^2	F	*p*	*B*
Step 1	Age	0.224	13.2	0.001	0.04
Step 2	CPT accuracy at t0	0.295	27.5	0.0001	0.69

In the third model of the forward hierarchical regression to predict CPT RT at t1, age was entered at step 1, CPT RT at t0, the two DSM-IV symptoms scales of CPRS (inattentive and hyperactive-impulsive) were entered at step 2, and the six DSM-oriented scales of CBCL (affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) were entered at step 3 as predictors. Overall, the regression model accounted for 41% of the variance. As reported in Table 5, age accounted for 10% of variance (with younger children improving less), the CPT RT at t0 accounted for 20.7% (with higher scores at t1 in participants who showed higher scores at t0) and the CBCL conduct problems scale accounted for 10.3% (with higher scores for higher CPT RT at t1). No interaction effect was found between any of the predictive variables.

Table 5. Hierarchical linear regression model predicting CPT RT at t1 after MPH administration.

Steps	Predictors	R^2	F	*p*	*B*
Step 1	Age	0.100	5.1	0.028	−0.13
Step 2	CPT RT at t0	0.207	13.4	0.001	0.43
Step 3	CBCL conduct problems	0.103	7.6	0.008	−0.32

Similarly, in the forward hierarchical regression to predict CPT RTV at t1, age was entered at step 1, CPT RTV at t0, the two DSM-IV symptoms scales of CPRS (inattentive and hyperactive-impulsive) were entered at step 2, and the six CBCL DSM-oriented scales CBCL

(affective problems, anxiety problems, somatic problems, ADHD problems, oppositional defiant problems, and conduct problems) were entered at step 3 as predictors. Overall, the regression model accounted for 48.5% of the variance. As reported in Table 6, the age accounted for 26.4% of variance (with younger children improving less), and CPT RTV at t0 accounted for 22% (with higher scores for higher CPT RTV at t1). The results did not show any significant effect of the CBCL DSM-oriented scales or DSM-IV symptoms scales of CPRS on CPT RTV at t1.

Table 6. Hierarchical linear regression model predicting CPT RTV at t1 after MPH administration.

Steps	Predictors	R^2	F	*p*	*B*
Step 1	Age	0.264	16.5	0.0001	−0.27
Step 2	CPT RTV at t0	0.220	19.2	0.0001	0.52

4. Discussion

This study aimed at a better characterization of different factors potentially associated with MPH response. Specifically, we explored whether age, EF measures at baseline, and behavioral/emotional symptoms could affect EF in a group of drug-naïve children and adolescent with ADHD after a single dose of MPH administration. We found that attention and working memory improved after a single MPH administration and that age, EF measures at baseline, the severity of ADHD symptoms, and conduct problems modulated MPH effect on EF performances.

MPH is the first-choice treatment for patients with ADHD. Although its exact mechanism is unclear, it seems to increase and stabilize catecholaminergic neurotransmission in prefrontal cortices [10]. The activity of prefrontal cortices affected by MPH participated in basically all of the EF [4,9], as the most impaired functions in ADHD [34].

Neuroimaging studies demonstrated that EF deficits were highly related to reduced activity in fronto-striatal and fronto-parietal networks of patients with ADHD [35]. In particular, deficits in inhibitory control were linked to abnormalities in the right-hemispheric fronto-basal ganglia networks, including the right inferior frontal gyrus and striatal regions [36,37], and deficits in working memory were associated with the decreased efficiency of the dorsal lateral prefrontal cortex. Thus, one may speculate that MPH, acting on prefrontal networks, could induce a positive effect on EF [38], ameliorating cognitive and behavioral deficits of children with ADHD [39]. These ameliorative effects on EF should be considered as indications of improvement due to the psychostimulant medication in children with ADHD [40,41].

Our results on attention and working memory improvements after a single MPH administration supported previous findings observing that MPH significantly ameliorating attention by reducing RT [19,42], and promoted the updating of information in visual-spatial working memory [15].

Moreover, we found that higher scores in N-back and CPT tasks at baseline favored performance in N-back and CPT after a single dose of MPH administration. Previous research in children with ADHD studied whether the performances on EF tasks before MPH administration were correlated with responses to MPH [19,43,44] with contrasting outcomes. While some studies observed that lower scores on neuropsychological tasks at baseline predicted higher responses to MPH [19,43,44], others observed that MPH did not modify the performance on tasks with executive components [45] or still others demonstrated that children with ADHD who had lower scores in tasks as CPT were less likely to respond to MPH [46,47]. We cannot easily compare our results with the previous ones because we studied the effects on EF of a single dose of MPH while the other studies evaluated long-term drug treatment effects (lasting at least 3 months).

Regarding age, we found that improvement in attention and working memory after a single dose of MPH administration was predicted by age. Specifically, older children with ADHD were those who got the most benefit from a single dose of MPH administration in EF (i.e., in N-back scores, CPT Accuracy, RT, and RTV). It could be that as patients with ADHD

develop, they learn to solve complex problems with increasing accuracy, reducing the variability in the performance and shortening times to information processing. Specifically, the performance of patients with ADHD in shifting attention (correct responses and errors) improved with age and children below 10 years old were less respondent to MPH [46].

Additionally, our results demonstrated that the MPH effect on working memory (N-back) depended on the severity of ADHD symptoms. In particular, we found that the children and adolescents who demonstrated less severe symptoms of ADHD (in the CPRS hyperactive-impulsive scale and CBCL ADHD scale) were the ones who improved the most in N-back scores. Our findings were in line with studies that found that patients with more severe ADHD symptoms also responded less to stimulants [23,48].

Among emotional and behavioral symptoms that may influence the MPH response, our results demonstrated that patients with more conduct problem symptoms (CBCL conduct problems) responded more to stimulants (CPT RT). Our findings are in line with previous studies demonstrating that children with ADHD and conduct problems respond better to medication [19,24,49,50]. This may likely be due to the fact that MPH is also effective in behavioral disorder with aggressive behaviors [51]. In the current study, no other emotional and behavioral symptoms from CBCL-mediated the MPH response.

However, it is difficult to compare our results with other studies, because the same CBCL scales to predict MPH response were not selected. Specifically, Ludwig and colleagues [52] selected the sluggish cognitive tempo scale to measure the response to MPH in children with ADHD, while Masi and colleagues [23] selected the dysregulation profile from the CBCL syndrome scales (i.e., anxious/depressed, attention problems, and aggressive behavior).

Further studies are needed in order to establish whether and how clinical characteristics impact pharmacological treatment for ADHD.

5. Conclusions

In the present study of a group of medication-naïve children and adolescents with ADHD, we investigated whether age, EF measures, and clinical characteristics before MPH administration influenced response to medication.

We found that improvement in attention and working memory performance after a single administration of MPH were predicted by age, EF measures, and severity of ADHD symptoms. Moreover, we found that children and adolescents with ADHD and conduct symptoms improved EF more than patients with ADHD and other symptoms after a single dose of MPH.

Early attention to these factors may help clinicians identify young patients with ADHD who are likely to gain greater benefit from MPH treatment, thereby optimizing the risk/benefit ratio in the pharmacologic treatment of ADHD.

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Informed Consent Statement: Informed consent was obtained from all individual participants included in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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Article

Distance Learning in Children with and without ADHD: A Case-control Study during the COVID-19 Pandemic

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Abstract

Objective: This research involved the parents of ADHD students to explore how their children coped with online distance learning during COVID-19 pandemic and what implications this schooling method had on their emotional and behavioral well-being. **Method:** Data were collected during lockdown using an online questionnaire addressed to 100 mothers and were compared with 184 matched controls from a national survey launched in the same period. **Results:** Attention span, spontaneous commitment, and autonomy in distance learning was found to be more limited in ADHD group. Compared to controls, 21.7% of ADHD students were not assessed and 40.9% did not receive grades. Behavioral changes were reported in both groups (64.2%), represented mainly by restlessness, aggressiveness, and anxiety. **Conclusion:** Distance education increases academic difficulties, especially in ADHD pupils. The effects of lockdown should be adequately evaluated upon school reopening and appropriate recovery interventions should be planned. *(J. of Att. Dis. 2022; 26(6) 902-914)*

Keywords

ADHD, case-control, distance education, coronavirus, child psychology, health services

Introduction

ADHD is a neurodevelopmental disorder characterized by specific deficit in brain functions underlying attention, motor, and behavioral self-modulation and impulse control (Wolraich et al., 2019). It is a very frequent disorder in the world and is present in 1.4% of the pediatric population, considering only subjects with diagnosis confirmed by clinical evaluation (Reale & Bonati, 2018).

Teachers play a significant role in the initial detection of children with ADHD, based on the behavior of children in class (Pearcy et al., 1993). The start of school is therefore the defining moment for suspecting and diagnosing ADHD (Sax & Kautz, 2003). Moreover, children born later in the school year are more likely to receive an ADHD diagnosis than their same school-year peers (Bonati, Cartabia, et al., 2018). One of the most important areas of intervention for ADHD is school. Poor academic functioning and academic underperformance, such as cognitive problems (working memory, planning, and inhibition) are associated with ADHD (Willcutt et al., 2005). The use of psychoeducational techniques in school is one of the cornerstones of therapy, not only strictly in terms of improving symptoms, but also with respect to the possibility of offering these subjects adequate schooling, supporting their self-esteem and motivation to study, also in the long term, and in general, in promoting their psychophysical well-being (Cortese et al., 2020). Decreased motivation in relation to academic tasks has been identified as one of risk factors associated with ADHD, and can reduce academic functions that could otherwise be prevented or adequately reduced (Morsink et al., 2021). In some countries children with moderate to severe ADHD or with comorbidity have a support teacher and/or professional educator in order to guarantee the support they need, but this is not always possible in school contexts, where the number of children is often quite high.

In many countries, the recent COVID-19 pandemic has led to the closure of schools or to restricted access to them (World Health Organization, 2020). In particular, in Italy schools were closed on 24 February, even before the

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lockdown began on 10 March. During the following months, in some cases after the usual summer closure, schools were closed, and/or opened in different periods of time, according to the prevalence of COVID-19 infection in the local setting and to the regional public health decisions. Unlike in many other countries of the world, schools in Italy were the first to close and the last to re-open. Online distance learning (ODL) was provided to substitute in-person schooling, even if the school system was not well equipped. In Italy, 850,000 students do not have technological tools such as PCs and tablets and 57% of Italian students have to share PCs with their families (ISTAT, 2020; Save the Children Italia Onlus, 2020). An interview study, conducted by our Laboratory research team during the quarantine period, revealed that school closure had an impact in educational aspects for the children, who were no longer surrounded by their main learning, socialization, and development contexts (Segre et al., 2021). This is particularly true for children with ADHD and for children with special needs, for whom the daily routine and structure is an important coping mechanism (Zhang et al., 2020). For parents this period had an impact in practical aspects due to the facts that they found themselves working from home and simultaneously following their children full time (Lee, 2020; UNESCO, 2020). According to the literature, both in adults and in children, numerous emotional and behavioral symptoms of anxiety, depression, PTSD, alteration of circadian rhythms, and psychophysical discomfort in general (Brooks et al., 2020; Fegert et al., 2020; Mukhtar, 2020; Orgilés et al., 2020; Wang et al., 2020). Same results were reported by another survey that our Laboratory launched during the first wave of COVID-19 (Bonati et al., 2021). The closure of schools, imposed by the lockdown during the pandemic, and the strict restrictions related to leaving the home affected mainly children (Bobo et al., 2020; Spinelli et al., 2020; Zhang et al., 2020). Socio-affective complications, insufficient physical activity, and play have been reported as main concerns in children due to the COVID-19 pandemic (Graber at al., 2021; López-Bueno et al., 2021). Some types of remote learning policies were quickly implemented in many countries, although in many situations children may have been unable to learn due to skill gaps in teachers, to a lack of parental support, or to the lack of necessary technology at home (UNICEF, 2020). Children with ADHD and their parents had more difficulties than children without ADHD with remote learning during the pandemic (Becker et al., 2020). Quarantine and social distancing determine a relevant obstacle for direct access also to children's mental health services (Lennon, 2021; Newlove-Delgado et al., 2021). The pandemic has generated the urgent need for integrating technology into innovative models of mental healthcare. The COVID-19 related conditions fueled a renewed interest and use in telehealth, with opportunities for transforming psychiatry (Torous & Wykes, 2020). Also the ADHD clinical services needed to reorganize in response to the pandemic to ensure care, and telemedicine and telepsychology were introduced or implemented to reach children and their parents during the pandemic (Evans et al., 2020; Fogler et al., 2020). The aims of the study were to assess if: (a) a long educational disruption caused by school closures has had negative consequences not only on learning, but also on the emotional and psychological well-being of students; (b) the limits of distance education and academic difficulties related to ADHD were risk factors in adapting to the new teaching and evaluation methods; (c) pandemic restrictions have led to a worsening of the clinical condition (increased inattention, hyperactivity, and emotional dysregulation) and of the overall well-being of ADHD children (increased symptoms in comorbidity).

Methods

Sample and Procedure

Following an already used approach (Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2000), during the first COVID-19 pandemic wave a nationwide online survey of mothers of primary and middle school students (children aged 6–15 years old) was conducted to explore the experiences in organizing school for children at home and its implications on children's psychological well-being and educational progress during the quarantine (Scarpellini et al., 2021 in press).

A dedicated website was created for the purpose of this study. An online, semi-structured questionnaire was developed by using Wordpress, a free open-source content management system (CMS), integrated with SurveyJS (survey library and survey creator), a library to facilitate survey creation and management. The survey script was available for all devices. The questionnaire was created in Italian and, to submit it to as many people as possible, a snowball sampling technique was used. The link to the questionnaire was sent by e-mail, WhatsApp, and other social media to the investigators' contacts. Once the link was clicked on, the participants were automatically directed to information on the study and to the informed consent. After accepting to take the survey, a set of socio-demographic questions appeared, followed by other questions.

During the same period, in May 2020, 100 mothers of 6 to 15 year old patients referred to the ADHD Regional Centre at the Neuropsychiatric Unit of the San Paolo Hospital in Milan were asked to participate in the survey as part of the regional ADHD project (Bonati, Reale, et al., 2018). Enrolled patients had received a diagnosis of ADHD according to Diagnostic and statistical manual-5 (DSM-5) criteria, confirmed by (1) a clinical anamnestic and

psychiatric interview; (2) a neurological examination; (3) an evaluation of cognitive level by Wechsler Scales (Wechsler, 2003); (4) the Schedule for affective disorders and schizophrenia for school-age children (Kiddie schedule for affective disorders and schizophrenia [K-SADS]) (Kaufman et al.,1997) for a complete psychopathology overview and comorbidity assessment; (5) the child behavior checklist (CBCL) and/or the Conners' parent rating scale-revised (CPRS-R) rated by parents; (6) the Conners' teacher rating scale revised (CTRS-R) rated by teachers (Conners et al., 1998); and (7) the clinical global impressions-severity scale (CGI-S) (Guy, 1976). Intellectual disability was defined by intelligence quotient (IQ) lower than 70. Only 5/92 (5.7%) patients were in treatment with medication, for this reason we excluded the possibility to conduct analysis aimed to explore the difference between those in pharmacological treatment and those in psychological treatment only. A case-control study was performed to compare children with and without ADHD. The control group was a random sample of 1,601 responders extracted from the questionnaire dataset and matched with ADHD cases for age, gender, school year level, and residential area (municipality of Milan, Lombardy Region), with no chronic condition. In all, 92 cases were matched with 184 controls (ADHD: control ratio 1:2). All data were encrypted. Two different links and data collection repositories were created for ADHD cases and controls. All the items of the STROBE checklist for observational studies have been met in the present report (see Supplemental Appendix).

Measures

A semi-structured questionnaire was created to collect a set of data consisting of four sections investigating:

- -Socio-demographic variables: about the mother (nationality, age, residential area, educational level, profession, number of rooms in the house, support from others such as relatives, friends, or nannies, before the quarantine) and about the children (age, gender, brothers or sisters, school grade and type of school, academic achievement, chronic disorders, and support teachers).
- -ODL organization (with or without special needs): types of tools (e.g., PC, tablet, books) adopted and frequency of use, changes in school routine, whether teachers were reachable, effort required of the child, and learning assessment.
- -Children's attitude and behavioral changes: level of attention during e-learning, frequency of breaks, time spent on screens, level of commitment, and autonomy in keeping up with the school program, behavioral changes (anxiety, restlessness, aggressiveness, and sleeping or mood disorders). Each symptom was rated as mild, moderate, or severe.
- -Mother's difficulties and opinion on ODL: difficulties in managing work tasks and home schooling, effort required and level of commitment in supporting children, ODL implications, and future perspectives for the upcoming school re-opening.

Statistical Analysis

Categorical variables were summarized using proportions and associations tested using chi-square or Fisher's exact test where applicable. Continuous variables were summarized using medians and interquartile range. The Wilcoxon's test was used to test difference of means for normally distributed continuous variables. To identify risk factors associated with ADHD, odds ratios (OR) were calculated between children with and without ADHD for the different categories of the explanatory variables through bivariate analyses. Where data were missing we used pairwise deletion, so that all variables were used. Statistical significance was evaluated using 95% confidence interval and a two-tailed p-value of $<.05$. All data management and analyses were performed with the use of SAS software, version 9.4 (SAS, Institute Inc., Cary, NC, USA).

Results

In all, 276 mothers of schoolchildren participated in the study: 92 mothers of ADHD cases, and 184 of controls. Concerning the group of cases, one third received a diagnosis of ADHD only, while the rest had at least one comorbid psychiatric disorder. Half of cases had ADHD of the combined type. By design, there was no difference in the gender and school level distribution of the two groups. In agreement with ADHD prevalence (Donfrancesco et al., 2015; Reale & Bonati, 2018), males were more numerous than females (ratio 7:1) and there was a small difference in age, with control subjects slightly younger than cases (median age 10 vs. 11 years) (Table 1). The number of rooms in the household, as well as being an only child, were not factors of difference between the two groups. A lower use of private school (OR = 0.17, CI 0.04–0.76), and more than good school performance (OR = 0.2, CI 0.10–0.40) was found in the ADHD sample. Mothers of ADHD students had a lower level of education (OR = 2.17, CI 1.21–3.89) and were more unemployed (OR = 1.84, CI 1.07–3.15) than mothers in the control group. Difficulties in reconciling the commitments as mother, worker, and home teacher were higher for mothers of ADHD sons compared to the controls (OR = 4.02, CI 1.14–14.12). Both before (OR = 4.32, CI 2.09–8.92) and after (OR = 3.91, CI 1.32–11.53) lockdown, more ADHD children were cared for by parents than control children, whose parents were more helped by grandparents and others (relatives and family friends).

Table 1. Characteristics of ADHD Patients and Controls.

	Cases (N = 92)	Controls (*N* = 184)	Total (276)	OR	95% CI	*p*
Age	11 (9–12)	10 (8–12)	11 (8–12)			.0483
Gender						
Male	80 (87.0)	160 (87.0)	240 (87.0)	1.00	Reference	1.0000
Female	12 (13.0)	24 (13.0)	36 (13.0)	1.00	0.48–2.10	
Missing	—	—	—			
School						
Primary	51 (55.4)	102 (55.4)	153 (55.4)	1.00	Reference	1.0000
Middle	41 (44.6)	82 (44.6)	123 (44.6)	1.00	0.60–1.65	
Missing	—	—	—			
House						
≤2 rooms	20 (22.0)	22 (12.1)	42 (15.4)	2.04	1.05–3.97	.0344
≥3 rooms	71 (78.0)	159 (87.8)	230 (84.6)	1.00	Reference	
Missing	1	3	4			
Brothers						
Yes	61 (66.3)	112 (61.5)	173 (63.1)	1.00	Reference	.4400
No	31 (33.7)	70 (38.5)	101 (36.9)	0.81	0.48–1.38	
Missing	—	2	2			
Type of school						
Public	90 (97.8)	148 (88.6)	238 (91.9)	1.00	Reference	.0094
Private	2 (2.2)	19 (11.4)	21 (8.1)	0.17	0.04–0.76	
Missing	—	17	17			
School performance						
Sufficient	29 (31.5)	25 (13.9)	54 (19.9)	1.55	0.81–2.95	<.0001
Good	51 (55.4)	68 (38.0)	119 (43.9)	1.00	Reference	
Very good/excellent	12 (13.1)	86 (48.0)	108 (36.2)	0.19	0.09–0.38	
Missing	—	5	5			
Mothers level of education						
First-second level	64 (79.5)	96 (54.9)	160 (59.9)	1.88	1.10–3.21	.0198
Third level	28 (30.5)	79 (45.1)	107 (40.1)	1.00	Reference	
Missing	—	9	9			
Currently employed						
Yes	53 (58.2)	118 (72.0)	171 (67.1)	1.00	Reference	.0256
No	38 (41.8)	46 (28.0)	84 (32.9)	1.84	1.07–3.15	
Missing	1	20	21			
Work						
Employers	64 (69.6)	124 (70.9)	188 (70.4)	1.00	Reference	.4362
Freelance	12 (13.0)	25 (14.3)	37 (13.9)	0.93	0.44–1.97	
Housewives	6 (6.5)	16 (9.1)	22 (8.2)	0.73	0.27–1.95	
Unemployed	10 (10.9)	10 (5.7)	20 (7.5)	1.94	0.77–4.90	
Missing	—	9	9			
Smart working						
Yes	44 (83.0)	83 (71.6)	127 (75.1)	1.00	Reference	.1095
No	9 (17.0)	33 (28.4)	42 (24.9)	0.51	0.23–1.17	
Missing	—	2	2			
Difficulties in balancing work/child						
Yes	50 (94.3)	91 (80.5)	141 (84.9)	4.03	1.15–14.13	.0204
No	3 (5.7)	22 (19.5)	25 (15.1)	1.00	Reference	
Missing	—	5	5			
Child care pre-lockdown*						
Parents	81 (89.0)	118 (65.2)	199 (73.2)	4.32	2.09–8.92	<.0001
Grandparents	20 (22.0)	82 (45.3)	102 (37.5)	0.34	0.19–0.61	.0002
Others	12 (13.2)	41 (22.7)	53 (19.5)	0.52	0.26–1.04	.0629
Missing	1	3	4			
Child care post-lockdown*						
Parents	88 (95.7)	152 (84.9)	240 (88.6)	3.91	1.32–11.53	.0086
Grandparents	16 (17.4)	50 (27.9)	66 (24.4)	0.54	0.29–1.02	.0556
Others	5 (5.4)	23 (12.8)	28 (10.3)	0.39	0.14–1.06	.0576
Missing	—	5	5			

*Multiple choice.

Online Distance Learning Organization

ODL was considered equally disorganized (26.1% cases vs. 28.4% controls) and its routine instable (83.9% and 73.6%), and great effort was required by children (81.5% and 81.4%) (Table 2). With respect to the organization of home schooling, overall, in the ADHD group all available communication platforms were used quite frequently, while the use of some specific platforms prevailed in the control group, such as web-based platforms (66.9%) and videoconference tools (63%). YouTube (OR = 3.52, CI 2.06–6.04) and e-mails (OR = 2.39, CI 1.41–4.03), however, were more often used by ADHD students than controls. The use of the technological tools required for ODL in most cases was not considered difficult, but 2% of the children, among both cases and controls, did not have access to any tool. In the ADHD group the dispensatory and compensatory measures were guaranteed more frequently than for the children with special educational needs (i.e., Specific learning disorder [SLD]) of the control group (59.8% vs. 25.6%). These were mainly nonspecific and dispensatory measures (fewer tasks, exemption from lessons), however, rather than interventions aimed at overcoming the specific learning difficulties for ADHD students (e.g., schemes, programmed breaks). Moreover, in both groups there was a deficiency in support teacher intervention for eligible children (ADHD group 63.3% vs. control group 54.4%), with support provided once a week in half of the overall sample. Compared to controls, ADHD students were not assessed by the teachers (OR = 4.75, CI 2.12–10.65) and 40.9% did not receive any grades. Teachers were not considered reachable for 31.3% of general population, in particular by the control group (OR = 0.53, CI 0.30 – 0.94).

Children's Attitude and Behavioral Changes

As expected, attention span was more limited (almost 20 minutes) in children with ADHD than in controls (OR = 2.27, CI 1.30–3.95), and, consequently, there were breaks every 10 minutes (OR = 2.74, CI 1.45–5.19) (Table 3). Similarly, spontaneous commitment (OR = 2.98 CI = 1.66–5.36) and autonomy (OR = 2.69, CI 1.28–5.63) in ODL were significantly more compromised in ADHD patients than in controls. Mothers reported that, during the exposure to online teaching, about half of pupils had motor restlessness (ADHD group 56.7% vs. control group 55.9%), with consequent interference in learning. Among ADHD cases without reported restlessness problems (43.3%), more than half perceived an increment in captured attention compared to the control group (OR = 3.64, CI 1.59–8.33). On the whole, the time spent on video by children with and without ADHD for the didactic activity was similar, while the recreational use prevailed in the ADHD group, who spent from 4 to 6 hours (OR = 2.40, CI 1.19–4.83) on video games (93.3 %) or tutorials (73.3%). In particular, in this group of cases an abuse of technological tools (use for 6–12 hours) resulted for 4% of subjects against 2% of the controls. The variable "media abuse" was calculated by adding time spent on video for educational learning and time spent on screen for other activities. The majority of children in both groups showed emotional and behavioral symptoms, with a non-statistically significant prevalence in the ADHD group versus controls (71.7% vs. 60.2%, respectively). In both cases, the change was represented mainly by restlessness, aggressiveness, and anxiety, observed by parents at mostly moderate intensity, with higher percentages in the ADHD group except for aggressiveness, sleep, and mood disorders, which were equally reported for cases and controls.

Parental Difficulties and Opinions on Online Distance Learning

The majority of participating mothers felt they had to ensure greater participation (71.0%) and greater commitment (78.9%) to follow their children in ODL, enough to have replaced the teacher (79.8%) (Table 4). Mothers of ADHD students reported more often that ODL did not provide their children with an adequate level of learning (OR = 1.89, CI 1.14–3.14). Only half of the sample believed that the right to education was guaranteed through the ODL experienced, and the number of mothers was slightly higher for ADHD students (56% vs. 39.1%). Mothers of the control group, however, were more likely to refuse the ODL (OR = 0.54, CI 0.32–0.91).

Discussion

This is the first Italian study focusing on the impact of school closure on ADHD children compared to the general population. The study setting is of particular relevance considering that the Lombardy Region was the first large European area in which the pandemic tragically spread (Jefferson et al., 2020). The research confirmed that a long educational disruption caused by school closure had negative consequences not only on students' education, but also on their psychological and emotional well-being, in particular in those with a chronic condition, such as ADHD. School closure and the suspension of care services, the social distancing, and home confinement can lead to a real struggle for children with neurodevelopmental conditions (Barlett et al., 2020). According to the literature, the main psychological and emotional consequences are increasing level of restlessness, anxiety, and aggressiveness (Brooks et al., 2020; Wang et al., 2020; Zhang et al., 2020). ODL was insufficient in replacing in-person schooling, both for practical and motivational issues. In Italy, 850,000 students do

Table 2. Online Distance Learning Organization of ADHD Patients and Controls.

	Cases (*N* = 92)	Controls (*N* = 184)	Total (276)	OR	95% CI	*p*
School organization						
Yes	68 (73.9)	121 (71.6)	189 (72.4)	1.00	Reference	.6893
No	24 (26.1)	4 (28.4)	72 (27.6)	0.89	0.50–1.58	
Missing	—	15	15			
Stable routine						
Yes	14 (16.1)	47 (26.4)	61 (23.0)	1.00	Reference	.0611
No	73 (83.9)	131 (73.6)	204 (77.0)	1.87	0.97–3.63	
Missing	5	6	11			
Effort required						
Yes	75 (81.5)	144 (81.4)	219 (81.4)	1.00	Reference	.9735
No	17 (18.5)	33 (18.6)	50 (18.6)	0.99	0.52–1.89	
Missing	—	7	7			
Tools*						
Web-platform	67 (72.8)	121 (66.9)	188 (68.9)	1.33	0.76–2.31	.3135
Videoconference	71 (77.2)	114 (63.0)	185 (67.8)	1.99	1.12–3.52	.0177
YouTube	46 (50.0)	40 (22.1)	86 (31.5)	3.52	2.06–6.04	<.0001
e-mails	62 (67.4)	84 (46.4)	146 (53.5)	2.39	1.41–4.03	.0010
Electronic register	60 (65.2)	87 (48.1)	147 (53.8)	2.03	1.21–3.40	.0072
WhatsApp/FaceTime	37 (40.2)	48 (26.5)	85 (31.1)	1.86	1.10–3.17	.0209
Missing	—	3	3			
Difficulties with technology						
None	72 (80.0)	141 (79.7)	213 (79.8)	1.00	Reference	
Some	16 (17.8)	32 (18.1)	48 (18.0)	0.98	0.50–1.90	
Not used	2 (2.2)	4 (2.3)	6 (2.2)	0.98	0.18–5.47	1.0000
Missing	2	7	9			
Target intervention						
Yes	55 (59.8)	45 (25.6)	100 (37.3)	1.00	Reference	<.0001
No	37 (40.2)	131 (74.4)	168 (62.7)	0.23	0.14–0.40	
Missing	—	8	8			
Dispensatory measures*						
Fewer tasks	33 (60.0)	17 (41.5)	50 (52.1)	2.12	0.93–4.82	.0721
Exemptions	26 (47.3)	4 (9.8)	30 (31.3)	8.29	2.60–26.44	<.0001
Schemes	22 (40.0)	19 (46.3)	41 (42.7)	0.77	0.34–1.75	.5344
Breaks	8 (14.5)	4 (9.8)	12 (12.5)	1.57	0.44–5.64	.4828
Additional times	21 (38.2)	23 (56.1)	44 (45.8)	0.48	0.21–1.10	.0814
None	4 (7.3)	3 (7.3)	7 (7.3)	0.99	0.21–4.70	1.0000
Missing	—	4	4			
Supportive lessons						
Yes	42 (63.6)	6 (54.5)	48 (62.3)	1.00	Reference	.7383
No	24 (36.4)	5 (45.5)	29 (37.7)	0.69	0.19–2.49	
Missing	—	1	1			
Frequency of supportive lessons						
Everyday	13 (31.0)	1 (16.7)	14 (29.2)	2.60	0.26–25.93	.8499
Once a week	20 (47.6)	4 (66.7)	24 (50.0)	1.00	Reference	
Occasionally	9 (21.4)	1 (16.7)	10 (20.8)	1.80	0.18–18.47	
Missing	—	—	—			
Assessment						
Yes	72 (78.3)	171 (94.5)	243 (89.0)	1.00	Reference	<.0001
No	20 (21.7)	10 (5.5)	30 (11.0)	4.75	2.12–10.65	
Missing	—	3	3			
Grades						
Yes	52 (59.1)	113 (63.5)	165 (62.0)	1.00	Reference	.4874
No	36 (40.9)	65 (36.5)	101 (38.0)	1.20	0.71–2.03	
Missing	4	6	10			
Teacher reachability						
Yes	71 (77.2)	111 (64.2)	182 (68.7)	1.00	Reference	.0297
No	21 (22.8)	62 (35.8)	83 (31.3)	0.53	0.30–0.94	
Missing	—	11	11			

*Multiple choice.

Table 3. Attitude and Behavioral Changes of ADHD Patients and Controls.

	Cases (*N* = 92)	Controls (*N* = 184)	Total (276)	OR	95% CI	*p*
Attention span						
≤20 minutes	37 (40.7)	40 (22.2)	77 (28.4)	2.27	1.30–3.95	.0043
20 min–1 hour	49 (53.8)	120 (66.7)	169 (62.4)	1.00	Reference	
>1 hour	5 (5.5)	20 (11.1)	25 (9.2)	0.61	0.22–1.72	
Missing	1	4	5			
Breaks						
Every 10 minutes	32 (35.2)	25 (14.3)	57 (21.4)	2.74	1.45–5.19	.0002
Every 30 minutes	42 (46.2)	90 (51.4)	132 (49.6)	1.00	Reference	
Every hour	17 (18.7)	60 (34.3)	77 (28.9)	0.61	0.32–1.16	
Missing	1	9	10			
Child commitment						
Yes	19 (20.7)	77 (43.8)	96 (35.8)	1.00	Reference	.0002
No	73 (79.3)	99 (56.3)	172 (64.2)	2.99	1.66–5.37	
Missing	—	8	8			
Child autonomy						
Yes	10 (10.9)	45 (24.7)	55 (20.1)	1.00	Reference	.0068
No	82 (89.1)	137 (75.3)	219 (79.9)	2.69	1.29–5.63	
Missing	—	2	2			
Restlessness during ODL						
Yes	51 (56.7)	99 (55.9)	150 (56.2)	1.03	0.62–1.72	.9090
No	39 (43.3)	78 (44.1)	117 (43.8)	1.00	Reference	
Missing	2	7	9			
Attention captured by video						
Yes	26 (68.4)	28 (37.3)	54 (47.8)	3.64	1.59–8.33	.0018
No	12 (31.6)	47 (62.7)	59 (52.2)	1.00	Reference	
Missing	1	3	4			
Time for ODL						
≤2 hours	42 (46.2)	77 (42.5)	119 (43.8)	1.18	0.69–2.03	.8364
2–4 hours	37 (40.7)	80 (44.2)	117 (43.0)	1.00	Reference	
4–6 hours	12 (13.2)	24 (13.3)	36 (13.2)	1.08	0.49–2.39	
Missing	1	3	4			
Time beyond ODL						
≤2 hours	14 (15.7)	82 (51.9)	96 (38.9)	0.23	0.12–0.46	<.0001
2–4 hours	43 (48.3)	58 (36.7)	101 (40.9)	1.00	Reference	
4–6 hours	32 (36.0)	18 (11.4)	50 (20.2)	2.40	1.19–4.83	
Missing	3	26	29			
Internet use (flag)						
Videogames	84 (93.3)	117 (66.1)	201 (75.3)	7.18	2.96–17.39	<.0001
Tutorials	66 (73.3)	53 (29.9)	119 (44.6)	6.43	3.65–11.34	<.0001
Social	34 (37.8)	40 (22.6)	74 (27.7)	2.08	1.20–3.61	.0088
Films/TV series	57 (63.3)	128 (72.3)	185 (69.3)	0.66	0.39–1.14	.1325
Missing	2	7	9			
Behavioral changes						
Yes	66 (71.7)	106 (60.2)	172 (64.2)	1.68	0.97–2.89	.0620
No	26 (28.3)	70 (39.8)	96 (35.8)	1.00	Reference	
Missing	—	8	8			
Symptoms*						
Restlessness	40 (65.6)	65 (65.7)	105 (65.6)	1.00	0.1–1.95	.9915
Aggressiveness	31 (50.8)	35 (35.4)	66 (41.3)	1.89	0.99–3.62	.0536
Anxiety	20 (32.8)	27 (27.3)	47 (29.4)	1.30	0.65–2.60	.4570
Mood lability	10 (16.4)	10 (10.1)	20 (12.5)	1.75	0.68–4.47	.2424
Sleeping rhythm	28 (45.9)	39 (39.4)	67 (41.9)	1.31	0.68–2.49	.4177
Missing	5	7	12			
Restlessness						
No	52 (56.5)	111 (63.8)	163 (61.3)	1.00	Reference	.1423
Mild	11 (12.0)	22 (12.6)	33 (12.4)	1.07	0.48–2.36	
Moderate	16 (17.4)	31 (17.8)	47 (17.7)	1.10	0.55–2.19	
Severe	13 (14.1)	10 (5.7)	23 (8.6)	2.77	1.14–6.74	
Missing	—	10	10			

(continued)

Table 3. (continued)

	Cases (*N* = 92)	Controls (*N* = 184)	Total (276)	OR	95% CI	*p*
Aggressiveness						
No	61 (66.3)	141 (81.5)	202 (76.2)	1.00	Reference	.0333
Mild	9 (9.8)	6 (3.5)	15 (23.8)	3.47	1.18–10.17	
Moderate	15 (16.3)	17 (9.8)	32 (50.8)	2.04	0.96–4.35	
Severe	7 (7.6)	9 (5.2)	16 (25.4)	1.80	0.64–5.05	
Missing	—	11	11			
Anxiety						
No	72 (78.3)	149 (84.7)	221 (82.5)	1.00	Reference	.0666
Mild	5 (5.4)	9 (5.1)	14 (5.2)	1.15	0.37–3.55	
Moderate	6 (6.5)	14 (8.0)	20 (7.5)	0.89	0.33–2.40	
Severe	9 (9.8)	4 (2.3)	13 (4.9)	4.66	1.39–15.63	
Missing	—	8	8			
Mood lability						
No	82 (89.1)	166 (94.3)	248 (92.5)	1.00	Reference	.2365
Mild	3 (9.8)	1 (3.5)	4 (5.7)	6.07	0.62–59.21	
Moderate	6 (26.3)	8 (9.8)	14 (12.1)	1.52	0.51–4.52	
Severe	1 (7.6)	1 (5.2)	2 (6.0)	2.02	0.13–32.77	
Missing	—	8	8			
Sleeping rhythm						
No	64 (69.6)	137 (78.3)	201 (75.3)	1.00	Reference	. 1953
Mild	5 (5.4)	7 (4.0)	12 (4.5)	1.53	0.47–5.00	
Moderate	17 (18.5)	17 (9.7)	34 (12.7)	2.14	1.03–4.46	
Severe	6 (6.5)	14 (8.0)	20 (7.5)	0.92	0.34–2.50	
Missing	—	9	9			

*Multiple choice.

Table 4. Mothers' Opinions on ODL of ADHD Patients and Controls.

	Cases (*N* = 92)	Controls (*N* = 184)	Total (276)	OR	95% CI	*p*
Effort required						
Yes	68 (74.7)	123 (69.1)	191 (71.0)	1.32	0.75–2.34	.3361
No	23 (25.3)	55 (30.9)	78 (29.0)	1.00	Reference	
Missing	1	6	7			
Commitment						
Yes	67 (72.8)	146 (82.0)	213 (78.9)	0.59	0.32–1.07	.0793
No	25 (27.2)	32 (18.0)	57 (21.1)	1.00	Reference	
Missing	—	6	6			
Replacing teachers						
Yes	73 (79.3)	140 (80.0)	213 (79.8)	0.96	0.51–1.80	.8997
No	19 (20.7)	35 (20.0)	54 (20.2)	1.00	Reference	
Missing	—	9	9			
Low level of learning						
Yes	50 (54.3)	70 (38.7)	120 (44.0)	1.89	1.14–3.14	.0137
No	42 (45.7)	111 (61.3)	153 (56.0)	1.00	Reference	
Missing	—	3	3			
Education's right guaranteed						
Yes	51 (56.0)	70 (39.1)	121 (44.8)	1.00	Reference	.0082
No	40 (44.0)	109 (60.9)	149 (55.2)	0.50	0.30–0.84	
Missing	1	5	6			
ODL in the future						
Yes	44 (48.4)	59 (33.9)	103 (38.9)	1.00	Reference	.0220
No	47 (51.6)	115 (66.1)	162 (61.1)	0.55	0.33–0.92	
Missing	1	10	11			

not have technological tools such as PCs and tablets, and 57% of Italian students have to share a PC with their family (ISTAT, 2020; Save the Children Italia Onlus, 2020). In our sample, ODL was not available for 2.2% of students. Mothers reported difficulties with technology, lack of organization, lack of a stable routine, and poorly structured activities. This was consistent with recent guidelines on managing ADHD children during COVID-19 pandemic

(Cortese et al., 2020). Providing routines and teaching work programming are key strategies to help pupils with ADHD feel secure, organize their own work, and attend lessons more effectively. Moreover, few, and often inadequate, specific strategies for ADHD were used and support teachers often did not provide individual lessons to their pupils or did so only sporadically. A total of 62.7% students did not receive any support. These data lead to the assumption that all these factors played a role in the poor learning reported by more mothers in the ADHD group than in control group. Moreover, a significantly higher percentage of mothers of ADHD students reported that video lessons captured the children's attention more than school in presence. In addition to the fact that these children were receiving pharmacological treatment with a control of symptoms, a broader consideration should be made. Children's use of electronic media, including Internet and video games, is part of the daily life of children who live in contexts of medium-high resources. Screen culture has more impact on children with ADHD than without ADHD, although the high-frequency use increased the risk of ADHD symptoms overall, and ADHD youths are more prone to Internet addiction (Enagandula et al., 2018; Ra et al., 2018; Weiss et al., 2011). In this regard, it is well-recognized that the clinician assessing children with ADHD should routinely inquire about these activities. Several mechanisms might explain their association with executive functioning, cognitive mechanisms, and mechanisms of emotional dysregulation. These are all factors that promote adolescent executive functioning and well-being through activities including sleep, physical activity, distraction-free homework, and positive interactions with family and friends. To explore novel mechanisms, hyperfocus, an intense fixation on an interest or activity for an extended period of time, is common in children and adults with ADHD when working intently on things of interest (Ashinoff & Abu-Akel, 2021). For children, the object of hyperfocus might be a video game, a program on TV, or the Internet. Like distractibility, hyperfocus is thought to result from abnormally low levels of dopamine that make it hard to shift one's attention from one thing to another. If unrestrained, intense focus is most often a liability, and can lead to failure in school (Goodwin & Oberacker, 2011). It's possible that the use of the same tools necessary for home schooling might favor an overuse of Internet, reducing parental control, and changing parents' feelings about time spent in front of screens by their children. Surprisingly, parents of children with and without ADHD observed attention deficit and hyperactivity during online lessons to the same extent. In particular, the youngest children in the control group showed more difficulties in maintaining concentration and attention during lessons and homework, similar to ADHD children. This was consistent with results on general emotional and behavioral changes, beyond the specific school setting (Bobo et al., 2020; Drane et al., 2020; Sasaki et al., 2020). In fact, no significant difference in affective symptoms and behavior disorders emerged in our study. In both groups, mothers reported more hyperactivity, more aggressive behavior, and more anxiety symptoms with similar frequencies. In particular, younger children in the control group showed more restlessness and aggression, behaviors similar to those of ADHD children. It's possible, however, that mothers of control children were more sensitive to changes in behavior, especially when these changes acted as obstacles to learning. The possibility of a continuation of ODL therefore appears to be rejected by most mothers, especially in the control group. We can assume that this is due to the fact that mothers of ADHD children are more accustomed to having to follow their children in teaching and to face problems related to school, compared to parents of children without ADHD, for whom certain behaviors were a novelty.

To address the school needs during quarantine parents had to act as teachers, both as an educational and resilient response.

Overall, findings showed that prolonged school closure and ODL caused a disorder in functioning and affected the psychological wellbeing of all students (Segre et al., 2021). A slight difference was found between ADHD pupils and controls, the first of whom seemed to be more destabilized, especially the younger ones. Quarantine in ADHD students can contribute to a deterioration of their clinical condition, often with difficulties in managing adequately.

Strengths and Limitations

This study has several limitations. Data were reported by mothers, and not directly by children. It's possible that children would rate their own emotional and behavioral changes differently. The relationship between changed behaviors among children with ADHD and their medication status was not directly tested; the use of pharmacological medication in Italian children is less used than in other countries (Clavenna et al., 2007). An interesting point of discussion would be around the effect of ADHD pharmacologic treatment. While it has been shown that it has a number of beneficial effects beyond ADHD core symptoms (Cortese, 2020), it would be interesting to test whether it is beneficial, and if so, to which extent, also to improve remote learning. The small clinical sample size and the use of a non-standardized questionnaire are the two main limits of our study, together with the low representativeness of control sample due to the snowballing method recruitment. We detected all qualitative variants that are strongly influenced by the responder's point of view, although we don't know the sensibility and specificity of the questionnaire used. We can therefore not be sure that emotional changes observed by mothers are caused effectively by ODL and not by other factors such as the lockdown or the emotional state of mothers themselves.

Conclusions

The majority of mothers of both ADHD students and controls rejected ODL. This schooling method has been judged inadequate in ensuring students' learning and in protecting their right to education, especially for the more vulnerable students. Even among children without specific difficulties, ODL led to a deterioration in, both, school efficiency and in behavior and psychological well-being, with aspects of functioning that were very similar to those of children with ADHD, in particular in younger children. Two percent of all students did not have access to any didactic tool, with a consequent zeroing of all school learning activities during quarantine. In that context, ODL can exacerbate disparities instead of adequately preventing or counteracting them (UNESCO, 2020).

The loss of the social, spatial, and time-related context has increased the instability of children. The social distancing between children and teachers has hindered the relationship and the level of trust built over the years, and has precluded visual and verbal feedback (eyes and physical contact). Technological tools and massive use of screens has led to an increase in attention deficit and in restlessness, except in those cases whose attention is captured by videos.

In planning the reopening of schools the institutions will have to keep in mind all the limits of ODL that have emerged during these months and weigh them against the real benefits of school closures as an intervention to control a pandemic, especially as these are not yet clearly demonstrated in the literature (Armitage & Nellums, 2020; Cachón-Zagalaz et al., 2020; Liu et al., 2021; Viner et al., 2020).

Parents and teachers genuinely observe different ADHD behaviors with unique aspects of expression in their respective setting. Even with a low level of parent-teacher agreement, information from both is important in detecting symptoms, defining trait levels and severity of impairment, and defining the diagnosis (Garcia-Rosales et al., 2021; McGrath, 2020). In particular, parents endorse more accurate information concerning low to moderate symptoms. Parental information through interview is therefore reliable in detecting changed ADHD behaviors also during quarantine. Following students' return to school, the evaluation of consequences of quarantine on students' academic functioning and performing should involve both teachers and parents in order to adequately understand the effects of quarantine and to plan appropriate recovery interventions.

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Ethics Declarations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on care and clinical research. Participants accepted to take part in the survey after filling out the consent form. Participants were provided information on the purposes of the research on the first page of the questionnaire, and had to check a box indicating their informed consent before they could proceed. Participants were also asked to answer sincerely, and were assured that their answers would be confidential. All data were encrypted, and the study protocol was approved by the Ethics Committee of the San Paolo hospital.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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Psychopathology and Adaptive Functioning in Children, Adolescents, and Young Adults with Noonan Syndrome

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ABSTRACT: ***Objective:*** **The objective of this study was to examine psychopathology and its impact on adaptive functioning in a sample of patients affected by Noonan syndrome (NS), a genetically heterogeneous condition with systemic manifestations.** ***Method:*** **Forty-two subjects affected by NS (23 males and 19 females), aged 5 to 21 years (mean 12.6 ± SD 5.1), were assessed for nonverbal cognitive abilities, with dimensional measures of psychopathology, adaptive functioning, and family quality of life.** ***Results:*** **The nonverbal intelligence quotient (IQ) mean was 99.4 ± SD 22.2, with 3 subjects (8%, 95% confidence interval [CI], 1.6%–20.9%) showing cognitive impairment (IQ<70). The Parent Child Behavior Checklist (CBCL) total psychopathology score was in the clinical range in 10% of sample and borderline in another 10%. On the Conners' Parent Rating Scales, scores suggestive of attention-deficit/hyperactivity disorder (ADHD) were in the clinical range in 20%. On the autism quotient, autism spectrum disorder symptoms were reported in 10%. Higher scores on the Adaptive Behavioral Assessment System–Second Edition and on the World Health Organization Quality of Life (26 items) were associated with lower problems on the CBCL ($r = -0.63$, 95% CI, −0.78 to −0.40 and $r = -0.48$, 95% CI, −0.69 to −0.20, respectively).** ***Conclusion:*** **Psychopathology was common in patients with NS and negatively correlated with global functioning and family quality of life. Treatable psychopathology, such as ADHD, may constitute a treatment target for improving adaptive functioning.**

(*J Dev Behav Pediatr* 43:e87–e93, 2022) **Index terms:** Noonan syndrome, RASopathies, adaptive functioning, psychopathology, ADHD.

RASopathies are a group of multisystemic congenital disorders with autosomal dominant transmission due to heterozygous germline mutations of genes encoding the RAS-mitogen–activated protein kinase (RAS-MAPK) cascade proteins, such as *PTPN11*, *SOS1*, *BRAF1*, *RAF1*, *MAP2K1*, *MAP2K2*, *KRAS*, *NRAS*, *SHOC2*, *HRAS*, *RIT1*, *CBL*, *LZTR1*, and *SOS2*.[1,2] Typical features include congenital heart defects, facial dysmorphisms, and skeletal abnormalities, which are associated with higher rates of hearing impairment, cryptorchidism, and kidney, skin, and other organ anomalies. Noonan syndrome (NS), with an estimated prevalence of 1 in 1,000 to 2,500 live births,[1] is the most frequent RASopathy.[3]

The RAS-MAPK cascade is a critically important cellular pathway that is activated by extracellular stimuli and controls multiple processes, including proliferation, differentiation, metabolism, and survival.[1,2] It plays a role in brain development and controlling memory and learning, and its disruption has been linked to neurodevelopmental delay, learning difficulties, cognitive deficit, and behavioral problems.[4–6] Available data indicate that most children with NS have intelligence in the normal range, with an intelligence quotient (IQ) generally ranging from 70 to 120, but that up to 20% have cognitive impairment (IQ <70) and a third have a borderline IQ (between 71 and 84).[7] About half of the children with NS usually receive some form of educational support in school, but despite impairment in some, most adults are able to work.[8]

A few studies have examined the presence of psychopathology in RASopathies. High rates of autism spectrum disorder ranging from 12% to 30%,[9–13] attention-deficit/hyperactivity disorder (ADHD) ranging from 22% to 35%,[6,13] and anxiety disorders have been reported.[7] Because of the low prevalence of RASopathies in the population, study sample sizes tend to be small, with consequent limitation in estimating prevalence.

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Patients affected by RASopathies face several health issues, each potentially contributing to lowering their adaptive functioning. A better understanding of the psychopathology associated with this condition and of its relationship with functioning may help identify treatment targets and thus improve quality of life. In this context, the aim of this study was to assess and characterize the presence of psychopathological symptoms in a relatively large sample of children, adolescents, and young adults with NS and evaluate the association between psychopathology and levels of functioning and family quality of life.

METHOD

Procedure and Participants

Patients aged 5 to 21 years diagnosed with Noonan syndrome (NS) or other RASopathies at the Pediatric Genetic Unit of a pediatric university hospital (University of Turin, Regina Margherita Children's Hospital, Turin, Italy), which serves an area of 4 million people in the northwest of Italy, were included. A minimum age of 5 years was set to ensure that the assessments were valid. A maximum age of 21 years was set to include young adults in transition from adolescence to adulthood.

Clinical diagnosis of RASopathy was made by an experienced pediatrician based on the presence of the phenotypic features of the syndrome. Genetic confirmation was sought for all participants by examining DNA for known mutations linked to RASopathies (i.e., *PTPN11*, *SOS1*, *BRAF1*, *RAF1*, *MAP2K1*, *MAP2K2*, *KRAS*, *NRAS*, *SHOC2*, *HRAS*, *RIT1*, *CBL*, *LZTR1*, and *SOS2*).

The clinical evaluation consisted of the administration of a battery of validated instruments to assess the presence and severity of psychopathological symptoms, nonverbal cognitive abilities, adaptive functioning, and quality of life. Patients and their parents were assessed by 5 trained child and adolescent psychiatrists. Parents were asked to complete the rating scales, and patients were tested for nonverbal intelligence. Lacking specific parent-rated instruments validated to assess attention-deficit/hyperactivity disorder (ADHD) symptoms or global psychopathology in the Italian population for subjects older than 18 and 19 years, respectively, we decided to administer the available scales to the full sample, including older patients. In doing so, while we gained information on the entire sample, we had to accept the possibility of underestimating symptomatology in the young adults. For patients aged 18 years or older, the Conners' Parent Rating Scale–Revised (CPRS-R) and Child Behavior Checklist (CBCL) were scored using the norms for 18-year-old subjects. In addition, all the clinical records were reviewed by child and adolescent psychiatrists for prenatal, neurodevelopmental, and medical history.

This study was approved by the Institutional Ethics Committee. The nature and purpose of the assessment were explained to the parents and patients, who gave informed consent as developmentally appropriate. Forty-two patients and their parents agreed to participate. Their full demographics and clinical characteristics are summarized in Table 1.

Table 1. Demographics and Clinical Characteristics of All Subjects and of the Subgroup with the *PTPN11* Genotype

	All Subjects (N = 42)	With *PTPN11* (n = 28)
Male, n (%)	23 (55)	14 (50)
Age, yrs, mean (SD)		
At diagnosis	3.5 (4.2)	3.7 (4.5)
At assessment (yrs)	12.6 (5.1)	12.2 (5.4)
Length of follow-up (yrs)	9.2 (4.9)	8.5 (4.7)
Genetics	N = 40	n = 28
Sporadic transmission, n (%)	36 (90)	25 (89)
Pregnancy	N = 41	n = 28
Complicated, n (%)	25 (61)	15 (56)
Delivery		
Preterm, n (%)	5 (12)	2 (7)
Vaginal, n (%)	23 (55)	16 (57)
Age of first steps, mo, mean (SD)	15.9 (4.8)	14.5 (3.5)
Motor development delay, n (%)	16 (38)	7 (25)
Age of first words, mo, mean (SD)	14.2 (6.5)	13.0 (5.8)
Speech delay, n (%)	9 (21)	4 (14)
Need for school support, n (%)	18 (43)	11 (39)
Received neuropsychiatric services, n (%)	29 (69)	18 (64)
Treatment		
Physiotherapy, n (%)	20 (48)	12 (43)
Speech therapy, n (%)	25 (60)	13 (46)
Associated conditions		
Epilepsy, n (%)	7 (17)	3 (11)
Brain tumors, n (%)	1 (2)	1 (4)
Arnold-Chiari I syndrome, n (%)	2 (5)	1 (4)
Short stature (<10° percentile) at diagnosis, n (%)	35 (83)	23 (82)
Congenital heart defects, n (%)	35 (83)	24 (86)
Myelodysplasia, n (%)	3 (7)	3 (11)
Hearing impairment, n (%)	6 (14)	4 (14)

Assessments

The participants were examined and their parents interviewed in-person by child and adolescent psychiatrists. Parents completed age-appropriate questionnaires about their children's psychopathological symptoms, adaptive functioning, and quality of life. Developmental history, including psychomotor development, education, neuropsychiatric services received, and other clinical data were obtained from the medical records and direct interview. The following domains were evaluated.

Nonverbal Cognitive Abilities

Nonverbal cognitive abilities were assessed with the Raven's Progressive Matrices Test (RPMT).[14] Participants were asked to complete a set of matrices of geometric designs with 1 piece of the picture missing, choosing between 8 possible answers. Standard Progressive Matrices or Colored Progressive Matrices were used depending on

Table 2. Gene Mutations Associated with Noonan Syndrome in the Study Sample (N = 42)

Gene	*PTPN11* (n = 28)	*SOS1* (n = 5)	*BRAF* (n = 2)	*RAF1* (n = 2)	*SOS2* (n = 1)	*SHOC2* (n = 1)	*MAP2K1* (n = 1)	Unidentified (n = 2)
Mutations	(3) Asn308Asp	(1) Arg552Gly	(1) Leu597Val	(1) Arg495Ser	(1) Thr367Sr	(1) Ser2Gly	(1) Asp67Asn	
	(2) Asn308Ser	(1) Glu433Lys	(1) Thr241Met	(1) Ser257Leu				
	(1) Asp106Ala	(1) Ile252Thr						
	(3) Asp61Asn	(2) Met269Thr						
	(1) Gln510Glu							
	(1) Gln79Arg							
	(2) Glu76Asp							
	(1) Glu139Asp							
	(1) Ile282Val							
	(2) Leu261His							
	(1) Leu262Arg							
	(1) Lys70Arg							
	(2) Met504Val							
	(1) Pro491His							
	(1) Pro491Ser							
	(1) Thr468Met							
	(1) Tyr279Cys							
	(3) Tyr63Cys							

the age of the subject. Based on the number of elements correctly identified, this test provides a score that corresponds to a specific nonverbal intelligence quotient.[15]

Psychopathology

Psychopathology was dimensionally assessed with the CBCL, a parent-completed standardized questionnaire that is widely used in both clinical and research settings and available in preschool (1.5–5 years) and school-age (6–18 years) versions.[16,17] It generates 8 syndromic scales (anxious/depressed, withdrawal/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), which are further gathered to obtain 2 general dimensions, internalization and externalization, and 1 total score. The checklist also allows assessing behavior through 6 scales based on the Diagnostic and Statistical Manual of Mental Disorders (DSM): affective problems, anxiety problems, somatic problems, ADHD problems, oppositional problems, and conduct problems. From the raw score, a T score is obtained for each scale: T scores are considered borderline between 65 and 70 and in the clinical range above 70.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder and its related symptoms were measured with the CPRS-R,[18] on which the parents score frequency of behaviors in the following areas: oppositional problems, cognitive problems, hyperactivity, anxiety-shyness, perfectionism, social problems, and psychosomatic problems. Items are aggregated into a global index, an ADHD index, and a DSM-IV index. Summary scores are computed by adding across items, obtaining for each area a T score based on a standard scale. T scores between 55 and 65 are considered borderline, and T scores above 66 are considered clinical.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) features were assessed with the Autism-Spectrum Quotient, a parent-rated instrument for measuring autistic traits, available in child (4–11 years), adolescent (12–15 years), and adult (>16 years) versions.[19] The Autism-Spectrum Quotient includes 50 questions related to 5 different domains: social skill, attention switching, attention to detail, communication, and imagination. The test is considered positive for significant ASD symptoms if the total score is greater than 76 in children, 30 in adolescents, and 32 in adults.

Adaptive Functioning

Adaptive functioning, the set of conceptual, social, and practical skills that people have learned and used in everyday life, was measured with the Adaptive Behavior Assessment System–Second Edition (ABAS-II) Parent Form (ages 5–21 years), a parent-administered, 232-item scale to rate how frequently the subject performs a correct behavior when necessary and without help. Items are grouped into 10 areas: communication, community use, functional academics, home living, health and safety, leisure, self-care, self-direction, social, and work.[20] Skill area scores are norm-referenced scaled scores with a mean of 10 and a SD of 3 and are combined into 3 composite scores: conceptual, social, and practical, as well as an overall general adaptive composite score. Composite scores are norm-referenced standard scores with a mean of 100 and a SD of 15.

Quality of Life

Quality of life was assessed with the World Health Organization Quality of Life—26 items (WHOQOL-BREF),[21] which was completed by the parent about the quality of life of the family. This scale investigates perception of the quality of life at the overall level and in 4 specific domains (physical, psychological, social, and environmental) for a total of 26 questions, each rated on a 5-point scale. The domain scores are converted into a 0 to 100 scale, where 100 indicates the best possible perceived quality of life.

Data Analysis

Based on validated norms, standardized scores were computed for the CBCL and CPRS-R scales, RPMT, and ABAS-II. Descriptive analyses were applied to the data, with relative 95% confidence intervals as appropriate. Subgroup analyses were performed for the patients aged 5 to 10, 11 to 17, and 18 to 21 years. Pearson's r coefficients were computed to assess correlations between indexes of psychopathology (CBCL and CPRS-R) on one side and measures of adaptive functioning (ABAS-II) and of quality of life (WHOQOL-BREF) on the other, both in the whole sample and in age subgroups.

Statistical significance was set at alpha = 0.05 (2-tailed), with Bonferroni correction in the case of multiple comparisons. Statistical processing was performed using the IBM SPSS Statistic software, version 24 (IBM Corp, Armonk, NY).

RESULTS

Sample Demographics and Clinical and Genetics Characteristics

The sample consisted of 42 patients (23 males and 19 females), with an mean age of 12.6 ± SD 5.1 years (range 5–21), who had been clinically followed for 9.2 ± 4.9 years (Table 1). Pregnancy complications were reported in 61% of cases, and preterm delivery in 12%. First steps occurred at 15.9 ± 4.8 months, and first words at 14.2 ± 6.5 months. Sixteen patients (38%) had delay in motor development (onset of autonomous walking after 18 months of age), and 9 patients (21%) had speech delay (first words after 24 months of age). The use of physiotherapy, speech therapy, and neuropsychiatric services was reported by 48%, 60%, and 69% of the patients, respectively (Table 1). Neuropsychiatric follow-up was often performed to monitor psychomotor development, given a history of motor or speech delay. In some cases, patients were treated for epilepsy, whereas others were assessed because of concerns about school learning. None of the study participants were in treatment with psychiatric medication at the time of the assessment. Seven patients had taken antiepileptic drugs in their lifetime, and of them, 5 were still in treatment at the time of the assessment.

In 28 patients (66.7%), pathogenic variants were identified in *PTPN11*, 5 in *SOS1*, 2 each in *BRAF* and *RAF1*, and 1 each in *SHOC2*, *SOS2*, and *MAP2K1*. In 2 patients meeting clinical criteria for Noonan syndrome, no pathogenic variant was found in any of the genes currently known to be involved in the pathogenesis of RASopathies. There was great heterogeneity of genetic variants also within the same gene, as reported in Table 2.

Cognitive Functioning

The mean nonverbal intelligence quotient (NVIQ) was 99.4 ± SD 22.2 (Table 3), with 32 participants (82%) having an NVIQ ≥85. Four patients had a total score in the borderline range (NVIQ = 70–84), and 3 had a total score under 70.

Psychopathological Dimensions

The numbers of patients with Child Behavior Checklist (CBCL) scores in the normal, borderline, and clinical range are reported in Table 3. Mean and SD are reported in Table 1 (see Supplemental Digital Content 1, http://links.lww.com/JDBP/A312). On the CBCL Total Problem indexes, 81% (95% confidence interval [CI], 65.9%–91.4%) had scores in the normal range, 10% (95% CI, 4.0%–23.1%) in the borderline range, and another 10% in the clinical range. Although 90% of the sample were in the normal range for externalizing problems, about a third had borderline or clinically abnormal scores for internalizing problems, which include anxiety and depression symptoms.

Attention-Deficit/Hyperactivity Disorder Symptoms

The numbers of patients with Conners' Parent Rating Scale–Revised (CPRS-R) scores in the normal, borderline, and clinical range are reported in Table 3. Mean and SD are reported in Table 1 (see Supplemental Digital Content 1, http://links.lww.com/JDBP/A312). Although most patients had scores in the normal range, 8 (20.0%, 95% CI, 9.3%–35.4%) had a CPRS-R Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV total score in the clinical range, suggestive of attention-deficit/hyperactivity disorder (ADHD).

Autism Spectrum Disorder Symptoms

On the Autism-Spectrum Quotient, 4 patients (10%, 95% CI, 2.8%–23.7%) had scores in the pathological range (Table 3).

Adaptive Functioning

The Adaptive Behavior Assessment System–Second Edition (ABAS-II) total score was 85.8 ± 24.1, about 1SD below the population mean (Table 3). Higher scores on the ABAS-II were associated with lower problems on the CBCL: negative correlations were found between ABAS-II global adaptive composite (GAC) score and CBCL total score (r = −0.63, 95% CI, −0.78 to −0.40), CBCL internalizing score (r = −0.40, 95% CI, −0.63 to −0.11), and CBCL externalizing score (r = −0.64, 95% CI, −0.79 to −0.42). Children rated to have more symptoms of hyperactivity-impulsivity on the CPRS-R were found to have lower scores on the ABAS-II GAC score (CPRS-R DSM-IV total

Table 3. Cognitive Functioning, Psychopathological Profile, Adaptive Behavior, and Quality of Life

	All Subjects (N = 42)	*PTPN11* (n = 28)
RPMT-NVIQ, n (%)	39 (100)	27 (100)
<70, n (%)	3 (8)	0 (0)
70–84, n (%)	4 (10)	3 (11)
≥85, n (%)	32 (82)	24 (89)
Total score, mean (SD)	99.4 (22.2)	102.4 (20.1)
CBCL, n (%)	42 (100)	28 (100)
Internalizing problems		
Normal (T score <65)	27 (64)	19 (68)
Borderline (T score = 65–70)	13 (31)	8 (29)
Clinical (T score >70)	2 (5)	1 (4)
Externalizing problems		
Normal (T score <65)	38 (90)	25 (89)
Borderline (T score = 65–70)	3 (7)	2 (7)
Clinical (T score >70)	1 (2)	1 (4)
Total problems		
Normal (T score <65)	34 (81)	23 (82)
Borderline (T score = 65–70)	4 (10)	3 (11)
Clinical (T score >70)	4 (10)	2 (7)
CPRS-R, n (%)	40 (100)	27 (100)
CPRS-R DSM-IV (I)		
Normal (T score <65)	30 (75)	22 (81)
Borderline (T score = 65–70)	3 (8)	2 (7)
Clinical (T score >70)	7 (18)	3 (11)
CPRS-R DSM-IV (H-I)		
Normal (T score <65)	31 (78)	22 (81)
Borderline (T score = 65–70)	3 (8)	1 (4)
Clinical (T score >70)	6 (15)	4 (15)
CPRS-R DSM-IV (T)		
Normal (T score <65)	31 (78)	21 (78)
Borderline (T score = 65–70)	1 (3)	1 (4)
Clinical (T score >70)	8 (20)	5 (19)
AQ, n (%)	40 (100)	26 (100)
Pathological score	4 (10)	3 (12)
ABAS-II, n (%)	42 (100)	28 (100)
Mean (SD)		
Total	85.8 (24.1)	89.9 (22.0)
Conceptual	90.4 (24.3)	94.2 (22.4)
Social	88.4 (18.9)	91.0 (17.8)
Practical	83.4 (23.5)	88.3 (20.7)
Family WHOQOL-BREF, n (%)	41 (100)	28 (100)
Mean (SD)		
Physical	72.3 (14.6)	71.0 (15.5)
Psychological	67.7 (15.2)	65.8 (16.9)
Social	66.7 (18.7)	62.1 (20.0)
Environmental	63.0 (14.9)	62.3 (15.5)

ABAS-II, Adaptive Behavior Assessment System–Second Edition; ADHD, attention-deficit and hyperactivity disorder; AQ, Autism-Spectrum Quotient; CBCL, Child Behavior Checklist; DSM-IV (I), Diagnostic and Statistical Manual of Mental Disorders–IV Inattentive; DSM-IV (H-I), Diagnostic and Statistical Manual of Mental Disorders–IV Hyperactive-Impulsive; DSM-IV (T), Diagnostic and Statistical Manual of Mental Disorders–IV total; RPMT-NVIQ, Raven's Progressive Matrices Test-Nonverbal Intelligence Quotient; WHOQOL-BREF, World Health Organization Quality of Life–Short Form (26 items).

score $r = -0.59$, 95% CI, -0.76 to -0.34, and CPRS-R DSM-IV inattentive symptoms and hyperactivity/impulsivity scores $r = -0.47$, 95% CI, -0.68 to -0.19 and $r = -0.62$, 95% CI, -0.78 to -0.38, respectively). Impairment of adaptive functioning related to more severe psychopathological problems was apparent in both 5 to 10 and 11 to 17 years of age subgroups: analyses showed that in the 11- to 17-year-old subgroup, the negative correlations between ABAS-II GAC score and CBCL global indexes (total, internalizing, and externalizing problems) were maintained. Moreover, in both 5 to 10 and 11 to 17 years of age groups, a negative correlation was found between the ABAS-II GAC score and the CPRS-R DSM-IV hyperactivity/impulsivity score ($r = -0.69$, 95% CI, -0.87 to -0.33 and $r = -0.77$, 95% CI, -0.93, -0.38, respectively; all p's <0.008 statistically significant after Bonferroni correction, Table 4).

Quality of Life

The scores of the 4 domains of the World Health Organization Quality of Life (WHOQOL-BREF) scale are summarized in Table 3. Although a score of 100 represents the highest possible level of perceived quality of life, the scores for the physical (mean 72.3 ± 14.6), psychological (mean 67.7 ± 15.2), social (mean 66.7 ± 18.7), and environmental (mean 63.0 ± 14.9) domains are overall indicative of reduced quality of life. Lower scores on the WHOQOL-BREF questionnaire were associated with higher scores on the CBCL problem scales. In particular, the WHOQOL-BREF physical domain scores were negatively correlated with both CBCL total scores ($r = -0.48$, 95% CI, -0.69 to -0.20) and CBCL externalizing scores ($r = -0.50$, 95% CI, -0.70 to -0.23), and the environmental domain scores with the CBCL externalizing scores ($r = -0.49$, 95% CI, -0.69 to -0.22) (all p's < 0.001, statistically significant after Bonferroni correction).

DISCUSSION

In this study, a cohort of children and youth with Noonan syndrome (NS) were systematically assessed for developmental milestones, cognitive abilities, dimensional psychopathology, adaptive functioning, and family quality of life. The evaluation took place on average 9.2 years after the initial diagnosis of NS, thus giving the opportunity to retrospectively examine almost a decade of life of these patients. The demographics of the sample are consistent with those previously reported, with about half of the subjects being male and two-thirds having a *PTPN11* mutation (Table 1).[1,3]

Because of the low population prevalence of NS, the study sample size (n = 42), even if it is one of the largest thus far reported, is still statistically rather small for precise estimates. Despite this limitation, several conclusions can be drawn. Nonverbal cognitive impairment (i.e., nonverbal intelligence quotient <70) affected 8% of the subjects, but in most cases, cognitive functioning was in the normal range (Table 3). These rates are generally consistent with previous reports.[4–7] The study also

Table 4. Association Between Psychopathology and Level of Functioning

	ABAS Total Score		
	Pearson's *r*	95% CI	*p*[a]
CBCL total problems			
All patients (n = 42)	−0.63	−0.78 to −0.40	**<0.001**
5–10 yrs (n = 19)	−0.54	−0.80 to −0.11	0.017
11–17 yrs (n = 14)	−0.71	−0.90 to −0.28	0.005
18–21 yrs (n = 9)	−0.68	−0.93 to −0.03	0.043
CBCL internalizing problems			
All patients (n = 42)	−0.40	−0.63 to −0.11	**0.008**
5–10 yrs (n = 19)	−0.19	−0.59 to 0.29	0.436
11–17 yrs (n = 14)	−0.70	−0.90 to −0.27	0.005
18–21 yrs (n = 9)	−0.31	−0.81 to 0.44	0.409
CBCL externalizing problems			
All patients (n = 42)	−0.64	−0.79 to −0.42	**<0.001**
5–10 yrs (n = 19)	−0.57	−0.81 to −0.16	0.011
11–17 yrs (n = 14)	−0.68	−0.89 to −0.23	0.008
18–21 yrs (n = 9)	−0.76	−0.95 to −0.19	0.017
CPRS-R DSM-IV (T)			
All patients (n = 40)	−0.59	−0.76 to −0.34	**<0.001**
5–10 yrs (n = 18)	−0.53	−0.80 to −0.08	0.022
11–17 yrs (n = 13)	−0.74	−0.92 to −0.32	0.004
18–21 yrs (n = 9)	−0.77	−0.95 to −0.22	0.015
CPRS-R DSM-IV (H-I)			
All patients (n = 40)	−0.62	−0.78 to −0.38	**<0.001**
5–10 yrs (n = 18)	−0.69	−0.87 to −0.33	0.002
11–17 yrs (n = 13)	−0.77	−0.93 to −0.38	0.002
18–21 yrs (n = 9)	−0.70	−0.93 to −0.07	0.036
CPRS-R DSM-IV (I)			
All patients (n = 40)	−0.47	−0.68 to −0.19	**0.002**
5–10 yrs (n = 18)	−0.30	−0.67 to 0.19	0.234
11–17 yrs (n = 13)	−0.67	−0.89 to −0.19	0.013
18–21 yrs (n = 9)	−0.77	−0.95 to −0.21	0.016

[a]Statistically significant *p* values after Bonferroni correction (alpha ≤0.008) are bolded.
ABAS, Adaptive Behavior Assessment System; CBCL, Child Behavior Checklist; CI, confidence interval; CPRS-R, Conners' Parent Rating Scale–Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders–IV (criteria for attention-deficit/-hyperactivity disorder: T, total; H-I, hyperactive and impulsive; and I, inattentive symptoms).

confirms that clinically significant autism spectrum disorder symptoms are much more prevalent in children, adolescent, and young adults with NS than in the general population,[22] affecting 10% of the cases.

Based on the Conners' Parent Rating Scale–Revised (CPRS-R) and Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV, the prevalence of attention-deficit/hyperactivity disorder (ADHD) was estimated to be 20% in our sample. This rate is consistent with previous reports, which had identified, in smaller samples, ADHD as a common psychiatric condition in children and youth affected by NS. An ADHD rate of 26% (10 of 39 patients) was reported in a US sample,[23] and a 22% rate (6 of 27) in an Italian study.[7] The possible neurobiological characteristics underlying symptoms of inattention, hyperactivity, and memory deficits in children affected by *PTPN11*-related form of NS were recently investigated with high-resolution structural magnetic resonance imaging, leading to the identification of alterations in temporal and frontal cortical regions known to be associated with ADHD and learning.[24]

In our sample, global psychopathology, measured with the Child Behavior Checklist (CBCL), and ADHD symptoms, measured with the CPRS-R, were negatively correlated with the level of adaptive functioning and family quality of life (Table 4), especially among patients aged 11 to 17 years. The strength of the correlation indicated that general psychopathology and, in particular, ADHD accounted for more than two-thirds of the variance in adaptive functioning (Table 4 and see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JDBP/A312). These results are consistent with a previous report that indicated that ADHD symptomatology was linked to social difficulties in children with NS.[23] The clinical implication of these data relates to the availability of effective treatments for ADHD and therefore to the potential of improving functioning through treatment.

Limitations

The main limitation of this study lies in the sample size (N = 42), which, although larger than that of previous reports, does not allow possible differences between the genetic subgroups to be statistically tested. Future studies combining samples from multiple sites may be able to address the genotype-phenotype relationship with adequate statistical power. Furthermore, the study was conducted at 1 clinical site, and this may limit generalizability of the findings. Another limitation is that the assessment of cognitive abilities was based only on a nonverbal test of intelligence (Raven's Progressive Matrices Test). This was performed to decrease patient burden and thus maximize study participation, but it prevented more in-depth assessment of cognitive functioning, especially verbal domains. Moreover, lacking the CBCL and CPRS-R normative data for subjects above 19 and 18 years, respectively, we applied to young adults the norms for adolescents. This might have resulted in underestimation of psychopathology in this age range. A final limitation that needs to be mentioned is that all domains were assessed solely through parent's questionnaires, providing a unique point of view on children adaptive functioning or psychopathology and possibly causing the different measures to be related among themselves.

CONCLUSIONS

This study documents the clinical relevance of psychopathology, and in particular attention-deficit/hyperactivity disorder (ADHD), to adaptive functioning and quality of life in children, adolescents, and young adults with Noonan syndrome. Importantly, because effective interventions are available for several psychiatric disorders, such as ADHD, these data suggest that early identification and treatment of psychopathology may result in improved functioning.

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ORIGINAL RESEARCH ARTICLE

Acute Tolerability of Methylphenidate in Treatment-Naïve Children with ADHD: An Analysis of Naturalistically Collected Data from Clinical Practice

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Abstract

Objectives The acute tolerability of methylphenidate (MPH) in children with attention-deficit/hyperactivity disorder (ADHD) has been studied mainly in research samples. Taking advantage of the mandatory test-dose procedure required for starting MPH in Italy, this study aimed to assess the incidence of intolerable adverse events after initial exposure to MPH in routine clinical practice.

Methods The medical records of 480 consecutively treated, previously drug-naïve children and adolescents with ADHD (90% male, mean age 10.6 ± 3.0 years) were retrospectively analyzed. All children received an initial single dose of MPH immediate release (5 or 10 mg) followed by a 4-hour direct medical observation. Heart rate and blood pressure were measured at dosing and 1, 2, and 3 hours afterwards. If the first dose was well tolerated, the child continued treatment with MPH 5–20 mg daily, and was reassessed a week later.

Results Eleven patients (2.3%, 95% CI 1.1–4.1) interrupted treatment within a week of initiation because of the following adverse events: irritability ($n = 3$), tics worsening ($n = 3$), reduced appetite ($n = 1$), enuresis ($n = 1$), hallucinations ($n = 1$), hyperfocus ($n = 1$), and 'rebound' behavioral worsening ($n = 1$). The most common adverse events were reduced appetite (20%), irritability (14.2%), headache (10.6%), sleep problems (9.4%), stomachache (9.4%), and tics (5%). Intellectual disability increased the risk of any adverse event in general and of irritability in particular. No cardiovascular symptom was clinically reported. However, routine assessments of vital signs during the first 3 hours after the first dose of MPH showed that 9% of the children had a 20% increase in heart rate, 8.8% had a 20% increase in diastolic blood pressure and 4.5% had a 20% increase in systolic blood pressure. Of these, 25.2% still had an elevated heart rate 1 week later.

Conclusions Among stimulant-naïve children in clinical practice, the incidence of acute MPH intolerance can be estimated to be between 1.2 and 4.1%. An asymptomatic elevation in cardiovascular parameters can be observed in about 1 out of 10 children and warrants monitoring during ongoing treatment.

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Key Points

Based on this study, it can be estimated that between 1.2 and 4.1% of school-age children with attention-deficit/hyperactivity disorder (ADHD) starting methylphenidate (MPH) will interrupt the medication within a week due to the emergence of some adverse event.

Children with intellectual disability were at greater risk of developing adverse events, in particular irritability, when starting MPH.

Compared with pre-treatment values, about 1 in 10 children had a 20% or greater increase in heart rate and/or blood pressure that was asymptomatic but persisted with time in 1 out of 4 cases.

1 Introduction

The incidence of intolerable or prohibitive adverse events upon starting a treatment, defined as the emergence of signs or symptoms that cause treatment to be discontinued, can be taken as an index of acute intolerance [1]. Methylphenidate (MPH) is commonly prescribed to treat children with attention-deficit/hyperactivity disorder (ADHD), and its safety profile has been thoroughly investigated in numerous controlled and observational studies [2, 3]. Commonly reported adverse events are decreased appetite, sleep disturbance, stomachache, and headache, while less frequent is the emergence or worsening of tics. In most cases, adverse events can be managed without interrupting treatment and tend to abate with continuous administration of the medication [1, 4, 5].

Less well documented, however, is the rate of intolerable adverse events that lead to treatment discontinuation in usual clinical practice. Available estimates of lack of tolerability to initial exposure to MPH are mainly derived from clinical trials or other research samples rather than usual practice. A 1.4% rate of intolerable adverse events was reported in the open-label lead-in of the Multimodal Treatment Study of ADHD (MTA), which included 289 children aged 7–9 years, of whom four had prohibitive adverse events (buccal movements; skin picking; tearfulness, appetite loss and sleep delay; and listlessness, emotional blunting, and anorexia) [6]. Higher rates of intolerable adverse events have been reported in children with ADHD in the context of autism spectrum disorder (ASD) [8%] and in preschoolers with ADHD (6%), mostly due to emotional outbursts and irritability [7, 8]. These estimates were based on research samples, which, being selected according to rather stringent inclusion and exclusion criteria, are not necessarily representative of the usual clinical population. In addition, participants in research studies are not necessarily drug-naïve, and this selection bias can affect estimates of tolerability.

More recently, a meta-analysis of non-randomized studies found an MPH discontinuation rate of 1.2% for serious adverse events and of 7.3% for adverse events of unknown severity, but with a low quality of evidence that made it impossible to make accurate estimates [9]. It should also be noted that this meta-analysis is prone to a possible bias, as it included observational studies without taking into account putative confounders.

In Italy, no medication for ADHD had been available until 2007, when the Italian Drug Regulatory Agency granted market authorization for immediate-release MPH (IR-MPH) and atomoxetine for children and adolescents (6–18 years old) on the condition that patients be enrolled into a dedicated national registry with standard operative procedures (SOP) for accessing medications [10]. This registry has been previously analyzed to compare MPH and atomoxetine safety [11]. As part of the SOP for starting MPH treatment, children must receive the first dose of MPH in a controlled clinical setting with monitoring for the first few hours after administration to detect possible adverse events, including repeated measuring of resting heart rate (HR) and systolic (sBP) and diastolic blood pressure (dBP). These assessments are to be repeated after 1 week of treatment. The data from this mandatory first-dose test could help estimate the incidence of intolerable adverse events after initial exposure to MPH in usual clinical practice.

The aim of this study was to assess the acute tolerability to initial exposure to MPH among treatment-naïve children with ADHD in usual clinical practice, with special attention to possible changes in HR, sBP, or dBP. Possible predictors of the most common adverse events (i.e., anxiety, irritability, reduced appetite, and sleep disruption) were explored.

2 Methods

2.1 Design and Procedure

This was a retrospective analysis of clinical records collected at two ADHD clinics (University of Pisa and University of Turin) as part of the Italian ADHD National Registry. All patients had been clinically referred and received the assessments required by the Italian medicine regulatory agency to be treated with MPH. Parents were informed of the procedures and risks and potential benefits of MPH, and gave written informed consent for their child to be assessed and treated and for the data to be included in the ADHD National Registry. Assent was obtained also from the child

when appropriate based on developmental stage and cognitive functioning.

2.2 Sample

All children (aged 6–18 years) consecutively referred in the years 2017–2020 for initiating pharmacological treatment of ADHD with MPH were included. These patients had been clinically diagnosed with ADHD according to DSM-5 criteria by trained child psychiatrists, and assessed with specific validated questionnaires (i.e., ADHD-Rating Scales or Conners Parent and Teacher ADHD Rating Scales). At the University of Pisa site, a semi-structured clinical interview, the Kiddie-SADS-PL, was also part of the clinical evaluation. Comorbidities with oppositional defiant disorder or conduct disorder (ODD/CD), mood disorder, anxiety disorder, ASD, and intellectual disability (ID) were identified. As appropriate, intellectual functioning was assessed with the Wechsler intelligence scales. Prior to initiating treatment, all patients received a physical examination to exclude treatment-relevant medical conditions and a standard 12-lead electrocardiogram (ECG) to exclude conduction abnormalities.

2.3 Methylphenidate Treatment

All patients were stimulant-naïve at intake. On the first day, an initial single dose of MPH 5 mg or 10 mg was given orally at the clinics in the morning. The dosage was based on age and weight (5 mg for children younger than 10 years or below 30 kg, and 10 mg in the older or heavier children) and parental preference. Based on these criteria, 209 (43.5%) received 5 mg, and 271 (56.5%) received 10 mg. If tolerability to the first dose was satisfactory, MPH was continued at the initial dose once or twice daily, based on clinical needs, and the child was reassessed after about a week (range 7–9 days).

2.4 Safety Assessments

On the morning of the first test dose of MPH, resting HR and sBP and dBP were measured after the child had been sitting for at least 5 minutes, by nurses using an automatic digital blood pressure arm monitor, immediately before receiving the MPH dose, and 1, 2, and 3 hours afterward. Only one reading was recorded for each measurement, but values considered abnormal (i.e., for children aged 6–11 years: HR >110 bpm, or sBP or dBP >95th percentile for age; for older youth: HR >100 bpm, sBP >120 mmHg, or dBP >80 mmHg) were re-checked, and MPH treatment was continued only if the parameters were within the normal range.

Spontaneously reported adverse events were collected up to 4 hours after the first MPH administration. After about 1 week, safety assessments were repeated. The child psychiatrist inquired with the child and their family about possible emergence in the past week of any adverse event known to be associated with stimulant medications (decreased appetite, insomnia, gastrointestinal symptoms, headache, tics, mood changes), and collected any other spontaneously reported adverse events.

2.5 Statistical Analyses

The data were analyzed with IBM SPSS Statistics 23. First, we imputed missing data (5.5% of the data were incomplete) using multiple imputations, under fully conditional specification, using the default setting "Impute Missing Data Values (Multiple Imputation)" available on SPSS 23.

As a preliminary analysis, we compared the patients enrolled at the Pisa center with those enrolled in Turin. There were no significant differences with respect to patients' age, gender, and main comorbidities, except for ID which was more prevalent in the Turin sample ($\chi 2 = 31.52$; $p < 0.001$). Descriptive statistics were applied to the data. We analyzed categorical variables using chi-square analysis, and continuous variables with univariate analyses of variance (ANOVA). We compared the following groups: patients receiving 5 mg versus 10 mg of MPH during the first week of treatment, subjects showing versus not showing irritability, reduced appetite, or sleep problems after a week of MPH administration. We explored possible age, gender, or comorbidity effect on HR, sBP, and dBP at baseline (T_0), and 1 (T_1), 2 (T_2), and 3 hours (T_3) after the first dose of MPH. At the individual level, differences in cardiovascular parameters were considered clinically significant if deviated by more than 20% from the baseline. At the group level, differences were considered statistically significant if $p < 0.05$.

One-way repeated measures ANOVA was used to test whether HR, sBP, and dBP significantly changed over time. As the sphericity assumption was violated (Mauchly's test: $p < 0.05$), we used Huynh–Feldt estimates [12, 13]. Pairwise comparisons with Bonferroni adjustment for multiple comparisons were conducted. To explore for possible predictors of acute intolerability to MPH, multivariate logistic analyses were performed using presence of adverse events as the dependent variable, and age, sex, dose (5 or 10 mg), ASD, ID, and ODD/CD as independent variables. The Hosmer–Lemeshow test was used to test the goodness-of-fit of the models.

3 Results

3.1 Sample Characteristics

The sample consisted of 480 children and adolescents (456 at Pisa and 24 at Turin), comprising 90.4% males, aged

6–18 years (mean age 10.6 ± 3.0), with ADHD (92.5% with hyperactive/combined type and 7.5% with inattentive presentation) (Table1). There was comorbidity with ODD/CD ($n = 120$, 25%), mood disorders ($n = 61$, 12.7%), anxiety disorders ($n = 42$, 8.7%), ASD ($n = 31$, 6.5%), tic disorder ($n = 17$, 3.5%), and ID ($n = 37$, 7.7%).

3.2 Tolerability to the Initial Test Dose of MPH

Less than 2% of the children had a clinically reported adverse event in the 4 hours after the first MPH dose while the patients were under direct medical observation at the clinic (Table 2). The most common adverse events were headache (1.9%), irritability (1.3%), and tics (1.3%). No reported adverse event was deemed a reason for not continuing MPH treatment. One child who received an initial dose of MPH 10 mg presented with sustained tachycardia (>130 bpm) 3 hours after administration, without any accompanying subjective complaints, or clinically observable symptoms, and with return to normal HR values after 4 hours. MPH treatment was discontinued. A few weeks later, the child was tested with a 5-mg dose and monitored for 3 h without presenting tachycardia. He continued treatment with this lower dose without any adverse events. No cases of persistent tachycardia or hypertension were observed.

HR, sBP, and dBP recordings at baseline, 1 h, 2 h, and 3 h after the first MPH administration are reported in Table 3. As expected, age was negatively correlated with HR (at baseline, $r = -0.36$; $p < 0.001$), and positively correlated with sBP ($r = 0.43$; $p < 0.001$) and dBP ($r = 0.23$; $p < 0.001$). There was a statistically significant time effect on HR ($F = 22.4$; $p < 0.001$, $\eta_p^2 = 0.045$). Pairwise comparisons showed that baseline HR was significantly lower that HR at T_1 (mean difference −2.7; $p < 0.001$), T_2 (mean difference −3.9; $p < 0.001$), and T_3 (mean difference −2.7;

Table 1 Demographics and clinical characteristics

	$N = 480$
Male sex (*N*, %)	434 (90.4)
Age, years, mean (SD)	10.6 (3.0)
ADHD (*N*, %)	
Hyperactive/combined	444 (92.5)
Inattentive	36 (7.5)
ODD/CD (*N*, %)	120 (25.0)
Mood disorder (*N*, %)	61 (12.7)
Anxiety disorder (*N*, %)	42 (8.7)
ASD (*N*, %)	31 (6.5)
Intellectual disability (*N*, %)	37 (7.7)
Tic disorder (*N*, %)	17 (3.5)

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *ODD/CD* oppositional defiant disorder/conduct disorder

Table 2 Clinically reported adverse effects during the first 4 h and after 1 week of methylphenidate treatment (sample $N = 480$)

Adverse effect, *n* (%)	After 4 h	After 1 week
Irritability	6 (1.3)	68 (14.2)
Reduced appetite	0	98 (20.0)
Headache	9 (1.9)	51 (10.6)
Sleep problems	0	45 (9.4)
Gastrointestinal symptoms	3 (0.6)	37 (7.7)
Anxiety symptoms	1 (0.2)	27 (5.6)
Tics	6 (1.3)	24 (5.0)
Tachycardia (> 130 bpm)	1 (0.2)	0
Hyperphagia	0	15 (3.1)
Enuresis	0	14 (2.9)
Obsessive-compulsive disorder symptoms	0	13 (2.7)
Mood symptoms	0	15 (3.1)
Fatigue	0	12 (2.5)
Hallucinations	0	1 (0.2)
Hyperfocus	0	9 (1.9)
Behavioral worsening ('rebound')[a]	0	16 (3.3)

[a]Worsening of behavioral symptoms about 5 h after the last methylphenidate dose

Table 3 Resting heart rate, and diastolic and systolic blood pressure at baseline and during the first 3 h after methylphenidate (MPH) administration

	Min	Max	Mean	SD
HR (bpm)***				
T_0	49	149	79.6	14.2
T_1	49	126	82.3	14.2
T_2	50	140	83.5	15.1
T_3	51	141	82.3	15.2
sBP (mmHg)				
T_0	60	171	109.3	13.6
T_1	40	204	110.3	14.0
T_2	75	144	110.1	12.1
T_3	71	154	110.0	11.9
dBP (mmHg)***				
T_0	38	99	66.2	9.2
T_1	40	109	66.7	9.3
T_2	43	110	68.1	9.3
T_3	46	89	68.0	8.0

T_0: at baseline, just before the MPH first dose; T_1, T_2, T_3: 1, 2, and 3 h, respectively, after the MPH dose

$N = 467$ for HR and dBP, and $N = 464$ for sBP

dBP diastolic blood pressure, *HR* heart rate, *Max* maximum, *Min* minimum, *sBP* systolic blood pressure, *SD* standard deviation

***Statistically significant increase in HR and dBP (time effect $p < 0.001$)

$p < 0.001$). There was also a statistically significant time effect on dBP ($F = 9.1$; $p < 0.001$, $\eta_p^2 = 0.019$). Pairwise comparisons showed that baseline dBP was significantly lower that HR at T_2 (mean difference −19.9; $p = 0.001$), and T_3 (mean difference −1.8; $p < 0.001$). Also, dBP at T_1 were significantly lower than dBP at T_2 (mean difference −1.4; $p = 0.013$) and T_3 (mean difference −1.3; $p = 0.016$). No statistically significant time effect on sBP was found ($F = 0.95$; $p = 0.411$, $\eta_p^2 = 0.002$).

During the first 3 h after the first dose, after excluding those with missing data (13 for HR and dBP, and 16 for sBP), 42 children (9.0%) presented an increase in HR >20% from the baseline; 41 (8.8%) had an increase in dBP >20%, and 21 (4.5%) had an increase in sBP >20%. Three patients (0.6%) presented an increase >20% in both dBP and sBP, eight patients in both HR and sBP, and five patients in both HR and dBP.

3.3 Tolerability During the First Week of Treatment

Eleven patients (2.3%, 95% CI 1.1–4.1) interrupted MPH treatment within the first week due to adverse events: three for irritability, three for worsening tics, one for reduced appetite, one for enuresis, one for transient auditory hallucinations, one for being hyperfocused, and one for marked behavioral worsening at the end of the MPH pharmacological effect ('rebound').

During the first week of treatment, the most reported adverse events were reduced appetite (20.0%), irritability (14.2%), headache (10.6%), sleep problems (9.4%), and gastrointestinal symptoms (7.7%) (Table 2). In 5% of the children there was onset or worsening of tics.

Children who presented irritability ($n = 68$, 14.2%) were on average younger than those without irritability (9.5 years ± SD 2.6 vs 12.6 years ± SD 3.0, $F = 10.8$; $p = 0.001$), and had a higher rate of comorbid ID (17.6% vs 6.1%, $\chi^2(2) = 11.0$; $p = 0.001$).

Multivariate logistic analyses indicated that occurrence of any adverse event during the first week of treatment was predicted by ID ($B = 0.828$, S.E. = 0.368, Wald = 5.068, $p = 0.024$, Exp (B) = 2.289), but not by any of the other tested variables (age, sex, dose, ASD, or ODD/CD). Reduced appetite was predicted by ODD/CD ($B = 0.538$, S.E. = 0.250, Wald = 4.635, $p = 0.031$, Exp (B) = 1.712); irritability by ID ($B = 1.104$, S.E. = 0.396 Wald = 7.764, $p = 0.005$, Exp (B) = 3.016) and higher MPH dose ($B = 0.760$, S.E. = 0.310, Wald = 6.016, $p = 0.014$, Exp (B) = 2.138); and sleep disturbance by ID ($B = 1.139$, S.E. = 0.447, Wald = 6.487, $p = 0.011$, Exp (B) = 3.125) and ODD/CD ($B = 0.786$, S.E. = 0.339, Wald = 5.367, $p = 0.024$, Exp (B) = 2.195).

After 1 week of treatment, 86 (18.4%) of the children presented an increase of 20% or more in HR over the pre-treatment baseline; 61 (13.4%) presented a similar increase in sBP and 51 (11.2%) in dBP. In particular, 25.2% of the children with 20% or more HR elevation after the first dose ($n = 42$), still had >20% elevated HR after a week.

4 Discussion

This study assessed the acute tolerability of MPH in stimulant-naïve children who received the first test dose of MPH as part of the required procedures for pharmacological treatment of ADHD in Italy. The large sample size and the inclusion of consecutively treated children who were referred for clinical rather than research purposes allow the incidence of intolerable adverse events to be estimated with adequate statistical precision in a clinically representative sample. Considering the observed incidence of 2.3% and 95% CI, it can be inferred that intolerance to MPH (i.e., discontinuation due to an adverse event within a week of starting treatment) occurs in between 1.2 and 4.1% of children first exposed to MPH. This rate is consistent with the 1.4% reported in the MTA study [6].

The adverse events that were reported, including those leading to MPH discontinuation, were generally part of the known safety profile of stimulant medications. After the first dose, 1.9% of the children developed headache, 1.3% presented with irritability and 1.3% with tics. Thus, the occurrence of any clinically important adverse event in the first week after starting MPH treatment can be considered infrequent and, in most cases, not a reason for discontinuation. The data confirm that psychotic symptoms (hallucinations), which were reported in one patient (0.2%), are rare and transient in MPH treatment [2, 14]. It can also be estimated that about 5% of children will present with onset or worsening of existing tics upon initial exposure to MPH, but, in most cases, this does not cause treatment discontinuation. This finding is consistent with existing literature on tics and stimulant medications [15]. A small number of children (14 or 2.9%) reported enuresis, which is not an adverse event typically associated with stimulant treatment, even though it has been anecdotally reported [16, 17].

The rates of common adverse events such as decreased appetite, sleep disturbance, headache, or stomachache were lower than reported in randomized placebo-controlled trials [4]. For example, based on a meta-analysis of 62 clinical trials, insomnia occurred in 42.1–53.3% of children randomized to MPH, as compared with 23.9–37.5% of those on placebo, and stomachache incidence was 19.0–28.9% on MPH versus 8.7–21.1% on placebo [4]. The discrepancy with the rates found in our study can be accounted for by the systematic elicitation of adverse events in controlled clinical

trials, which yields high rates of mild symptoms that are not necessarily clinically significant or due to the medication, as shown by the high rate of adverse events on placebo (a possible 'nocebo' effect). In fact, in the same meta-analysis, the rates of 'serious' adverse events (e.g., 10.9% for insomnia and 5.2% for stomachache) was close to those found in our database (i.e., 9.4% for sleep problems and 7.7% for gastrointestinal symptoms). Another possible contributor to the lower rate of adverse events in this study is the low doses of MPH administered in the initial week of treatment, while in clinical trials, dosage is usually increased more rapidly to reach full therapeutic levels. In fact, MPH-induced adverse events are typically dose-dependent, as also shown by the higher rate of irritability on 10 mg as compared with 5 mg in our study.

Presence of ID, but not ASD per se, was a risk factor for presenting with any adverse event and, in particular, with irritability. These findings are consistent with the higher rate of treatment-emergent irritability observed in a randomized trial of MPH in a sample of children with ASD and mean IQ of 62.6 [7]. Our data suggest that it is ID, as an index of severe neurodevelopmental disorder, and not ASD that is linked with a lower tolerability to MPH [18, 19].

No cardiovascular symptoms, such as palpitations or dizziness, were clinically reported in this sample. However, routine assessments of vital signs during the first 3 hours of treatment and 1 week later revealed an increase in HR, sBP, and dBP (Table 3). These data confirm that MPH treatment is in general associated with small, although statistically significant, increases in HR, sBP, and dBP, although without clinical implications in most cases [1, 20–22]. In reviewing available data, Hammerness et al. found that MPH treatment was associated with mean elevations of 5 mmHg in blood pressure and 10 bpm in HR [23]. A more recent review reported that MPH was linked with elevation in sBP only, but not in dBP or HR [24]. In our study, by selecting a priori a 20% or greater increase over the pre-treatment baseline, we attempted to estimate the incidence of more evident effects on cardiovascular function. We found that about one in ten children had a 20% or greater increase in HR, sBP, or dBP in the 3 h following the initial dose, and that about one in five had a similar increase after 1 week of treatment. These data indicate a lack of tolerance to the cardiovascular effects of MPH, at least in the short-term, and are consistent with the conclusions of previous reports [1, 16]. One patient (0.2%) had sustained tachycardia, without subjectively reported palpitations, in the first 3 hours after first MPH dosing with 10 mg. The tachycardia later resolved, and the child was rechallenged with a 5-mg dose on a subsequent day without emergence of tachycardia. It should be noted that all children in this sample had documented normal ECG prior to treatment. This case indicates that clinically significant, although asymptomatic, elevation in cardiovascular parameters, though rare and transient, can occur upon starting stimulant medication. The importance of monitoring HR and blood pressure during early phases of MPH treatment is reaffirmed by these data.

The study has several limitations that should be considered in interpreting the results. The data were collected as part of the clinical management of children with ADHD in Italy, rather than for research purposes. Assessment of adverse events relied on clinical observation and reports from patients and parents rather than on a structured and systematic inquiry of possible health. The cardiovascular measurements were done by nurses or physicians using standard equipment but without following research procedures (e.g., there was no averaging of three consecutive readings of HR and blood pressure). MPH was administered in an immediate-release formulation (as required by the Italian register regulations), while extended-release preparations are more commonly used in chronic treatment, and the formulation of stimulant medication can have implications for adverse events [25]. The dose of MPH (5 mg or 10 mg) can be considered a starting dose, to be then gradually adjusted based on clinical needs. As adverse effects to stimulants are dose-related, it is possible that a greater rate of adverse events would have emerged with higher doses. Furthermore, the period of observation was limited to the initial few weeks of treatment. Finally, the generalizability of the results is limited because this was not a population-based study, and the data came from only two clinics. These limitations must be considered in the light of the strengths of the study, including the clinically representative sample of children with ADHD and typical comorbidity, the large sample size, and the direct medical observation for several hours after the first dose. In addition, the fact that all children were drug-naïve at intake prevented the exclusion of participants with previous intolerable adverse events, which constitutes a common selection bias in clinical trial samples.

5 Conclusions

The results from this study indicate that intolerance to acute administration of starting doses of MPH is infrequent and can be estimated to be between 1.2 and 4.1% within 1 week of treatment. The results confirm the safety profile of MPH with irritability, headache, reduction in appetite, and sleep problems being the most common adverse events, reported in >10% of the sample. The study also further documents the cardiovascular stimulating effects of MPH, which warrant monitoring of HR and blood pressure during the medication management follow-up visits.

Declarations

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Conflicts of interest/Competing interests In the last 2 years, GM was a member of advisory boards for Angelini Pharmaceuticals, received institutional grants from Lundbeck and Humana, and was a speaker for Angelini, FB Health, Janssen, Lundbeck, and Otsuka. BV has received consultant fees or honoraria from Medice, Lundbeck, and Angelini Pharmaceuticals, and from law firms Goodwin & Procter and Haynes & Boone. The other authors report no biomedical financial interests or potential conflicts of interest.

Consent to participate All the parents signed written informed consent for their child to receive the assessment procedure, the first-dose test, and the subsequent pharmacological treatment, according to the standard operative procedure defined by the Italian Ministry of Health. The protocol (Italian ADHD National Registry) has been approved by the Italian Ministry of Health.

Consent to publication Not applicable.

Code availability Not applicable.

Author contributions Conceptualization: GM and BV; design and methods: GM, CP and BV; data collection: FL, FL, AV, GD, PF, and IF; data management: FF, VS, PM, and VL; manuscript preparation: GM and BV; review and editing: CP, FL, FL, AV, GD, PF, FF, VS, PM, VL, IF, FA, and CD. All authors approved the published version of the manuscript and agreed to be accountable for the work outlined in the manuscript.

Availability of data and material (data transparency) Study data are available from the authors upon reasonable request.

Ethics The protocol (Italian ADHD registry) has been completed and approved by the Italian Ministry of Health. Anonymized data from registry, with parental consent to inclusion.

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The pediatric psychopharmacology of autism spectrum disorder: A systematic review - Part I: The past and the present

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Abbreviations: Outcome measures: ABC, Aberrant Behavior Checklist; ABC-CV, Aberrant Behavior Checklist-Community Version; ABC-I, Aberrant Behavior Checklist-Irritability subscale; ACTeRS, ADD-H Comprehensive Teacher Rating Scale; ADHD-RS, ADHD–Rating Scale; ADHDRS-IV, ADHD Rating Scale IV; ARS, Aggression Rating Scale; ABDP, Alpern-Boll Developmental Profile; ASFQ, Antipsychotics and Sexual Functioning Questionnaire; ASDS, Asperger Syndrome Diagnostic Scale; ADOS, Autism Diagnostic Observation Schedule; ASIEP-2, Autism Screening Instrument for Educational Planning, 2nd ed.; ATEC, Autism Treatment Evaluation Checklist; BPI, Behavior Problems Inventory; BSE, Behavioral Summarized Evaluation; BPRS, Brief Psychiatric Rating Scale; BAS, Brown Aggression Scale; B-FCRS, Bush-Francis Catatonia Rating Scale; CCI, Caregiver-Child Interaction; CGSQ, Caregiver Strain Questionnaire; CIIS, Cattell Infant Intelligence Scale; CASI, Child and Adolescent Symptom Inventory; CDRS, Child Depression Rating Scale; CARS, Childhood Autism Rating Scale; CBI, Children's Behavior Inventory; CSBQ, Children's Social Behavior Questionnaire; CDI, Children's Depression Inventory; CGAS, Children's Global Assessment Scale; CPRS, Children's Psychiatric Rating Scale; CSHQ, Children Sleep Habits Questionnaire; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; CYBOCS-ASD, Children's Yale-Brown Obsessive-Compulsive Scale-Modified for ASD; CYBOCS-PDD, Children's Yale-Brown Obsessive Compulsive Scale-Modified for Pervasive Developmental Disorders; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression - Severity; CGI-E, Clinical Global Improvement-Efficacy Index; CADHD-IS, Conners' Attention-Deficit Hyperactivity Disorder Index Scale; CCPT, Conners' Continuous Performance Test; CPT, Continuous Performance Test; CGI-P, Conners' Global Index for Parents; CPRS-R, Conners' Parent Rating Scale Revised; PTQ, Conners' Parent-Teacher Questionnaire; CRSR, Conners' Rating Scale Revised; CTRS-R, Conners' Teacher Rating Scale Revised; CTS, Conners' Teacher Scale; EIDP-L, Early Intervention Developmental Profile - long; DOTES, Dosage Record and Treatment Emergent Symptoms; DISCUS, Dyskinesia Identification System: Condensed User Scale; EPEC, Evaluation and Prescription for Exceptional Children; FFQ, Food Frequency Questionnaire; GAF, Global Assessment of Functioning; GAS, Global Assessment Scale; GCJS, Global Clinical Judgments Scale; HSQ, Home Situations Questionnaire; SSQ, School Situations Questionnaire; HSQ-ASD, Home Situations Questionnaire adapted for ASD; HCBS, Hopkins Child Behavioral Score; HADS, Hospital Anxiety and Depression Scale; HALP, Hyperactivity, Attention, Learning Problems; JAMES, Joint Attention Measure from the ESCs; LIPT, Leiter International Performance Test; LPR, Leiter Parent Report; M-P PSPT, Merrill-Palmer Pre-School Performance Test; MRRS, 10-item Modified Roger's rating scale; MADRS, Montgomery-Asberg Depression Rating Scale; NCBRF, Nisonger Child Behavior Rating Form; NRS, Numerical Rating Scale; NGI, Nurses Global Impressions; OA-S, Overt Aggression Scale; PSI, Parenting Stress Index; PSI-SF, Parenting Stress Index-Short Form; PTP, Parent Target Problem; PedsQL, Pediatric Quality of Life Inventory; PNSS, the Positive and Negative Syndrome Scale; PONS, Profile of Neuropsychiatric Symptoms; RBS-R, Repetitive Behavior Scale-Revised; RF-RLRS, Ritvo-Freeman Real Life Rating Scale; RAHMOF, Royal Alexandra Hospital for Children Measure of Function; RABRS, Rutter's Autistic Behavioral Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SHARP, Scale for Hostility and Aggression Reactive/Proactive; SQoLS, Schalock Quality of Life scale; SCARED, Screen for Child Anxiety Related Emotional Disorders; SIBQ, Self-Injurious Behavior Questionnaire; SIT, Self-Injurious Trauma Scale; SMBC, Sensory Motor Behavior Checklist; SPQ, Sensory Profile Questionnaire; SPS, Sensory Profile Scale; SP-SAS, Skin Picking Symptom Assessment Scale; SAI, Social Awareness Inventory; SRS, Social Responsiveness Scale; SVATB, de Sonneville Visual Attention Task Battery; SCAS-P, Spence Children's Anxiety Scale Parent Report; SOAP, Standard Observation Analogue Procedure; SSOA-S, Suicidality Subscale of Overt Aggression Scale; SNAP-IV, Swanson, Nolan, and Pelham Questionnaire; TEI, Therapeutic Efficacy Index; TBRS, Timed Behavioral Rating Sheet; TSRS, Timed Stereotypies Rating Scale; TESS, Treatment Emergent Symptom Scale-Write In; TPDDRS, Turgay DSM-IV Pervasive Developmental Disorder Rating Scale; VABS, Vineland Adaptive Behavior Scales; VMBD, Vineland Maladaptive Behavior Domain; VSMS, Vineland Social Maturity Scale; VAS, Visual Analog Scale; WSRS, Ward Symptom Rating Scale; WWPAS, Werry-Weiss-Peters Activity Scale; YGTSS, Yale Global Tic Severity Scale; YAPA-SIBS, Yale-Paris self-injurious behaviors scale.; *Drugs*: AGO, agomelatine; AMA, amantadine; ARI, aripiprazole; BRO, bromocriptine; CIT, citalopram; CLON, Clonidine; DES, desipramine; DEX, dexamphetamine; DUL, duloxetine; ER, extended release; FEN, fenfluramine; FLU, fluphenazine; FLUO, fluoxetine; FLUV, fluvoxamine; HALO, haloperidol; IR, immediate release; Li, lithium; LOR, lorazepam; MPH, methylphenidate; NAL, naltrexone; OX, oxcarbazepine; PAR, paroxetine; PLA, placebo; QUE, quetiapine; RIS, risperidone; SER, sertraline; ZIP, Ziprasidone; *Disorders*: ASD, Autism Spectrum Disorder; BPD, bipolar disorder; HF-ASD, high-functioning Autism Spectrum Disorder; ID, intellectual disability; LF-ASD, low-functioning Autism Spectrum Disorder; OCD, obsessive-compulsive disorder; PDD NOS, pervasive developmental disorder not otherwise specified; TS, Tourette syndrome; *Other abbreviations*: 5-HTTLPR, serotonin transporter gene promoter region polymorphism; BP, blood pressure; CBT, cognitive behavioral therapy; ECG, electrocardiogram; EEG, electroencephalogram; EPS, extrapyramidal symptoms; HR, heart rate; N.A., full text not available (complete information could not be retrieved); PET, Positron Emission Tomography; PT, parent training; RUPPAN, Research Units on Pediatric Psychopharmacology Autism Network; SLC6A4, Serotonin transporter gene..

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ABSTRACT

Autism Spectrum Disorder (ASD) is a severe and lifelong neurodevelopmental disorder, with high social costs and a dramatic burden on the quality of life of patients and family members. Despite its high prevalence, reaching 1/54 children and 1/45 adults in the United States, no pharmacological treatment is still directed to core symptoms of ASD, encompassing social and communication deficits, repetitive behaviors, restricted interests, and abnormal sensory processing. The purpose of this review is to provide an overview of the state-of-the-art of psychopharmacological therapy available today for ASD in children and adolescents, in order to foster best practices and to organize new strategies for future research. To date, atypical antipsychotics such as risperidone and aripiprazole represent the first line of intervention for hyperactivity, impulsivity, agitation, temper outbursts or aggression towards self or others. Tricyclic antidepressants are less prescribed because of uncertain efficacy and important side effects. SSRIs, especially fluoxetine and sertraline, may be effective in treating repetitive behaviors (anxiety and obsessive-compulsive symptoms) and irritability/agitation, while mirtazapine is more helpful with sleep problems. Low doses of buspirone have shown some efficacy on restrictive and repetitive behaviors in combination with behavioral interventions. Stimulants, and to a lesser extent atomoxetine, are effective in reducing hyperactivity, inattention and impulsivity also in comorbid ASD-ADHD, although with somewhat lower efficacy and greater incidence of side effects compared to idiopathic ADHD. Clonidine and guanfacine display some efficacy on hyperactivity and stereotypic behaviors. For several other drugs, case reports and open-label studies suggest possible efficacy, but no randomized controlled trial has yet been performed. Research in the pediatric psychopharmacology of ASD is still faced with at least two major hurdles: (a) Great interindividual variability in clinical response and side effect sensitivity is observed in the ASD population. This low level of predictability would benefit from symptom-specific treatment algorithms and from biomarkers to support drug choice; (b) To this date, no psychoactive drug appears to directly ameliorate core autism symptoms, although some indirect improvement has been reported with several drugs, once the comorbid target symptom is abated.

1. Introduction

Autism spectrum disorders (ASD) is a severe neurodevelopmental disorder characterized by social and communication deficits, repetitive and stereotyped behaviors, restricted interests, and abnormal sensory processing (American Psychiatric Association, 2013). This disorder currently represents a significant public health problem due to its high prevalence, recently up to 1/54 children and 1/45 adults in the United States (Dietz et al., 2020; Maenner et al., 2020) and to 1/87 children in Italy and 1/102 adults in England (Brugha et al., 2011; Narzisi et al., 2018). Its onset in early childhood, lifelong persistence and need of support due to marked disability pose a huge emotional and economic burden on families and on society (Peacock et al., 2012; Valicenti-McDermott et al., 2015; Rogge and Janssen, 2019). Many genetic and environmental contributors to the pathogenesis of ASD have been identified, resulting in great interindividual variability also at the clinical level (Persico et al., 2020). As yet, currently available pharmacological treatment in autism is not primarily directed to the core symptoms, but rather to comorbid disorders/symptoms and to problematic behaviors, such as irritability, hyperactivity, anxiety, aggression, self-injurious behavior, sleep disorders and others (Jobski et al., 2017). Until the 1990s, classical neuroleptics and tricyclic antidepressants were the two main pharmacological options available to reduce behavioral symptoms, with the later adjunct of naltrexone (Rosenbaum et al., 2005; Erickson et al., 2007). During the last two decades, these compounds have generally become second-line treatments, as several new classes of psychoactive drugs have been shown to ameliorate maladaptive behaviors. First-line treatments include atypical antipsychotics and psychostimulants, which hold the highest rates of prescription in Western Europe and North America due to their better perceived profile of efficacy and tolerability (Bachmann et al., 2013; Hollander and Anagnostou, 2007; Hsia et al., 2014; Politte and McDougle, 2014). Several other drugs have been found to ameliorate specific symptoms and to improve the management of ASD as part of a multimodal intervention, including behavioral, educational and pharmacological treatments (Doyle and Mc Dougle, 2012; Weitlauf et al., 2014). In the past, pharmacological therapies were viewed as often negatively interfering with behavioral interventions and quality of life, due to their side effects. Within this modern framework, pharmacological therapies, though still relatively unspecific, aim to allow autistic children and adolescents to maximize their benefits from behavioral and psychoeducational interventions, by removing the problematic behaviors which negatively interfere with non-pharmacological therapies and social adjustment (Arnold et al., 2003).

Clinicians prescribing psychoactive drugs to children and adolescents with ASD encounter multiple difficulties (Persico et al., 2015). Two of these difficulties are at the root of the present work: (a) The great interindividual variability present in ASD also spans clinical response to psychoactive drugs and side effect sensitivity. Clinicians experience a lower level of predictability when prescribing a drug to children with ASD, compared to children with other idiopathic neurodevelopmental disorders (ADHD, OCD, anxiety disorders, affective disorders, etc). Symptom-specific treatment algorithms providing strategic indications could be helpful to clinicians, while research strives to discover biomarkers able to support drug choice; (b) To this date, no psychoactive drug appears to directly ameliorate core autism symptoms, although partial and indirect improvements in social functioning have been observed with several drugs, once the comorbid target symptoms are abated. This is an active area of investigation and several compounds are currently under trial to verify their efficacy on the core symptoms of ASD in children and adolescents.

The present contribution is a systematic review, describing the past and current state of the pharmacotherapy of idiopathic ASD. It represents the overarching foundation of two follow-up contributions, defining clinically useful algorithms for pharmacological intervention in ASD using currently available psychoactive drugs, and describing

current and future directions of psychopharmacological research in the ASD field.

2. Methods

2.1. Research strategy

A systematic review of the literature was performed initially via the PubMed interface, and subsequently completed with EBSCO, PsycINFO (psychology and psychiatry literature) and the Cochrane Database of Systematic reviews, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (last PRISMA guidelines update: November 30, 2018) (Moher et al., 2015). Databases were searched for articles that discussed psychoactive drugs employed in ASD, using the following string:

[autism OR autistic OR pervasive OR Asperger] AND [the specific name of each psychotropic agent]

This string was defined after verifying that it was able to detect all of the articles retrieved by single searches regarding "autism", "autism spectrum disorder", "autistic disorder", "pervasive developmental disorder", "Asperger disorder" and "Asperger syndrome". All psychotropic drugs present in each class, as listed in the Stahl textbook (2013) with the addition of a few compounds more commonly used in Europe, were searched. General classes of psychotropic drugs ("antidepressants", "antipsychotics", etc) were not used as search items, because they proved to be too non-specific. Classes, drugs and number of records retrieved in PubMed for each drug are listed by study design in Suppl. Table S1. The complete list of all records retrieve from PubMed is provided in Suppl. Table S2. Database searches were updated until February 13-March 3, 2021, depending on each drug as detailed in Suppl. Table S2. Additional studies were identified from reference lists of relevant reviews.

2.2. Study selection

Articles were included in our review according to the following criteria: (a) English, French, Italian, or Spanish languages; (b) publication in peer reviewed journals; (c) articles dealing only with the human pharmacotherapy of idiopathic ASD; (d) studies partly or exclusively involving participants aged <18 y.o. and diagnosed with ASD using either a standardized diagnostic instrument or established diagnostic criteria, and (e) article format, focusing on randomized double-blind placebo-controlled trials (RCT). Also open-label (OL) "prospective" observational studies and "retrospective" chart reviews and cross-sectional studies, as well as case reports (CR), were retrieved and are being provided as Supplementary Material. Specific exclusion criteria encompass: (a) all articles not providing clearly the number of pediatric cases and/or the number of autistic patients recruited, (b) reviews and commentaries, which were merely used to verify and integrate, if necessary, the results of database searches, (c) clinical case discussions, (d) methodological studies not reporting outcome data, (e) articles regarding syndromic forms, ASD secondary to epilepsy or the treatment of epilepsy in autistic patients, drugs for single-time use administered for sedation in dental procedures or surgical operations, and as part of pediatric emergency treatment protocols, (f) surveys or registry data analyses of drug prescription in geographical areas or ethnic groups, (g) pharmacogenomics studies. All retrieved RCTs and follow-up articles are listed in Tables 1-4, whereas prospective/retrospective OL studies and CRs are listed in Suppl. Tables S3-S10.

2.3. Data extraction and quality assessment

For each section of this systematic review, data were independently extracted by 2 authors according to the Cochrane guidelines. A third author then performed quality control on all data extracted from each article, including: (a) experimental design, (b) study duration, (c) sample size, (d) age range (yr), (e) mean dose and range, (f) outcome measures, (g) therapeutic effects, (h) side effects. Whenever study duration was not specified, it is missing in Suppl. Tables S3-S10.

3. Results

3.1. Tricyclic antidepressants

Tricyclic Antidepressants (TCAs), together with First Generation Antipsychotics, represent the two main classes of drugs used to control behavioral problems in Autism Spectrum Disorder and co-morbid intellectual disability until the introduction of more tolerable psychoactive compounds in the early/mid-Nineties. The two 5-HT/NE re-uptake blockers most studied in ASD since 1966 are nortryptiline and clomipramine (Table 1 and Suppl. Table S3). Gordon et al. (1992, 1993) performed two double-blind studies comparing **clomipramine**, **desipramine** and placebo. These two TCAs were chosen, because the former exerts 5-HT>NE reuptake blockade, whereas the latter has the reverse pharmacodynamics, blocking NE>5-HT reuptake. Clomipramine was superior both to placebo and desipramine in improving autistic symptoms, anger, and repetitive behaviors in 57% of the autistic subjects (Gordon et al., 1992; Gordon et al., 1993). On the contrary, Remington et al. (2001) compared the efficacy of clomipramine to haloperidol and placebo in 31 subjects with ASD (10-36 years) and found no significant difference between clomipramine and placebo in stereotypy, irritability or hyperactivity measured using the total scores of the Aberrant Behavior Checklist (ABC). Moreover, the trial was completed by significantly fewer patients taking clomipramine (12/32=37.5%), compared with haloperidol (23/33= 69.7%) and placebo (21/32= 65.6%), due to more frequent side effects, behavioral activation or lack of efficacy (Table 1). Clomipramine frequently causes anticholinergic side effects (dry mouth, dizziness and constipation) and heart rate changes; it lowers seizure threshold, imposing caution in prescribing this drug to patients with epilepsy or gross EEG abnormalities. Nonetheless, some ASD patients may benefit from clomipramine, which is generally safe and well-tolerated in the absence of cardiological abnormalities and/or seizures. For this reason, clomipramine has maintained to this date a second-choice indication especially for repetitive behaviors in ASD and for co-morbid obsessive-compulsive disorder (OCD), especially in adolescents and young adults. No RCT has been published providing evidence of efficacy for the serotoninergic and noradrenergic TCAs **nortriptyline** and **imipramine.** Some OL and CR studies suggest that, after the first few days of therapy, children may frequently become hyperactive and agitated (Kurtis, 1966; Campbell et al., 1971) (Suppl. Table S3). Instead the noradrenergic TCA **desipramine** has shown some efficacy, but only on hyperactivity (Gordon et al., 1992; Gordon et al., 1993) (Table 1).

3.2. First Generation Antipsychotics

First Generation Antipsychotics (FGAs), also named typical antipsychotics, represent the class of psychopharmacological agents most widely prescribed to autistic patients over three decades until the 1990s in the Western world (Rosenbaum et al., 2005) and haloperidol is still the drug most prescribed to autistic individuals in Japan (Hsia et al., 2014). Since the 1970s, several RCTs have been published addressing the efficacy of haloperidol in children and adolescents with autism (Table 1). A small number of OL and CR studies also addressed the efficacy and/or reported the adverse reactions of other FGAs, like loxapine and pimozide (Suppl. Table S4). FGAs were found most effective on aggressiveness, temper outbursts, hyperactivity, stereotypic behaviors, sensory self-stimulation, and social withdrawal. The dark side of FGAs is represented by their potential for adverse effects, ranging from dry mouth and sedation, to neuroleptic malignant syndrome or tardive dyskinesia. Autistic children may be especially sensitive to acute and chronic extrapyramidal side effects (EPS), namely akathisia, acute

Table 1
The "past" pharmacology of ASD: randomized placebo-controlled trials (RCT) of tricyclic antidepressants, first-generation neuroleptics and opioid receptor antagonists, with related follow-up open label (OL) extensions and secondary analyses in the pediatric ASD population.

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
Tricyclic Antidepressants								
Desipramine	Gordon et al. (1992 and 1993)	RCT, 10-wk CLO vs DES after a 2-wk single-blind, placebo phase	24	6-23	25-250 mg/d	CGI, CPRS, 3 modified versions of OCD and anxiety scales	CLO>DES= placebo on autistic symptoms (including stereotypies), anger, and compulsive ritualized behaviors. CLO=DES> placebo in improving hyperactivity.	CLO: mild insomnia, constipation, sedation, twitching, tremor, flushing, dry mouth, decreased appetite. QTc prolongation (1), severe tachycardia (1), grand mal seizure (1). DES: tremor, dry mouth constipation. Severe irritability, temper outbursts, and uncharacteristic aggression in 8/12 (66.%), including two cases who required discontinuation.
Clomipramine	Remington et al. (2001)	RCT, 7 wks CLO vs HALO vs placebo	35	10-36	CLO: 100-150 mg/d HALO: 1–1.5 mg/d	ABC, CARS	HALO> CLO = placebo in improving autistic symptom severity, irritability and hyperactivity. HALO = CLO > placebo on stereotypy.	CLO: fatigue, lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, decreased appetite. HALO: fatigue, lethargy, dystonia, depression. Significantly fewer patients taking CLO completed the trial (12/32=37.5%), compared with HALO (23/33=69.7%) and placebo (21/32= 65.6%).
First Generation Antipsychotics								
Haloperidol	Campbell et al. (1978)	RCT, HALO vs PLA ±behavior therapy.	40	2.6-7.2	0.5-4.0 mg/d	CPRS, CBI, CGI, NGI, DOTES, NIMH rating scales	HALO alone: decreased stereotypic behaviors and improved social withdrawal. No change in abnormal object relations, hyperactivity, hypoactivity, angry affect and speech development. HALO+behavior therapy: imitative speech acquisition.	Transient dose-dependent sedation (12), insomnia (3), excitement/agitation (4), acute dystonia (2).
	Cohen et al. (1980a, 1980b)	RCT, 11 wks	10	2.1-7.0	0.5-4.0 mg/d	VAS	Decreased stereotypies, increased attending to the rater ("Look at me").	Excessive sedation (8), irritability (3), hypoactivity (2), acute dystonia (1).
	Campbell et al. (1982)	RCT, crossover, 14 wks	33	2.3-7.9	0.5-4.0 mg/d	Discrimination task, CRPS, CGI, PTQ, TBRS	Improved discrimination learning. Reduced hyperactivity, agitation, irritability, stereotypies, social withdrawal.	Excessive sedation, irritability, acute dystonia (9).
	Anderson et al. (1984)	RCT crossover, 12 wks	40	2.3-6.9	0.5-3.0 mg/d	CPRS, CGI-I, Conners PTQ	Improved withdrawal, stereotypies, hyperactivity, restlessness, anger, mood lability. Increased discrimination learning.	None
	Perry et al. (1989a)	RCT, continuous vs discontinuous administration	60	2.3-7.9	0.5-4.0 mg/d 6 mo (5 d/wk on HALO and 2 d/wk off vs 7 d/wk HALO) + 4 wks PLA	CPRS, CGI-I, TSRS.	Efficacy over irritability, anger, labile affect, and uncooperativeness. No difference in efficacy and side effects between continuous vs discontinuous administration.	Dyskinesia during treatment (3) or following drug withdrawal (9).
	Anderson et al. (1989)	RCT crossover, 12 wks	45	2-7	0.25-4 mg/d	CPRS, CGI-I, Conners PTQ	Improved behavioral symptoms, but not discrimination learning.	None reported
Opioid receptor antagonist								
Naltrexone	Herman et al. (1987, 1989a)	RCT (drug blind) single dose	3 5	10-17 4-12	0.5, 1.0, 1.5, 2.0 mg/kg	Self-injury test HR, BP	Reduced self-injury at 0.5-1.5 mg/kg. No effect at 2.0 mg/kg/d	None reported. No significant effect of HR and BP
	Herman et al.		14	3-12		ECG, HR, BP, body temp., liver enzymes	Not reported	No significant effect

(*continued on next page*)

Table 1 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
	(1989b)							cardiovascular and biochemical parameters
	Herman et al. (1993)							
	Campbell et al. (1993)	RCT	41	2.9-7.8	0.5-1.0 mg/kg/day	CPRS, CGI, CGC, NGI, ARS	Reduced hyperactivity, trend on self-injurious behavior. No effect on discrimination learning.	Mild sedation, decreased appetite, vomiting
	Campbell et al. (1990)	Preliminary report	18					Non-significant weight loss
	Gonzalez et al. (1994)						No correlation between NAL plasma concentration and clinical response	
	Leboyer et al. (1992)	RCT crossover, 1-wk per dose + 1 wk placebo	4	4-19	0.5, 1.0, and 2.0 mg/kg	CGI, BSE, self-injury scale	Increased attention and social behavior (0.5 mg/kg); decreased hyperactivity (2.0 mg/kg); decreased self-injurious behavior.	None
	Kolmen et al. (1995)	RCT, 2 wks NAL vs 2 wks PLA	13	3.4-8.3	1.0 mg/kg/d	CGI, CPRS, TRF, EIDP-L, analysis of videotaped behavior	Decreased hyperactivity and restlessness. Responders: 8/13 (61.5%). Overall, modest though measurable benefits.	Drowsiness, increased aggressiveness. Difficult to administer a bitter tablet to small children.
	Kolmen et al. (1997)		24	3.0-8.3				
	Feldman et al. (1999)		24	3.0-8.3		Spoken language measures in videotapes	Modest improvement in hyperactivity and inattention, not in learning. Responders: 11/24 (45.8%)	Loss of appetite, drowsiness, runny nose
							No improvement in communication	
	Bouvard et al. (1995)	RCT, 1 mo	10	5-14	0.5 mg/kg/d	CPRS, BSE	Overall, non-significant improvement in hyperactivity, hostility, restraint. Great interindividual variability in response: 4/10 strong responders and 3-4 non responders.	None reported.
	Willemsen-Swinkels et al. (1995)	RCT, single dose	23	2.8-7.4	40 mg, single dose (1.48-2.35 mg/kg)	Playroom observation, actometers, ABC parents' checklist	Decreased irritability and hyperactivity, increased attention. No efficacy on social deficits and stereotypic behaviors.	None reported.
	Willemsen-Swinkels et al. (1996)	RCT, 4 wks	23	3-7	40 mg/d (0.74-1.18 mg/kg/d).	ABC, CGI and other checklists; playroom observation	Modest decrease in hyperactivity and irritability (teacher reports only). Responders: 7/23 (30.4%)	None. No effect on social behavior. Difficult to administer a bitter tablet to small children.
		OL ext, 6 mo	6					
	Willemsen-Swinkels et al. (1999)				20 mg/d (0.9-1.1 mg/kg/d)	ABC, PEP	Responders maintained reduction in hyperactivity over 6 months.	Drug discontinuation due to dehydration (1).
	Scifo et al. (1996)	RCT, 15 wks	12	7-15	0.5, 1.0, 1.5 mg/kg/d every 48 hrs	BSE, CARS	Increased attention, social motivation, decreased mood liability, stereotypies and self-injurious behavior at 0.5-1.0 mg/kg/d	Emotional and behavioral worsening at 1.5 mg/kg/d.
	Williams et al. (2001)	RCT crossover, NAL vs PLA (acetaminophen)	8	2-9	1.5 mg/kg every other day	CARS, GARS, VAS, PSI, CBCL	More social initiation, less stereotypies, improved attention.	High dropout rate (2/8=25%) due to the bitter taste of the medication.

dystonia, parkinsonism, and tardive dyskinesia. EPS can occur following single low doses of FGAs and following prolonged treatment. In an RCT involving 60 children treated with haloperidol, 9 (15%) developed withdrawal dyskinesias, while another 3 (5%) showed dyskinesias during treatment (Perry et al., 1989a). In an OL study (Campbell et al., 1997), 40 out of 118 (33.9%) children treated with haloperidol (mean dose 1.75 mg/day) developed withdrawal dyskinesias, at times resembling Tourette Syndrome (Perry et al., 1989a, 1989b; Littlejohns et al., 1990), in other cases with repetitive movements difficult to distinguish from the motor stereotypies typical of ASD (Meiselas et al., 1989; Campbell et al., 1997). Assessing stereotypic movements with appropriate scales or, even better, videorecording children just prior to starting neuroleptic drug treatment can aid clinicians in correctly diagnosing abnormal movements once the drug is tapered down (Meiselas et al., 1989). Tardive dyskinesia is also relatively more common after prolonged use, among autistic girls and in children with a history of pre- and perinatal complications (Armenteros et al., 1995; Campbell et al., 1997; Syamkumar and Dossetor, 2020). Despite these caveats, in most children the incidence and severity of adverse effects can be limited by prescribing a low initial dose, by increasing the dosage slowly and gradually over time and by limiting the duration of neuroleptic treatment (Serrano, 1981). The clinical efficacy of haloperidol and other FGAs, paired with their usually limited side effects and with the relative lack of safer alternatives at the time, ultimately explains their widespread use in the autism clinics until the 1990s (Rosenbaum et al., 2005).

The first RCT addressing the efficacy and safety of **haloperidol** in a pediatric population involved 40 children, aged 2-7 y.o., with autism diagnosed according to DSM-III criteria (Campbell et al., 1978). The active compound produced significant positive effects on global functioning and on multiple behavioral problems, measured using the Children's Psychiatric Rating scale (CPRS) and the Clinical Global Impression (CGI) scale, while improvement in learning and cognition was recorded in some (Campbell et al., 1982; Anderson et al., 1984), but not all studies (Anderson et al., 1989) (Table 1). The long-term efficacy of haloperidol over problem behaviors, irritability, and labile mood was demonstrated applying a one-month discontinuation protocol following 6 months of continued haloperidol administration to 60 autistic children, 2.3-7.9 y.o. (Perry et al., 1989a). Later RCTs contrasted haloperidol with other agents, like clomipramine (Remington et al., 2001), risperidone (Miral et al., 2008; Gencer et al., 2008), and olanzapine (Malone et al., 2001). Altogether, these studies support the greater efficacy of haloperidol over placebo and TCAs, while it appears somewhat less effective compared to newer antipsychotics (see par. 3.4) and produces more side effects, yielding higher discontinuation rates in some studies (Remington et al., 2001; Gencer et al., 2008).

Aside from haloperidol, only a very limited number of OL studies and CRs has provided descriptive and/or anecdoctal suggestions of possible efficacy for other FGAs (Suppl. Table S4). **Loxapine** is a medium potency, classic dibenzoxazepine antipsychotic drug developed in the 1970s to resemble clozapine, but devoid of risk of producing agranulocytosis. Three OL trials involving altogether 22 pediatric patients out of a total combined sample of 65 ASD individuals, described decreased irritability and problem behaviors after low dose loxapine (Hellings et al., 2015a, 2015b; Jain et al., 2016). Hence this drug has been proposed as an alternative to risperidone and aripiprazole, when contraindicated (Hellings et al., 2017), but its efficacy and safety in children and adolescents with ASD still await to be tested applying a rigorous RCT design. Few anecdoctal reports involve **pimozide, pericyazine, fluphenazine** and **sulpiride** (Suppl. Table S4). Other FGAs, like **trifluoperazine** and **thioridazine**, have been often prescribed in clinical practice (Sloman, 1991; Hsia et al., 2014), but no studies addressing efficacy and safety in autistic children and adolescents have been published. Single-dose **chlorpromazine** has been widely used for the acute treatment of psychomotor agitation in emergency settings (Kendrick et al., 2018).

3.3. Opioid receptor antagonists

Naltrexone is a μ opioid receptor antagonist initially prescribed to autistic patients under the hypothesis that an excessive opioid neurotransmission in ASD, especially during critical periods in neurodevelopment, would hamper social cognition (Panksepp, 1979; Panksepp et al., 1980). Functional studies have been inconsistent, outlining a much greater interindividual variability with autistic individuals displaying either high (Bouvard et al., 1995) or low plasma beta-endorphins (Willemsen-Swinkels et al., 1996), associated with greater self-injurious behavior. In addition, response to naltrexone is highly variable. Evidence from a dozen RCTs (Table 1) and as many OL/CRs (Suppl. Table S5) shows that a sizable percentage of autistic children and adolescents may actually respond to naltrexone, especially in reducing self-injurious behavior and hyperactivity, whereas evidence regarding motor stereotypies, low social motivation, lack of eye contact, and communication deficits is mixed. Several studies indicate that naltrexone may exert dose-dependent effects, with higher doses (1.0-1.5 mg/kg) able to ameliorate self-injurious behavior, hyperactivity and emotional dysregulation, whereas lower doses (0.4-0.5 mg/kg) may improve social cognition and communication (Table 1, Suppl. Table S5). It is however clear that response is very individualized: indeed there are "responders" and "non-responders" and, among responders, some children may benefit from lower doses (0.5 mg/kg) and lose behavioral improvement as the dose is titrated upward, while other children seemingly require higher doses to control self-injurious behavior and hyperactivity (Leboyer et al., 1992; Bouvard et al., 1995; Scifo et al., 1996) (Table 1, Suppl. Table S5). Some investigators have tried to link clinical response to blood levels of beta-endorphin and other hormones or neurotransmitters (Leboyer et al., 1992; Willemsen-Swinkels et al., 1995). However, attempts to identify biochemical markers of "responder" status have been inconclusive. No serious adverse reaction to naltrexone was ever observed (Herman et al., 1989b), with transient sedation representing the most commonly reported side effect and the bitter taste of tablets a limitation to compliance in small children (Kolmen et al., 1995; Willemsen-Swinkels et al., 1996; Williams et al., 2001). Therefore, although published research is limited by small sample sizes, short trial durations, and inconsistent evaluation methods, naltrexone can be viewed as a viable second-choice therapeutic option, especially for autistic children and adolescents with drug-resistant self-injurious behavior and hyperactivity (Symons et al., 2004; Elchaar et al., 2006). It is advisable to initially prescribe a low dose of naltrexone (0.4-0.5 mg/kg/day) every 2-3 days and to verify clinical response to this low-dose intermittent administration scheme, before passing to daily dosage and titrating up the dose to 1.0-1.5 mg/kg/day.

3.4. Atypical antipsychotics

Atypical Antipsychotics, also known as Second Generation Antipsychotics (SGAs), emerged in the 1980s as a new class of drugs sharing some effects with FGAs, but differing in their neurochemical profile and tolerability. Indeed, the major factor promoting the widespread use of SGAs was their lower risk of extrapyramidal side effects, despite their potential to induce other side effects, like weight gain, metabolic syndrome and elevated prolactin blood levels. Compared to FGAs, a more moderate binding to D2 receptors and the increased dopaminergic output produced at the nigrostriatal level by 5-HT2A antagonism allows SGAs to exert a more balanced modulation of dopaminergic neurotransmission, resulting in a safer adverse effect profile (Stahl, 2013). Atypical antipsychotics primarily include risperidone, aripiprazole, paliperidone, olanzapine, clozapine, quetiapine, ziprasidone, lurasidone. The Food and Drug Administration (FDA) approved risperidone in 2006, and aripirazole in 2009, for the treatment of irritability in ASD, including tantrums, aggression and self-injury, while in Europe risperidone only has been approved for aggressiveness in intellectual disability.

Risperidone acts mainly as an antagonist at dopamine D2, serotonin 5-HT2, and noradrenergic α2 receptors. It is the most extensively studied medication in ASD. Ten RCTs, as well as a wealth of OL and CR studies addressing the effects of risperidone in autistic patients, have provided converging and definitive evidence of its efficacy in the treatment of irritability, as well as suggestive evidence for reduction of repetitive behaviors (Table 2, Suppl. Table S6). For example, the RUPPAN RCT study (McCracken et al., 2002; McDougle et al., 2005) found risperidone to effectively treat agitation, aggression, motor stereotypes, hyperactivity and impulsivity. In addition to its direct pharmacological action, risperidone has also been shown to modulate astroglial functions and to exert an antioxidant and neuroprotective effect in brain disorders, such as ASDs (He et al., 2009). The adverse effect profile of risperidone in individuals with autism appears generally acceptable. The most common side effects are increased appetite and weight gain with enhanced risk of metabolic syndrome (diabetes, elevated blood cholesterol and triglyceride levels), and hyperprolactinemia. However, the incidence of neurologic side effects is drastically reduced compared to FGAs, even if acute extrapyramidal symptoms still can occur and possibly more often with risperidone than with other SGAs. Moreover, risperidone appears superior to haloperidol in controlling problem behaviors, stereotypies, and other autism-associated symptoms (Miral et al., 2008; Gencer et al., 2008). Finally, several add-on therapies, such as N-acetylcysteine, memantine and pioglitazone, may enhance the positive effects of risperidone on reducing behavioral symptoms in ASD (Nikoo et al., 2015;

Table 2
The "present" pharmacology of ASD: randomized placebo-controlled trials (RCT) of second-generation antipsychotics, with related follow-up open label (OL) extensions and secondary analyses in the pediatric ASD population.

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
Risperidone	Hellings et al. (2001)	RCT, 16 wk, OL ext 24 wk	11 (age <18), 19 total	8-16	1-4.5 mg/d, 1-3 mg/d ext (<0.05 mg/kg/d)	Weight measurement	Not reported	Mean weight gain: age 8-12 (n = 5), 8.2 kg (range = 2.7-17.7 kg); age 13-16 (n=6), 8.4 kg (range 3.6-15.5 kg).
	Hellings et al. (2005a)		10			Prolactin blood levels	Not reported	Mean PRL levels: from 13.2 ng/ml at baseline to 31.0 ng/ml acutely and remain elevated at 37.9 ng/ml in maintenance.
	RUPPAN, McCracken et al. (2002)	RCT, 8 wks	101	5-17	0.5-3.5 mg/d	ABC, CGI-I. Parental reports.	Decreased irritability, hyperactivity, inappropriate speech, social withdrawal.	Increased appetite, weight gain, somnolence, enuresis, fatigue, drowsiness, dizziness, rhinitis, drooling, constipation.
	Arnold et al. (2003) Levine et al. (2016)		101				Responders:34/49 (69.4%). Greatest benefits on irritability and lethargy in moderate to severe ASD.	
	McDougle et al. (2005)		38			CY-BOCS, RF-RLRS, VABS	Decreased irritability, restricted interests and stereotypies, but no improvement in sociocommunication deficits.	
	Aman et al. (2005)		65					
	Scahill et al. (2013)	RCT, 8 wks (RIS only) + OL extension, 16 wks	63			ABC		No negative effect on cognitive performance.
			48			ABC, CGI-I, Cognitive assessment	Improved social withdrawal	
	Aman et al. (2008)		20	5-13	Mean 1.8±0.5 mg/d		Improved verbal learning task andcancellation task, possibly also spatial memory.	No increase in QTc
	Vo et al. (2016)		63			ECG	No change in hand-eye coordination and timed math test.	Weight gain during the first 5 mo, decelerates over time and is not predicted by serum leptin levels at 2 mo.
	Martin et al. (2004)	OL extension, 16 wks + DB discont, 8 wks	38			Weight measurement, serum leptin levels		
	Williams et al. (2006)	OL prospect, 22 mo	30 (at 22 mo)			VABS		Weight increase. No significant change in nutritional balance.
	Lindsay et al. (2006)	OL extension, 21 mo	84			FFQ	Improvement in adaptive skills	Long-term side effects: increased appetite, weight gain (mean 5.1 kg), fatigue, drowsiness, occasional abnormal movements and galactorrhea.
	RUPPAN (2005)					ABC, CGI-S/I	Improvement inirritability, hyperactivity, stereotypies, lethargy, social withdrawal and tolerability persisted over 16 wks. Transition to placebo caused relapse in 62.5% vs 12.5% for continued risperidone.	
	Anderson et al. (2007)					Prolactin serum levels		Sustained 2- to 4-fold increase in prolactin serum levels.
	Aman et al. (2015)					ABC,M-RLRS, CGI-S/I, CY-BOCS-PDD		Enuresis, increased appetite, weight gain.
							Sustained and sizable improvement in maladaptive behaviors and also in core ASD symptoms, including social skills.	
	Shea et al. (2004)	RCT, 8 wks	79	5-12	0.01-0.06 mg/kg/d (mean dose 1.17 mg/d)	ABC, NCBRF, CGI-I	Decreased irritability, motor stereotypy, hyperactivity, anxiety. Improved social functioning, and language .	Somnolence, weight gain, increased pulse rate and systolic blood pressure.
	Hellings et al. (2006)	RCT crossover 22 wks + OL prospect, 24 wks on 40 ID (36 LF-ASD)	21 19 total=40	8-18 y 19-56 y	1.2–2.9 mg/d 2.4–5.2 mg/d	ABC-C Irritability	Decreased irritability: full responders 23/40 (57.5%) and partial responders 35/40 (87.5%).	Increased appetite and weight gain. Dose-related intolerable side effects (mainly sedation and gastrointestinal) when dose was raised toward 0.05 mg/kg/d.
	Nagaraj et al. (2006)	RCT, 6 mo	40	2–9	1 mg/d	CARS, CGAS	Improved global functioning, social responsiveness and nonverbal communication; reduced hyperactivity andaggression.	Increased appetite, mild weight gain, mild sedation, transient dyskinesias

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Table 2 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
	Luby et al. (2006)	RCT, 6 mo	24	2.5–6	1.14 mg/d	CARS	Minimal improvement in autism severity	Weight gain, hypersalivation, hyperprolactinemia without lactation
	Pandina et al. (2007)	RCT, 8 wks	55	5–12	1.37 mg/d	ABC, N-CBRF, VAS, VABS, CGI-I	Improving irritability, hyperactivity, aggressiveness	Mild and transient somnolence,upper respiratory infection, rhinitis, fever, sialorrhoea, coughing, increased appetite, anorexia, flu-like symptoms, weight gain, EPS.
	Miral et al. (2008) Gencer et al. (2008)	RCT, 12-wks RIS vs HALO OL prospect, 12 wk follow-up	28 27	8–18	RIS 1.2-4.0 mg/d HALO 1.0-5.7 mg/d >RIS 1.2-3.8 mg/d HALO 1.0-6.0 mg/d	ABC; RF-RLRS, CGI-S/I, TPDDRS.	Improved impulsivity, language skills, and social relations (RIS > HALO) Improved stereotypic movements, problem behaviors and CGI (RIS > HALO)	HALO: constipation, enuresis, blunted affect, rigidity, difficulty sleeping, increased appetite, upper respiratory tract infection. RIS: constipation, enuresis, upper respiratory tract infection, hyperprolactinemia. EPS effects (HALO>RIS). Weight increase and hyperprolactinemia (HALO=RIS).
	Aman et al. (2009) RUPPAN Scahill et al. (2012) Handen et al. (2013)	RCT, 24 wk, RISvsRIS+PT. If RIS not effective, switch to ARI	124 124 124 87 206	4-13 5-17	RIS from 0.5 to 3.5 mg/d ARI 2-15 mg/d	HSQ, ABC, CGI-S/I, VABS, CY-BOCS-PDD VABS SOAP	Reduced irritability, stereotypic behaviors andhyperactivity (RIS + PT > RIS alone) Improved adaptive functioning (RIS + PT > RIS alone) Decreased inappropriate behaviors and increased compliance to parental requests	Rhinitis, cough, appetite increase, weight increase, somnolence, fatigue, enuresis, excessive salivation, insomnia, headache, diarrhea, constipation.
	Arnold et al. (2012) Carroll et al. (2014)	OL prospect follow-up, 12.5–37.5 mo Post-RCT analysis of RUPPAN studies 2002 & 2009	73 96 87	5-17 7-17 4-13		ABC, CGI-S/I, VABS, CY-BOCS-PDD, ADI-R Ferritin measurement	Not reported 53% of RIS and 67% of RIS+PT are still taking RIS at follow-up. Most needed dose adjustments or additional medication. The advantage of RIS+PT over RIS alone becomes non-significant over time.	Not reported Not reported
	Calarge et al. (2015) Scahill et al. (2016)	ABC, CGI-S/I, ADI-R, VABS, Tanner staging, biochemical and physical parameters. 1) Post-RCT analysis 2) Follow-up study Post-RCT analysis					All five subtypes of aggressiveness respond positively to RIS Not reported Not reported	Weight gain is associated with reduced body iron storage. Risperidone may inhibit iron absorption. Mean weight gain 5.4±3.4 kg/24 wks, significantly associated with increased appetite during the initial 8 wks. Increased fasting glucose,hemoglobin A1c, ALT, insulin resistence, leptin. Decreased adiponectin. Drug-induced metabolic syndrome 12/97 (12.4%)
	Kent et al. (2013a) Kent et al. (2013b)	RCT, 6 wks OL extention	96 79	5-17 5-17	0.125/0.175 or 1.25/1.75 mg/d by wt 0.125-1.25 mg/d or 0.25-2.0 mg/d by wt	ABC-I, CGI-S, CY-BOCS ABC-I, CGI-S, CY-BOCS, VAS	Reduced irritability and motor stereotypies (high RIS > low RIS > PLA). Improvement is maintained over time. Maximum improvement in sleep quality and duration.	Somnolence, sedation and rhinitis (High RIS only); increased appetite (high RIS > low RIS > PLA). Increased appetite (11%), increased weight and vomiting (9% each); sedation, pyrexia, and upper respiratory tract infection (8% each); nasopharyngitis (6%), somnolence and fatigue (5% each), EPS (8%). No significant change inmean fasting glucose, cholesterol, LDL serum

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Table 2 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
								levels and modest increase in triglycerides.
	Ghanizadeh et al. (2014)	RCT, 8 wks ARI vs RIS	59	6-17	ARI up to 10-15 mg/d (mean 5.5 mg/d). RIS up to 2-3 mg/d. (mean 1.12 mg/d)	ABC, CGI-I	Both ARI and RIS equally improved irritability, hyperactivity, social withdrawal, stereotypic behaviors, and inappropriate speech.	Increased appetite, drooling, and drowsiness. No difference in adverse events between ARI and RIS. Discontinuation due to epilepsy (ARI=1), and severe crying and agitation (RIS=1).
	BAART study DeVane et al. (2019)	RCT, 10 wk + 12 wk blind ext ARI vs RIS	61	6-17.5	ARI 2-15 mg/d RIS 0.5-3 mg/d	ABC, CSHQ, CGI-I	Both drugs reduce irritability with increasing efficacy over time. RIS slightly more effective than ARI, but also yielding more adverse effects.	ARI>RIS sedation, stomach ache, enuresis. RIS>ARI increased appetite and weight gain.
Aripiprazole	Owen et al. (2009)	RCT, 8 wks	98	6-17	2-15 mg/d (mean 10 mg/d)	ABC-I; CGI-S/I, PedsQL, CGSQ	Decreased irritability, hyperactivity, stereotypies, inappropriate speech;better child quality of life and reduced caregiver strain. Responders: 52.2%. Residual symptoms in many patients. Serum prolactin levels decreased.	Fatigue, somnolence, vomiting, EPS (mainly tremors), weight gain.
	Marcus et al. (2009)	RCT, 8 wks	218	6-17	Fixed dose (5, 10 or 15 mg/d)	ABC-I; CGI-S/I, CY-BOCS, PedsQL, CGSQ	Decreased irritability, hyperactivity, stereotypy; better child quality of life and reduced caregiver strain (15 mg/d only); no change in social functioning.	Sedation, fatigue, drooling, nausea, vomiting, pyrexia, weight gain, EPS (tremor). Two serious AE: presyncope (5mg/d), aggression (10mg/d). No change in EKG.
	Marcus et al. (2011)	OL, 52 wks expansion	330	6-17	1.1-15 mg/d (mean 10.6 mg/d)		Improvements described above are sustained and long-term.	Increased appetite, weight gain, vomiting, insomnia, aggression, EPS. Discontinuation: 131 (39.7%)
	Aman et al. (2010)	Line time analysis	316 subjects described in the Owen et al. (2009) and Marcus et al. (2009) RCTs.			ABC-I	Improvement in irritability and tantrum behaviors, hyperactivity, stereotypic behaviors, inappropriate speech. No effect on social withdrawal.	As in Owen et al. (2009) and Marcus et al. (2009): sedation, fatigue, vomiting, increased appetite, somnolence, tremor.
	Robb et al. (2011)	*post-hoc* analysis on polled data from RCTs by Owen et al. (2009) & Marcus et al. (2009)				PedsQL™, ABC-I		Not analyzed.
	Varni et al. (2012)					ABC-I, CGI-S	Improved quality of life of ASD patients with irritability. Improved emotional and social functioning.	Mild-to-moderate somnolence, sedation, fatigue, drooling, EPS, pyrexia, tremor and weight gain are more frequent in antipsychotic-naïve (AN) than in prior antipsychotic exposed (PAE) patients, who display more frequent nasopharyngitis and rhinorrhea. Discontinuation in AN=10.8% and in PAE=8.3%.
	Mankoski et al. (2013)						Not analyzed	
	Findling et al. (2014)	Single-blind stabilization for 13-26 wks, followed by RCT for ≤16 wks	157 85	6-17	2-15 mg/d	ABC-I; CGI-S/I	No difference between ARI and placebo in time to relapse	Phase I: weight gain, somnolence, vomiting. Phase II: upper respiratory tract infection, constipation, EPS.
	Ichikawa et al. (2017)	RCT, 8 wks	92	6-17	1-15 mg/d (mean 5.7 mg/d whole trial, 8.2 mg/d endpoint)	ABC, CGI-S/I, CY-BOCS, CGAS	Decreased irritability, also maintained long-term.	Somnolence, decreased appetite, nausea and vomiting, fatigue.
	Ichikawa et al. (2018)	OL extension, ≥48 wks (mean 694.9 days)	70		mean: 7.2 whole trial, 8.5 mg/d endpoint)			Nasopharyngitis, somnolence, nasopharyngitis, increased weight.
Olanzapine		RCT, 8wks	11	6-14	10 mg/d	CGI-S, CY-BOCS		

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Table 2 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
	Hollander et al., 2006a						Improvement in global functioning	Weight gain, rhinitis, "glazed eyes", constipation and insomnia, no EPS
Lurasidone	Loebel et al. (2016)	RCT,6 wks	150	6-17	20 mg/d 60 mg/d	ABC-I, CGI-I, CY-BOCS, CGSQ	No significant efficacy on irritability.	Vomiting, sleepiness.
Amisulpride	Dollfus et al. (1992) Dollfus et al. (1993)	RCT, 4 wks AMI & 4 wks bromocriptine	9	4-13	AMI:1.5 mg/kg/d BRO:0.15-0.20 mg/kg/d	CARS, BSE, PTQ, CPRS, DOTES	AMI: improves some ASD symptoms and hypoactivity, increases alertness. BRO: improved hyperactivity and inattention.	AMI: insomnia, hyperactivity, excitation/agitation. BRO: reduced appetite, nausea and vomiting, insomnia, hypoactivity.

Ghaleiha et al., 2013, 2015).

Aripiprazole has been approved by the FDA to treat irritability associated with autistic disorder in children and adolescents 5–16 years of age. Aripiprazole is a neural pathway-specific antagonist or partial agonist at the dopamine D2, able to act either as an antagonist in hyperdopaminergic states/brain regions or as an agonist in hypodopaminergic states/brain regions, respectively; it also exerts partial agonistic effects on serotonin 5-HT1A and 5-HT2C receptors, antagonistic effects on serotonin 5HT2A receptors and exerts relatively weak antagonism at H1, M1, and α1-adrenergic receptors (Shapiro et al., 2003). After several OL studies (Suppl. Table S6), two similarly designed RCTs provided strong evidence for the short-term efficacy of aripiprazole in reducing irritability, hyperactivity and stereotypies in autistic children (Owen et al., 2009; Marcus et al., 2009), later replicated by a third RCT (Ichikawa et al., 2017) (Table 2). Open-label follow-ups (Marcus et al., 2011; Ichikawa et al., 2018) and secondary analyses of data merged from the first two RCTs (Owen et al., 2009; Marcus et al., 2009), confirmed both short-term efficacy and long-term maintenance of beneficial effects (Aman et al., 2010; Robb et al., 2011; Varni et al., 2012; Mankoski et al., 2013). Side effects mainly include fatigue, somnolence and weight gain, the latter less pronounced and with slower onset than observed with risperidone and other antipsychotic drugs (Table 2, Suppl. Table S6). Most studies were carried out in children aged 6 years or older. A prospective 8-wk OL study conducted on 10 preschoolers with autistic disorder aged 3-6 years demonstrated in all children a reduction in irritability, stereotypic behaviors and hyperactivity (Habibi et al., 2015). Side effects were mild and included increased appetite and weight gain, sedation and agitation, in the absence of EPS (Habibi et al., 2015), which were relatively rare also in other studies (Table 2, Suppl. Table S6). Aripiprazole and risperidone were directly compared head-to-head on efficacy and tolerability, with either no significant difference recorded between the two medications (Wink et al., 2014; Ghanizadeh et al., 2014; Lamberti et al., 2016) or risperidone resulting slightly more effective and also more likely to produce side effects compared to aripiprazole (DeVane et al., 2019). After risperidone discontinuation due to side effects, switching to aripiprazole was effective and well-tolerated, providing relief especially to disturbed nighttime sleep, hyperprolactinemia, and excessive appetite (Ishitobi et al., 2013). Despite its proven efficacy and tolerability, aripiprazole has a sizable positive effect for irritability and hyperactivity in approximately 30-50% of ASD children and adolescents, with approximately two thirds either not responding or still showing residual symptoms in need of add-on therapies (Masi et al., 2009; Owen et al., 2009).

Olanzapine shows greater D4 than D2 receptor antagonism, and is also a serotonin 5HT2A and 5 HT2C receptor antagonist (Stahl, 2013). To date, it has been tested only in one small 8-wk RCT contrasting active drug (10 mg/d) vs placebo in 11 children with ASD aged 6-11 years (Hollander et al., 2006a). Patients receiving olanzapine displayed a significant change in the primary outcome measure (CGI-I), but not in secondary outcome measures, including Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and Overt Aggression Scale-Modified. Common adverse effects include sedation and weight gain; also rhinitis, "glazed eyes", constipation and insomnia were reported (Hollander et al., 2006a) (Table 2). A decrease in irritability was reported in several OL and CR studies (Suppl. Table S6). Altogether, the limited available evidence suggests that olanzapine may be beneficial, but not as significantly as risperidone and aripiprazole. Further caution is raised by the higher liability to weight gain, metabolic syndrome and diabetes observed in adolescents with first-episode psychosis treated with olanzapine, as compared to other SGAs and to adults receiving the same treatments (Arango et al., 2004; Arango et al., 2009; Galling et al., 2016).

Lurasidone has both atypical antipsychotic and antidepressant properties. On the one hand, it is a D2, 5-HT2A, 5-HT7 receptor antagonist, but on the other hand it also exerts antidepressant effects through partial agonism at 5-HT1A receptors, antagonism at α1 noradrenergic and 5-HT2A serotonin receptors, and by exerting norepinephrine reuptake inhibition (Fountoulakis et al., 2015). This drug is known to have greater affinity than risperidone for 5-HT1A receptors (Stahl, 2013) and, in contrast to aripiprazole, exerts full antagonism on D2 receptors. It has been approved by the FDA in 2010 for the treatment of schizophrenia and bipolar I depression in adults, and by the EMA for the treatment of schizophrenia in adolescents aged 13 y.o. and above (Arango et al., 2020). One initial CR showed improvement in irritability, perseveration, and aggression in a 13 year old boy with ASD, treated at an initial dose of 10 mg/day raised to 30 mg/day without significant adverse effects (Suppl. Table S6). A recent large, 6-wk multicenter RCT involved 150 autistic patients aged 6-17 years, randomized into lurasidone 20 mg/day (n=50), 60 mg/day (n=49) or placebo (n=51) (Table 2). Lurasidone did not significantly differentiate from placebo in any ABC subscale nor in CY-BOCS (Loebel et al., 2016). Adverse events were mild, mainly vomiting and somnolence. Modest changes were observed in body weight and metabolic parameters. Its relatively favorable side-effect profile and its antidepressant properties suggest this drug may be more useful in controlling internalizing symptoms than irritability and agitation.

One RCT employing low-dose **Amisulpride**, a benzamide endowed with partial agonism on dopamine D2 receptors, displayed activating effects able to contrast some ASD symptoms and hypoactivity, while increasing alertness (Dollfus et al., 1992). Interestingly these effects can be distinguished from those of a dopaminergic agonist like bromocriptine, which instead improves hyperactivity and inattention (Dollfus et al., 1993). Also the side effect profile is distinct, with amisulpride yielding insomnia, hyperactivity, and excitation/agitation, whereas bromocriptine can reduce appetite and induce nausea (Table 2)

No RCT specifically geared toward the pediatric population with ASD has been published to this date for clozapine, quetiapine, ziprasidone or newer SGAs, including paliperidone, iloperidone, and asenapine. Several OL and CR studies have reported a decrease in hyperactivity and aggressiveness in autistic children, adolescents and adults treated with **Clozapine** after failing to respond to several FGAs and SGAs (Suppl.

Table S6). Clozapine is a weak D2 receptor antagonist, but exerts strong antagonism on D4 dopamine receptors, 5-HT2A/2C serotonin receptors, as well as on other serotonin, histamine and noradrenergic receptors (Stahl, 2013). It also decreases the expression of astrocytic glutamate transporter GLT-1, boosting glutamatergic neurotransmission in the prefrontal cortex (Melone et al., 2001). Clozapine is rarely prescribed to pediatric patients because of its potentially serious side effects, including agranulocytosis, seizures, sedation, obesity, and cardiomyopathy (Chen et al., 2001; Beherec et al., 2011; Yalcin et al., 2016). Despite this limited available evidence of efficacy and safety, treatment-resistance does spur clozapine prescription to children and adolescents with ASD. While awaiting for more rigorous studies in the pediatric population, single treatment-resistant cases require close monitoring of white blood cell counts to prevent agranulocytosis and, especially relevant to many autistic children, periodic EEGs to assess for the need to associate an antiepileptic drug (Gobbi and Pulvirenti, 2001). **Quetiapine** exerts weak antagonism on dopamine D2 and serotonin 5-HT1A, and 5-HT2A receptors, as well as moderate to high affinity for noradrenergic α1 and α2 receptors and for H1 histamine receptors (Stahl, 2013). Quetiapine was generally ineffective and poorly tolerated in two initial OL studies on patients with PDD (Martin et al., 1999; Findling et al., 2004) (Suppl. Table S6). Two retrospective studies provided more optimistic percentages of responders, ranging between 40 and 60% of autistic children, adolescents and young adults treated with quetiapine (Corson et al., 2004; Hardan et al., 2005). Another OL study administering low doses of quetiapine (50-150 mg/d) to 11 high functioning adolescents with ASD yielded a satisfactory outcome, with reduced aggression levels and improved sleep quality, as well as greater tolerability (Golubchik et al., 2011). **Ziprasidone** is a high-affinity serotonin 5-HT2A receptor antagonist, and a moderate-affinity dopamine D2, noradrenergic α1 and histamine H1 receptor antagonist; it also exerts antagonistic effects on 5-HT1D receptors and an anxiolytic/antidepressant action due to 5-HT1A receptor antagonism and norepinephrine reuptake inhibition (Stahl, 2013). It has shown some beneficial preliminary beneficial effects in patients with ASD, especially on irritability and hyperactivity, without any consistent weight gain and with usually tolerable side effects (Suppl. Table S6). Two prospective OL studies found ziprasidone moderately effective in 6 (50%) and 9 (75%) of 12 autistic children and adolescents each (McDougle et al., 2002; Malone et al., 2007). A retrospective chart review involving 42 ASD patients yielded 40% response rates on irritability (Dominick et al., 2015). The drug was relatively safe, with side effects including transient sedation, mean QTc increase of 14.7 msec and acute dystonic reactions in 2 subjects (McDougle et al., 2002; Malone et al., 2007; Dominick et al., 2015).

Paliperidone acts primarily as an antagonist at dopamine D2, serotonin 5-HT2, and noradrenergic α2 receptors. This drug is the major active metabolite of risperidone. It was approved by the FDA in 2006 for the treatment of schizophrenia in adolescents and adults. Regarding its use in ASD children and adolescents, only three CRs and one OL study have been published to date, suggesting efficacy in a high percentage of patients and a relatively safe profile, with weight gain as its most common side effect (Suppl. Table S6).

Finally, no studies at all have been published about the use of the newer SGAs asenapine, cariprazine and iloperidone in ASD. These drugs are both D2 and 5-HT2A receptors antagonists, approved by FDA in 2009 for the treatment of adults affected by schizophrenia.

3.5. *Selective serotonin reuptake inhibitors (SSRIs)*

This group of medications held interest for autism researchers, because of the consistent finding of elevated serotonin blood levels recorded in 22-28% of individuals with autism (Gabriele et al., 2014). These agents are potent blockers of serotonin re-uptake and could potentially reverse the serotoninergic dysregulation documented in many ASD patients (Chandana et al., 2005). Furthermore, some core ASD symptoms, especially repetitive behaviors and insistence on sameness, do often respond to SSRIs and to clomipramine when part of an obsessive-compulsive disorder in children (Varigonda et al., 2016). To date, three SSRIs have received regulatory approval in Europe for specific use in the paediatric population: fluoxetine for moderate to severe major depressive episodes starting at age 8, sertraline and fluvoxamine for obsessive–compulsive disorder starting at age 6 and 8, respectively (Persico et al., 2015). A Cochrane systematic review (Williams et al., 2013) identified nine RCTs with a total of 320 participants with ASD involving fluoxetine (three studies), fluvoxamine (two studies), and citalopram (two studies), in addition to fenfluramine (two studies), an indirect serotoninergic agonist which will not be discussed in the present review because, after initial promising results in ASD, it was withdrawn from the market in 1997 due to its association with cardiac valvular disease (for review see Aman and Kern, 1989). Five RCTs enrolled children (Table 3), while four RCTs included only adults. A much more recent systematic review and meta-analysis reports no significant difference between SSRIs and placebo in the treatment of restricted/repetitive behaviors (RRBs) in ASD (Yu et al., 2020).

Fluoxetine and fluvoxamine have been the most investigated SSRIs for the ASD population. **Fluoxetine** yielded promising results in initial prospective OL and retrospective chart reviews, showing some efficacy in reducing the frequency and intensity of RRBs, including both motor stereotypies and more classic compulsions (Suppl. Table S7). Also a series of CRs published between 2010 and 2018 appeared very favorable (Suppl. Table S7). These positive findings were apparently reinforced by the first crossover RCT providing some evidence of efficacy on RRBs for low-dose (5-20 mg/day) fluoxetine in 39 children and adolescents with ASD (Hollander et al., 2005) (Table 3). The anti-anxiety effects of fluoxetine may also have indirectly improved sustained attention and environmental engagement (Hollander et al., 2005). Instead, little improvement in other autistic symptoms was noted, including eye contact, social initiation and responsiveness, although some patients showed decreased social withdrawal and an expanded repertoire of interests (Hollander et al., 2005). Low-dose fluoxetine was well tolerated, but in practically all studies titrating up the dosage triggered hyperactivity, irritability, impulsive behavior and sleep disturbance. These side effects are dose-related and can be minimized with a careful and conservative dose titration. Interestingly, optimal dosage may display a bimodal distribution, with some children responding better at 4-8 mg/day and develop side effects raising the dose, while others require 15-40 mg/day (DeLong et al., 1998, 2002). Unfortunately, careful analysis of the first RCT already unveils statistically significant improvements in CY-BOCS scores not sufficient to yield a clinically meaningful change (Hollander et al., 2005). This relatively modest effect size was conclusively shown by two more recent large-scale RCTs, involving 158 and 143 children and adolescents with ASD (Reddihough et al., 2019; Herscu et al., 2020) (Table 3). The efficacy on RRBs of fluoxetine administered for 14 and 16 weeks, respectively, was either superimposable to the effects recorded with placebo (Herscu et al., 2020) or marginally greater at best (Reddihough et al., 2019). **Fluvoxamine,** a highly effective drug in obsessive-compulsive disorder, was also found to be effective on RRBs, maladaptive behaviors, and aggressiveness in 8/15 (53%) adults with autism (McDougle et al., 1996). These encouraging results spurred interest into the potential efficacy of fluxovamine in children and adolescents with ASD. The first RCT involving 34 children and adolescents with ASD, aged 5-18 years (mean dose: 106.9 mg/day), found fluvoxamine to be minimally effective and poorly tolerated in this age group (Table 3). In fact, only 1 subject (5.5%) showed clinical improvement, while 14/18 (77.7%) experienced adverse effects to blinded drug administration (McDougle et al., 2000). It is worthwhile to notice that the starting dose in this study was 50 mg/d, which may have been too high for the pediatric population. A later study showed that 10/18 (55.6%) ASD children responded to lower doses (1.0-1.5 mg/kg/d), but side effects were still frequent in children, including insomnia, aggressiveness, increased rituals, anxiety, anorexia, increased appetite, irritability, decreased concentration, and increased impulsivity (Sugie et al.,

2005) (Table 3). Overall, fluvoxamine may represent a better option in adults than in children with ASD and certainly requires low doses and careful titration. Also **Citalopram** displays similarly limited efficacy in the management of repetitive behaviors in children and adolescents with ASD. After two promising retrospective chart reviews (Suppl. Table S7), in a large RCT involving 149 children with ASD aged from 5 to 17 years old, no significant difference in repetitive behaviors between citalopram- and placebo-treated cases was observed using the CGI-I and CY-BOCS PDD (King et al., 2009) (Table 3). Side effects included increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypies, diarrhea, insomnia, prolonged seizure, skin drying or itching (King et al., 2009). A reanalysis of these same results later linked response to citalopram to pretreatment levels of disruptive behaviors, signs of depression and autism severity, level of parental strain (King et al., 2013), although the overall negative result remains valid. Another line of research employing fMRI in adult autistic individuals, confirmed that the sizable response to citalopram seen in some is accompanied by increased prefrontal cortical activity, especially in the anterior cingulate cortex (Dichter et al., 2010), but this does not apply to the majority of ASD cases and not significantly more often that placebo (Dichter, 2012). The use of **Sertraline** in ASD raised interest after two initial OL studies involving only adults with ASD yielded promising results: the first, involving 9 patients with Intellectual Disability including 5 patients with co-morbid ASD, described reduced self-injury and aggression after at least 28 days of sertraline administered at variable doses (25-150 mg/d) (Hellings et al., 1996). The second trial reported significant reductions in repetitive behaviors and aggressiveness in 24/42 (57%) adults with ASD treated with 25-200 mg/d sertraline for 12 weeks (McDougle et al., 1998). Adverse effects were minimal and dose-dependent. Subsequently, a very small number of studies involving pediatric cases was published. Three case reports described anecdoctal efficacy on anxiety in ASD (Suppl. Table S7). An OL case series of 9 children, aged 6 to 12 years, treated with sertraline (25-50 mg/d) reported an improvement in anxiety, irritability, and agitation, although 3 of these 9 children lost response after a few months of drug treatment (Steingard et al., 1997). Ultimately, a single RCT contrasting long-term (6 months), low-dose (2.5-5.0 mg/d) sertraline vs placebo was performed in 58 small autistic children, aged 2-6 y.o., with primary measures focused on expressive language and a variety of secondary measures tapping into different domains of cognitive and adaptive functioning (Potter et al., 2019) (Table 3). This study addresses rather specific and peculiar aspects of ASD, as it follows two previous studies on Fragile X Syndrome (FXS) from the same group, one retrospective chart review supporting greater improvement in expressive and receptive language development among sertraline-treated FXS children compared with children treated with other drugs (Indah Winarni et al., 2012), and one RCT of low-dose sertraline demonstrating modest changes in expressive language scores, but significant improvements in fine motor skills, visual perceptual abilities, and social motivation in FXS children from the same age group (Greiss Hess et al., 2016). The RCT by Potter et al. (2019) was negative both for primary and for secondary measures, indicating that improvements recorded with low-dose sertraline in the two previous studies were likely specific to FXS and may not extend to idiopathic ASD.

There are no RCTs of escitalopram, and paroxetine. **Escitalopram**, the active S-enantiomer of racemic citalopram, has been administered in two OL studies (Suppl. Table S7). The first study involved 28 ASD children and adolescents with ASD (Owley et al., 2005), later expanded to 58 to assess pharmacogenetics influences by the 5-HTTLPR polymorphic repeat located in the promoter region of the *SLC6A4* gene, which encodes the serotonin transporter, on response to escitalopram treatment (Owley et al., 2010). Improvement was recorded in ABC scores for irritability, lethargy, stereotypies, hyperactivity, and inappropriate speech, while side effects, namely irritability and hyperactivity, occurred at doses above 10 mg/d. The 5-HTTLPR SS genotype and consequently lower levels of platelet 5-HT were associated with reduced clinical response to escitalopram (Owley et al., 2010). Superimposable therapeutic and side effect profiles were also reported in another more recent OL trial involving 89 children, adolescents and adults with ASD (Suppl. Table S7). Unfortunately, the lack of a randomized placebo control limits the reliability of these promising findings. Evidence regarding **paroxetine** treatment in ASD is even more limited to only three CRs, describing efficacy on self-injurious behaviors, stereotypies, anxiety, temper tantrums, and co-morbid with OCD where other treatments had failed (fluoxetine, fluvoxamine, risperidone, haloperidol) (Suppl. Table S7). Two of these cases underwent either behavioral activation or enhanced irritability and sweating while tapering up the dosage. The large difference in minimum effective dose (i.e., 10, 20, and 40 mg/d) between these three patients is noticeable. The highly personalized and relatively unpredictable response to SSRIs in ASD and in Intellectual Disability is confirmed by a retrospective chart review of 37 adults with intellectual and neurological disabilities who received either fluoxetine (25 patients) or paroxetine (12 patients) in addition to other psychotropic drugs for perseverative and maladaptive behaviors (Branford et al., 1998). The response was quite divergent, with an improvement observed in 13 (35%), no benefit in 15 (40%) and a worsening in 9 (25%) cases, while no difference between fluoxetine and paroxetine was recorded (Branford et al., 1998).

Collectively, results with SSRIs are mixed at best (Table 3, Suppl. Table S7). Response to SSRIs appears very variable, with many patients not responding at all, others developing quickly psychomotor agitation and a global behavioral worsening, while others respond especially in the domains of RRBs, anxiety and irritability, but at highly different optimal dosages: some patients display great sensitivity (i.e., respond to lower doses and develop side effects at lower doses), while others respond to higher doses and do not develop side effects until high doses are reached (DeLong et al., 1998, 2002). Age may represent an important factor influencing drug efficacy and adverse events, as adolescents and young adults may tolerate and respond to SSRIs better than children.

3.6. *Selective serotonin/norepinephrin reuptake inhibitors (SNRIs) and other antidepressants*

Venlafaxine is a newer antidepressant that inhibits the reuptake of serotonin, norepinephrine, and, to a lesser extent, dopamine (Ellingrod and Perry, 1994). Very few data are available on its use in autistic individuals. The possible efficacy of low-dose venlafaxine on core autistic and ADHD-like symptoms was proposed in an OL retrospective study (Hollander et al., 2000) and in one CR involving three adolescents/young adults with self-injurious behavior and hyperactivity (Carminati et al., 2006) (Suppl. Table S7). Later, a small-sized RCT enrolled six low-functioning mainly adult ASD patients, who received venlafaxine in add-on to their usual clonazepam and/or zuclopenthixol treatment and were compared with seven patients who received placebo (Carminati et al., 2016) (Table 3). At the end of the study, global improvement and decreased irritability were recorded in the entire sample, with no significant difference between the venlafaxine and placebo groups. Principal component analysis was able to distinguish the two groups based on ABC factor 2, Behavior Problems Inventory (BPI) scores, blood ammonia at treatment day 28 and cumulative doses of clonazepam/zuclopenthixol, which tended to be lower in the venlafaxine-treated group. However, none of these factors singled out reaches statistical significance, possibly due to small sample size.

Mirtazapine is a tetracyclic noradrenergic and serotonergic antidepressant that acts by antagonizing adrenergic α2-autoreceptors and α2-heteroreceptors, by blocking 5-HT2 and 5-HT3 receptors, thus enhancing norepinephrine release and 5-HT1A-mediated serotonergic transmission, and by antagonizing H1 histamine receptors (Anttila and Leinonen, 2001). This drug yielded some promising results (Suppl. Table S7), but no conclusive evidence based on RCTs has yet been published. Several case reports and one OL study (Coskun et al., 2009)

Table 3
The "present" pharmacology of ASD: randomized placebo-controlled trials (RCT) of selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine uptake inhibitors (SNRI), other antidepressants, antianxiety agents, antiepileptic drugs and mood stabilizers, with related follow-up open label (OL) extensions and secondary analyses in the pediatric ASD population.

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
SSRI/SNRI								
Fluoxetine	Hollander et al. (2005)	RCT, crossover 8 wks FLUO, 4 wks wash out, 8 wks PLA.	39	5-16	4.8–20 mg/d (mean 10.6± 3.65 mg/d)	CY-BOCS, CGI-AD, SSOA-S	Reduced repetitive behaviors	Sedation, agitation, diarrhea, anorexia. No significant difference between FLUO and PLA.
	Reddihough et al. (2019)	RCT, 16 wks	146	7.5- 17	From 4-6 mg/d, up to 20-30 mg/d	CY-BOCS-PDD, CGI-S/I, ABC, SCAS, RBS-R.	Marginally greater decrease in RRBs.	Nausea and diarrhea, insomnia, agitation. No difference in side effects between FLUO and placebo. High drop-out rate (41% FLUO and 30% placebo).
	Herscu et al. (2020)	RCT, 14 wks	158	5-17	Mean dose 11.8±6.3 mg/d	CY-BOCS-PDD, CGI-S/I, CGSQ	No efficacy on RRBs (responders to FLUO vs placebo = 36% vs 41%, respectively)	Insomnia, diarrhea, vomiting. No difference in side effects between FLUO and placebo.
Fluvoxamine	McDougle et al. (2000)	RCT, 12 wks	34 (18 FLUV, 16 PLA)	5-18	25-250 mg/d	Y-BOCS, RF-RLRS, BAS, VABS, CGI-I	Only 1/18 (5.5%) responder	14/18 (77.7%) experienced insomnia, hyperactivity, agitation, aggression, increased rituals, anxiety, anorexia.
	Sugie et al. (2005)	RCT, crossover, 12 wks, based on 5-HTTLPR	18	3-8.4	1-3 mg/kg/d for 6 wks, 1.5 mg/kg/d for 2 wks, 2 wk wash-out.	CGI-I, BAS, CARS	Full responders (clinical and CGI): 5/18, Minimal responders (CGI): 5/18. Improved eye contact and inappropriate or delayed speech.	Transient nausea and hyperactivity
Citalopram	King et al. (2009, 2013)	RCT, 12 wks	149	5-17	2.5 mg/d up to 20 mg/d	CYBOCS-PDD, CGI-I, ABC, RBS-R	No difference in RRBs between citalopram and placebo (response may be associated with pretreatment disruptive behavior, signs of depression, and caregiver strain).	Impulsiveness, increased energy level, decreased concentration, hyperactivity, stereotypies, diarrhea, insomnia, prolonged seizure, skin drying or itching.
Sertraline	Potter et al. (2019)	RCT, 6 mo	58	2-6	2.5-5.0 mg/d	MSEL, PLS5, PVET, CGI-S/I, EOT, VABS-II, ABC-C, PAS, SRS, SPM-P	No difference between low-dose sertraline and placebo in primary (MSEL) and secondary outcome measures	No difference between low-dose sertraline and placebo in adverse events.
Venlafaxine	Carminati et al. (2016)	RCT, 14 wks	13	18-45	18.75 mg/d in association with zuclopenthixol and/or clonazepam	ABC, BPI, CGI, CGI-I, CGI-S	Decreased irritability and problem behaviors. Decreased doses of zuclopenthixol and/or clonazepam needed in several patients.	Excess salivation and other side effects due to concomitant treatment with zuclopenthixol and clonazepam (slight EPS signs and increased ammonia).
Other Antidepressants								
Tianeptine	Niederhofer et al. (2003)	RCT, crossover 12 wks	12	4.2–14.9	37.5 mg/d	ABC, CPRS, CGAS, CGI	Modest improvement in irritability, hyperactivity, eye contact and inappropriate speech according to teachers, not to clinician ratings.	Drowsiness and decreased activity
Antianxiety agents								
Buspirone	Ghaleiha et al. (2015)	RCT, 8 wks add-on to RIS 2-3 mg/d	40	4-17	Up to 10 or 20 mg/d (mean 6.7±2.7 mg/d)	ABC	Decreased irritability in 13/16 (81.3%) buspirone- and in 8/18 (44.4%) placebo-treated patients.	Increased appetite (10), drowsiness (2), and fatigue (2).
	Chugani et al. (2016)	RCT, 24 wks	166	2-6	2.5 or 5.0 mg b.i.d.	ADOS, VABS, ABC, RBS, CY-BOCS, MSEL, SPS, LPR.	Improvement in RRBs in conjunction with behavioral interventions for the 2.5 mg dose.	None reported more frequently in buspirone vs placebo-treated groups
Flumazenil	Wray et al. (2000)	RCT (pilot study)	2	11, 3.3	1) 2 mg i.v 2) 4-11.5 mg i.v.	Clinical observation	1) None reported 2) No clear benefit, except for 20% higher rate of interaction at peak effect	None reported
Antiepileptic drugs and mood stabilizer								
Valproate		RCT, 8 wks	30	6-20		ABC-C, CGI-I		

(*continued on next page*)

Table 3 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
	Hellings et al. (2005b)				20mg/kg/d (level 75.5-100μg/ml)		No efficacy on irritability and aggressiveness.	Increased appetite, skin rash (1), increased serum ammonia (2), slurred speech and mild cognitive impairment (1).
	Anagnostou et al. (2006)	RCT, add-on to fluoxetine, 8 wks	6	Mean 9.5 y	Up to mean valproate level of 69.75 μg/ml	OAS-M, CGI-I	Pretreatment with valproate for 2 wks prevents increase in irritability induced by fluoxetine	Mild weight gain and fatigue.
	Hollander et al. (2006b)	RCT, 8 wks	13	5-17	500-1500 mg/d (level 50-100 μg/ml)	CY-BOCS	Reduced repetitive behaviors	Irritability (4), weight gain (3), anxiety (1), aggressiveness (1)
	Hollander et al. (2010)	RCT, 12 wks	27	5-17	Dose to a mean level 89.9 μg/ml	ABC-I, CGI-I	Reduced irritability in 62.5 % cases (correlated with higher blood levels of valproate).	Skin rash, irritability
Levetiracetam	Wasserman et al. (2006)	RCT, 10 wks	20	5-17	20-30 mg/kg/d (max mean 862.50 mg/d)	CGI-I, ABC, CY-BOCS, CRSR	No efficacy on global functioning, irritability, repetitive behaviors, impulsivity and hyperactivity.	Increased aggressiveness and agitation
	Wang et al. (2017)	Single-blind RCT, 6 mo	70	4-6	60 mg/kg/d	PEP-3, CARS, ABC, 24-hr EEG	Improves subclinical epileptiform discharges, behavior and cognition	Dose-dependent fatigue and somnolence (1), and irritability (1).Transient anorexia (1).
Lamotrigine	Belsito et al. (2001)	RCT, 18 wks	28	3-11	5 mg/kg/d	ABC, VABS, PL-ADOS, CARS	No difference in irritability over PLA	Insomnia, increased stereotypies, echolalia, aggressiveness.
Topiramate	Rezaei et al. (2010)	RCT, 8 weeks Add-on to RIS	40	4-12	TOP: 100-200 mg/d + RIS: 2-3 mg/d	ABC-C	Reduction of irritability, stereotypic behavior, hyperactivity in TOP+RIS compared to PLA+RIS.	Mild sedation and decreased appetite.

provide preliminary evidence of efficacy in blunting compulsive masturbation and other sexually inappropriate behaviors (Suppl. Table S7). Another OL study showed that 9 out of 26 children and adolescents with ASD (3-23 y.o., mean age 10 y) treated with mirtazapine (7.5-45 mg/d, mean dose 30.3 mg/d) were judged "much improved" or "very much improved" on the CGI, based on improvement in a variety of symptoms including aggression, self-injurious behavior, irritability, hyperactivity, anxiety, depression, and insomnia (Posey et al., 2001). Mirtazapine did not improve core ASD symptoms; adverse effects were minimal and included increased appetite, irritability, and transient sedation (Posey et al., 2001). **Tianeptine** is an atypical antidepressant which attenuates stress-induced glutamate release and prevents the upscaling of NMDA receptor-mediated currents (McEwen et al., 2010); it also acts as a mu opioid receptor agonist, thereby enhancing dopamine release (Samuels et al., 2017). One 12-week crossover RCT reported no significant difference between tianeptine and placebo, as recorded by clinician ratings of videotaped sessions, whereas teacher and parent ratings provided marginal evidence of improved irritability, hyperactivity, eye contact and inappropriate speech (Niederhofer et al., 2003). The only side effect was increased drowsiness and reduced activity levels (Table 3, Suppl. Table S7). **Trazodon**e is a heterocyclic antidepressant with serotoninergic, antihistamine, and anti-α1-adrenergic actions, devoid of anticholinergic effects and often prescribed to children and adolescents with neurodevelopmental disorders, especially as a sleep-promoting agent (Blackmer and Feinstein, 2016). The general paucity of studies investigating its efficacy is also reflected by the autism literature, which includes only four CRs of trazodone prescription to ASD children and adolescents, mostly reporting beneficial effects on sleep quality (Suppl. Table S7). One case study (Gedye, 1991) also showed reduction of aggressiveness and hyperactivity in a low-functioning (LF) autistic teenager treated with relatively low-dose trazodone (250 mg/d) not administered only at bedtime, but rather distributed t.i.d. in monotherapy. Finally, Golubchik et al. (2013) performed an open-label trial in 11 children with ASD to test the safety and efficacy of the noradrenergic antidepressant **Reboxetine**, which produced a significant decrease in the severity of depressive symptoms and a more modest improvement in co-morbid ADHD (Suppl. Table S7).

3.7. Anxiolytics

Anxiety is a frequent comorbid symptom in ASD, affecting as many as 39.6% of autistic individuals (van Steensel et al., 2011). However, **benzodiazepines** (BZD) have been much less studied in autism compared to other drug classes, because of the common fear of "paradoxical reactions", namely behavioral activation with disinhibition, hyperactivity, and irritability. It is, however, curious that this commonly held belief is based almost exclusively on clinical experience, while scientific evidence remains extremely scanty and has been drawn almost exclusively from adult patients with intellectual disability (Kalachnik et al., 2003; Mancuso et al., 2004). The only study directly addressing paradoxical reactions to BZD in autistic children reports anxiogenic effects and aggressive behavior, up to explosive aggression, following parenteral administration of diazepam (10 mg i.m.) to seven autistic children (Marrosu et al., 1987). Obviously, this does not represent the usual route of administration of BZD to children, not allowing an acritical extension of these findings to the entire pediatric population. In fact, 16% of ASD children take BZD per os (Fusar-Poli et al., 2019), most often for anxiety and for sleep difficulties (Chevreuil et al., 2010; Malow et al., 2016), though occasionally for more serious conditions, like catatonia (see CRs in Suppl. Table S8 and Wachtel, 2019, for review). Rectal, buccal or parenteral administration of BZD is preferred in over 70% of emergency room interventions for acute agitation (Kendrick et al., 2018) and for dental work in children and adolescents with autism and/or intellectual disability (Pisalchaiyong et al., 2005; Jo et al., 2017). Therefore, although paradoxical reactions to BZD are indeed observed in medical practice, more research is necessary to define the percentage of

autistic children prone to develop these reactions and to characterize them from a clinical, electrophysiological and molecular standpoint. The bzd receptor antagonist **flumazenil** has been used in a single pilot RCT with minimal or absent benefits (Wray et al., 2000) (Table 3). On the contrary, the "atypical" anxiolytic **buspirone,** a 5-HT(1A) receptor agonist used to treat generalized anxiety disorder, has been tested in multiple RCTs and OL studies (Table 3 and Suppl. Table S8). An 8-week RCT has found low-dose buspirone, administered as an add-on to risperidone, effective over irritability in 13/16 autistic outpatient children and adolescents (Ghanizadeh and Ayoobzadehshirazi, 2015). Another large-scale RCT provided some evidence of efficacy over RRBs at a low-intermediate dose (2.5 mg b.i.d.), but not at a higher dose (5 mg b.i.d.), in combination with behavioral interventions (Chugani et al., 2016). Side effects appear occasional, tolerable and dose-dependent, most often including appetite changes and sedation. Hence, studies performed to date have collectively documented the efficacy of buspirone over anxiety, irritability, tension, and RRBs, despite the usual large interindividual variability in drug response and in optimal dosage (Table 3, Suppl. Table S8).

3.8. Antiepileptic drugs and mood stabilizers

Antiepileptic drugs (AEDs) are frequently prescribed for behavioral symptoms in the ASD population, but this indication has been addressed only in a limited number of OL studies and RCTs (Canitano, 2015). A systematic review and meta-analysis reported a total of seven randomized placebo-controlled trials in ASD: four involving valproate, and one lamotrigine, levetiracetam and topiramate each (Hirota et al., 2014). These RCTs are listed in Table 3 and additional OL and CR studies are available in Suppl. Table S9.

Valproic acid was initially found to slowly reduce irritability in an open trial including 14 young ASD patients (with and without seizures) using the CGI scale for evaluation (Hollander et al., 2001) (Suppl. Table S9). Subsequently, three RCTs, 8-12 week long, enrolling 13, 27 and 30 ASD patients, respectively, produced contrasting results (Hellings et al., 2005b; Hollander et al., 2006b, 2010) (Table 3). Hellings et al. (2005b) found no significant difference in ABC-irritability subscale scores between valproate and placebo, with high inter-subject variability. On the contrary, applying more stringent inclusion criteria, Hollander et al. (2006a) first reported positive results of sodium divalproex on repetitive behaviors in 13 autistic children, and later replicated and extended these findings in a larger sample of 27 children and adolescents, confirming a significant difference between sodium divalproex and placebo in favor of the active compound (Hollander et al., 2010). Additionally, valproate was also found to attenuate the irritability induced by fluoxetine treatment in ASD (Anagnostou et al., 2006). Collectively, results from the valproate studies support efficacy on irritability in a subset of autistic children, while many patients do not respond or sometimes display increased irritability as a side effect.

Levetiracetam acts by binding to synaptic vesicle protein 2 (SV2) and inhibiting glutamate release, while reducing intracellular Ca^{2+} levels by inhibiting ryanodine and IP3 receptor-dependent Ca^{2+} release from endoplasmic reticulum (Deshpande and Delorenzo, 2014). Data on its possible efficacy for behavioral symptoms in ASD appear scanty and not encouraging. An initial small OL study found levetiracetam to improve attention, hyperactivity, emotional lability, and aggressive behaviors in 10 drug-naive autistic boys (Rugino and Samsock, 2002) (Suppl. Table S9). The only double-blind RCT involved 20 autistic children for 10 weeks and found no difference between levetiracetam and placebo in global functioning, irritability, repetitive behaviors, impulsivity and hyperactivity; the most relevant side effect was increased aggressiveness (Wasserman et al., 2006) (Table 3). A subsequent single-blind RCT suggested that efficacy on behavior and cognition may be related to improvement in subclinical epileptiform discharges (Wang et al., 2017), but the significance of EEG anomalies in the absence of seizures in ASD remains highly debated, as its neurobiological underpinnings and clinical consequence may largely differ from patient to patient (Precenzano et al., 2020) (Table 3). Two case reports describing a levetiracetam-induced autistic regression in a 6-year-old girl with cerebral palsy (Camacho et al., 2012) and a drug-induced acute pancreatitis spur further caution to its prescription for indications outside the epileptic spectrum.

Topiramate has been primarily investigated in reference to reducing weight gain and for its mood stabilizing properties (Table 3, Suppl. Table S9). A randomized add-on OL trial showed a relatively modest impact on the excessive weight gain induced by risperidone or pimozide (Canitano, 2005). Furthermore, 3 out of 10 children had to interrupt the trial due to drug-induced behavioral activation (Canitano, 2005). Modest effects on body weight were also confirmed by the small retrospective case series of children and adolescents with ASD analyzed by Mazzone and Ruta (2006), also reporting limited benefits in irritability and hyperactivity observed only in a minority of patients (2 out of 5). Beneficial effects on irritability, hyperactivity and stereotypic behaviors were reported only in the RCT by Rezaei et al. (2010), when topiramate was administered in add-on to risperidone.

Lamotrigine, a voltage-gated Na^{+} channel blocking agent with antiepileptic effects, has been investigated in only one RCT involving 28 children with ASD (Belsito et al., 2001). This study showed no significant effect on irritability and social behavior using multiple instruments (Table 3).

Only OL and CR studies have been published involving other antiepileptic drugs and mood stabilizers, and not RCTs (Suppl. Table S9). In reference to **carbamazepine** and its structural analog **oxcarbazepine**, few CRs describe mainly rare side effects. One retrospective study addressing irritability and agitation in 30 ASD patients, aged 5-21 years, assessed after 6 and 10 weeks at a stable dose of oxcarbazepine, reports 18 patients continuing to take the drug at the end of the study period, including 14 (47%) and 10 (33%) patients showing CGI-I scores of "much improved" and improvement on CGI-S scores, respectively (Douglas et al., 2013). On the other hand, the drop-out rate is high and as many as 7 (23%) patients presented clinically significant adverse events leading to drug discontinuation, with increased irritability as the most common side effect. Hence, if replicated in controlled trials, these results again point toward a large divergence between "responders" and "non-responders" also with oxcarbazepine on irritability/agitation. An interesting case report describes the efficacy of low dose **phenytoin** (2 mg sublingual up to 5 mg/d) on the core symptoms of ASD in a 19 years old young man treated with stimulant medication since early childhood for comorbid ADHD (Bird, 2015). Stable improvement was observed on verbal and non-verbal communication, eye contact, social motivation, attention and reading. Symptoms relapsed soon after drug discontinuation and abated upon drug resumption (Suppl. Table S9). **Lithium**, the best-established and longest-standing mood stabilizer, has initially been used in ASD patients affected by co-morbid bipolar disorder (Suppl. Table S9). Siegel et al. (2014) reported on the use of lithium in 30 children and adolescents with ASD in the presence of mood disorder symptoms, especially mania, euphoria or elevated mood. In this retrospective chart review, 13 (43%) patients improved in CGI-Irritability score. The mean lithium blood level was 0.70 mEq/L, and the mean duration of lithium treatment was 29.7 days. Adverse effects, reported by 14 (47%) patients, included vomiting, tremor, fatigue, irritability, and enuresis. According to this report, ASD responders to lithium therapy were those suffering from mania and elevated mood (Siegel et al., 2014). However, additional evidence points toward lithium efficacy beyond the strict comorbidity with overt bipolar symptoms. Two prior CRs, Kerbeshian et al. (1987) and Steingard and Biederman (1987), suggest efficacy on severe and psychostimulant-resistant hyperactivity, which in small children often represents a prodromic form of mania (Biederman et al., 2009) (Suppl. Table S9). Maladaptive behaviors associated with ADHD, namely severe hyperactivity and emotional dysregulation, may also frequently improve already at relatively low lithium serum levels (0.6 ± 0.3 mEq/l in Mintz and Hollenberg (2019).

Interestingly, in two cases of syndromic ASD, a 21 years-old man and a 17 years-old girl with Phelan-McDermid syndrome due to chr. 22q13.3 deletions involving the SHANK3 gene, lithium successfully rescued a severe form of regression with catatonic features (Serret et al., 2015). Lithium doses yielding blood levels of 0.7-0.8 mEq/l produced over several months a progressive amelioration of cognitive regression (urinary and fecal incontinence stopped), agitation, heteroaggressiveness, impulsivity and behavioral problems, motor and verbal disabilities, and social isolation. Both patients eventually recovered their previous level of functioning, completely overcoming their regression. In both cases lithium was well tolerated (Serret et al., 2015). Future research will thus have to establish if this long-known drug may benefit children and adolescents with ASD above and beyond its usual indication for co-morbid bipolar disorder.

3.9. Stimulants and anti-ADHD agents

Many autistic children and adolescents also show inattention, hyperactivity and impulsivity. However, it was not until DSM-5 that a comorbid diagnosis of attention deficit/hyperactivity disorder (ADHD) could be given to individuals already diagnosed with ASD. Applying DSM-5 criteria, the percentage of ASD children and adolescents also affected with ADHD ranges from 14 to 33% (Dalsgaard et al., 2013), and many ASD children are prescribed drugs to treat comorbid ADHD. Prescription rates for ADHD drugs among children and adolescents with ASD vary between different countries in the EU, ranging from 16% in Denmark (Dalsgaard et al., 2013), to 12.5% in Germany (Bachmann et al., 2013) and to 7.1 % in the U.K., as prescribed by General Practitioners (Hsia et al., 2014). Pharmacological treatments for ADHD symptoms are especially important in the clinical management of autistic children, because untreated co-morbid ADHD may negatively impact social adaptation and reduce the efficacy of behavioral interventions in autistic children.

Methylphenidate (MPH) is a psychostimulant well known for its efficacy over ADHD symptoms. Collectively, five RCTs of immediate-release (IR) MPH, including the large RUPPAN study (RUPPAN, 2005), and two RCTs of extended-release (ER) MPH (Pearson et al., 2013; Kim et al., 2017) converge in indicating that this psychostimulant is also effective upon ADHD symptoms comorbid with ASD (Table 4). However, its efficacy is somewhat lower, while adverse effects tend to occur more frequently among children and adolescents with ASD compared to children with idiopathic ADHD (RUPPAN, 2005). In contrast to the 75% responders to MPH among children with idiopathic ADHD, only 50%-60% of children with ASD and hyperactivity respond to MPH, with a mean 20-25% symptom reduction in parent and teacher ratings compared to the average 50% improvement observed in ADHD (Scahill and Pachler, 2007). Furthermore, hyperactivity-impulsivity tends to respond more than inattention (Table 4, Suppl. Table S10). Also age may play a role, since children with ASD seemingly respond better than adolescents and adults, although ADHD co-morbid with HF autism in adults has been shown to positively respond to MPH in many cases (Joshi et al., 2019). Overall, there is much greater variability in clinical response in ASD comorbid with ADHD compared with pure ADHD (Table 4, Suppl. Table S10). This wide range of response to methylphenidate on the one hand likely reflects the greater neurobiological heterogeneity of ASD compared to idiopathic ADHD, on the other hand it may also depend on genetic background, especially on monoaminergic gene variants (McCracken et al., 2014). Improvement in some specific components of social cognition, like joint attention and emotional self-regulation, has been recorded, but in general core autism symptoms do not seem to benefit significantly from psychostimulant treatment. Also improvement in oppositional behaviors is highly variable (Table 4, Suppl. Table S10).

Among the seven RCTs published to date (Table 4), the RUPPAN study (RUPPAN, 2005) is certainly the largest, involving 72 children with ASD or PDD NOS, aged 5-14 years, randomized to a double-blind cross-over design. Significant improvements were recorded using the ABC-hyperactivity subscale, as 49% of participants responded to all dose increments, with greatest benefits achieved at medium and high doses (0.625 and 1.25 mg/kg/d, respectively). Using SNAP-IV and CY-BOCS, the improvement in hyperactivity/impulsivity and inattention was confirmed, without significant worsening of repetitive behaviors or oppositional-defiant behaviors (Posey et al., 2007). Other studies analyzing the same sample described improved joint attention and emotional self-regulation (Jahromi et al., 2009) and reduced parent-target problems (Scahill et al., 2017), extending the initial results and confirming the greater efficacy of 0.625 and 1.25 mg/kg/d over the 0.31 mg/kg/d dose. The most common adverse effects were irritability, appetite loss, insomnia, and emotional outbursts, resulting in the withdrawal of 13/72 (18%) children (RUPPAN, 2005). Furthermore, 16/66 (24.2%) participants did not tolerate the highest MPH dose (Posey et al., 2007). Four other RCTs (Quintana et al., 1995; Handen et al., 2000; Ghuman et al., 2009; Pearson et al., 2013) and several OL/CR studies involving IR-MPH have provided similar results, both in terms of 50-60% response rates and 20-30% of withdrawal due to side effects (Table 4, Suppl. Table S10). Response rates may be somewhat higher using ER-MPH (Pearson et al., 2013; Kim et al., 2017). An interesting observation by Di Martino et al. (2004) suggests that a single acute effective dose of IR-MPH may suffice in discriminating patients who will suffer from MPH-induced hyperactivity, stereotypies, dysphoria, and motor tics, as recorded in 5/13 (38.5%) of their patients. The association between low IQ and increased risk of paradoxical activation with MPH is widespread in clinical practice, but somewhat controversial in the Literature, with some studies reporting lower response rates and more side effects in children with intellectual disabilities compared to nomal-IQ children (Aman et al., 2003), while other studies find no correlation (Simonoff et al., 2013). Finally, several interesting case reports describe MPH efficacy on rare ASD comorbidities, including narcolepsy and chronic pain, as well as rare adverse reactions, like trichotillomania, oral dyskinesias, as well as behavioral signs of MPH withdrawal (Suppl. Table S10).

Atomoxetine (ATX) is a selective dopamine and norepinephrine reuptake inhibitor, approved for the treatment of ADHD both in children and adolescent and adults. Three RCTs and several open-label/chart review studies have been published to date (Table 4, Suppl. Table S10). The first RCT, involving 16 ASD children and adolescents for 3 weeks, reported greater efficacy on hyperactivity-impulsivity than on inattention (Arnold et al., 2006). One large RCT involved 97 ASD children and adolescents with ADHD symptoms (Harfterkamp et al., 2012), including 88 patients who underwent an open-label follow-up for 28 additional weeks (Harfterkamp et al., 2013). ATX was found to improve hyperactivity-impulsivity after the initial 2-3 weeks of treatment (i.e. ATX has a slower onset of therapeutic action compared to MPH). Also inattention responded, but with an even longer latency. Improvements were recorded also in stereotyped behaviors, inappropriate speech and fear of change (i.e., rigid adherence to routines). Positive drug effects were sustained over the 28-week follow-up period. Side effects were usually tolerable and included nausea, decreased appetite, fatigue and early morning awakenings; especially nausea and fatigue tended to decrease with continued ATX administration. A third large RCT involved 128 children and adolescents who were randomized according to a 2 x 2 design involving ATX and parent training (PT). The combination of ATX+PT and ATX alone were superior to PT+placebo and placebo alone in improving ADHD symptoms (Handen et al., 2015). However. ATX+PT required a lower mean drug dose compared to ATX alone (Handen et al., 2015). The therapeutic effects were sustained over 1.5 years of follow-up, but only 1/3 of children were still taking ATX, while 27% passed to a stimulant and 13% to an α2 agonist (Arnold et al., 2018). This high spontaneous drug discontinuation rate over time was explained as due to either side effects or partial satisfaction with the drug. Adverse effects, including gastrointestinal symptoms, irritability, tinnitus, mood swings and sedation, were generally transient and/or

Table 4
The "present" pharmacology of ASD: randomized placebo-controlled trials (RCT) of psychostimulants and ADHD drugs, with related follow-up open label (OL) extensions and secondary analyses in the pediatric ASD population.

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
Methylphenidate	Aman et al. (1993)	RCT, crossover, MPH vs FEN vs PLA, 4 wks each	28	5-13	MPH: 0.4 mg/kg/d FEN 1.5 mg/kg/d	Neuropsychological testing and examiner ratings	FEN>PLA in memory test; MPH decreased/FEN increased reaction time; MPH=FEN>PLA both decreased hyperactivity and inattention, and improved mood.	None reported
	Quintana et al. (1995)	RCT, crossover	10	7-11	MPH 10/20 mg vs PLA b.i.d.	CARS, ABC, CTRS, CPRS	Improvement in hyperactivity and irritability.	Lack of appetite (20%, insomnia (5%) and irritability (4%) only at 20 mg b.i.d.
	Handen et al. (2000)	RCT, crossover	13	5-11	0.3 mg/kg vs 0.6 mg/kg vs PLA either b.i.d. or t.i.d., each for 7 days.	ABC, CTS, IOWA-CTRS CARS	Reduced hyperactivity, stereotypies and inappropriate speech. Responders: 8/13 (61.5%).	Social withdrawal and irritability especially at 0.6 mg/kg. Discontinuation in 3/13 (23.1%) due to crying, tantrums, aggression and skin picking.
	RUPPAN (2005)	RCT, crossover, 4 wks	72	5-14	7.5-50 mg/d divided t.i.d. (by weight 0.31, 0.625, 1.25 mg/kg/d)	CGI, ABC-hyperactivity, SNAP-IV, CYBOCS-PDD.	Improved hyperactivity (49% responder).	13/72 (18%) withdrawn due to adverse effects, including irritability, decreased appetite, insomnia, emotional outbursts. 6/72 (8.3%) did not stand MPH and 16/66=24.2% of participants did not tolerate the highest dose.
	Posey et al. (2007)		66	5-14			Improved hyperactivity and impulsivity, less improved inattention, no effect on RRBs and ODD.	
	Jahromi et al. (2009)		34	5-13		JAMES, CCI tasks		
	Scahill et al. (2017)		66	5-14		PTPs, CGI-S/I, ABC	Improved joint attention and self-regulation. Reduced parent-target problems especially with the mid and high dose	
	Ghuman et al. (2009)	RCT	10	3-5	5-20 mg/d	CPRS-R,CGAS, NCBRF-parent, CGI-S/I	Improved ADHD symptoms in 7/10 children.	Increased stereotypic behavior, upset stomach, sleep-related difficulties, emotional lability.
	Pearson et al. (2013) Pearson et al. (2020)	RCT crossover, 4 wks	24	7-12	ER MPH: 10-40 mg a.m.+ IR MPH: 2-5-10 mg p.m. (PLA vs low vs mid vs high dose by wt)	SNAPIV, ABC, ACTeRS, CGI, VAS, CPRS-R, CTRS-R Neuropsychological testing	Improved hyperactivity, impulsivity, and emotional liability (parents & teachers); inattention, oppositional behavior and social skills (parents only) Dose-dependent increase in selective and sustained attention, and decrease in impulsivity.	Loss of appetite and sleeping problems at higher doses.
Methylphenidate ER	Kim et al. (2017)	RDT, 6 wks	27	5-17	ER MPH: 20 vs 40 mg/d; no PLA.	CGI-I, ABC, ADHD-RS, HALP sleep questionnaire.	Decreased hyperactivity, irritability, lethargy, stereotypy and inappropriate speech with 40 mg/d, but not with 20 mg/d.	Greater aggressiveness, irritability and rebound at end of day with 40 mg/d more than with 20 mg/d.
Atomoxetine	Arnold et al. (2006)	RCT crossover, 3 wks	16	5-15	0.25-1.4 mg/kg/d (20-100 mg/d, mean 44.2±21.9 mg/d).	CGI-S/I, ABC, DSM-IV rating scale	Improved hyperactivity-impulsivity more than inattention	Mild transient stomach ache (5), nausea (5), fatigue (5), tachycardia (3). Serious recurrent violence needing rehospitalization (1).
	Harfterkamp et al. (2012, 2014) Harfterkamp et al. (2013, 2015), van der Meer et al. (2013)	RCT, 8 wks OL ext., 20 wks	97 88	6-17	0.5 mg/kg/d wk 1, 0.8 mg/kg/d wk 2, 1.2 mg/kg/d from wk 3 onward.	ADHD-RS, CTRS-R:S, ABC, CGI-I, CSBQ	Improved hyperactivity/impulsivity and inattention, which requires longer treatment to improve. No beneficial effects on ODD and social functioning, but may ameliorate RRBs, fear of change and	Mild nausea, decreased appetite, fatigue, early-morning awakening. Side effects tend to decrease with prolongued use.

(*continued on next page*)

Table 4 (*continued*)

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
							communication. Improved response inhibition, but not interference control. Improvement is sustained up to 20 wks.	
	CHARTS: Handen et al. (2015) Tumuluru et al. (2017) Hollway et al. (2018) Lecavalier et al. (2018) Smith et al. (2016) Arnold et al. (2018)	RCT, 10 wks +/- parent training OL extension to wk 24 OL extension to wk 78 (1.5 yrs)	128 54 128 117 94	5-14	Starting dose: 0.3 mg/kg/d Target dose: 1.2 mg/kg/d Maximum dose: 1.8 mg/kg/d	SNAP-IV, HSQ, SSQ, SOAP, CGI, cognitive test, CSHQ, PSI-SF	ATX alone and ATX+parent training were equally superior to placebo alone and to placebo+parent training in decreasing ADHD symptoms, irritability and disruptive behavior. Also parental stress decreases in responders. After 1.5 yrs improvement is largely sustained, but only 1/3 have continued taking ATX, while 27% passed to a stimulant and 13% to an α2 agonist. Response to ATX not modulated byCYP2D6 metabolizer status.	Fatigue, decreased appetite, mood lability. ATX is sleep-neutral: it does not produce sleep disturbances.
Amantadine	King et al. (2001)	RCT, 4 wks	39	5-19	2.5 mg/kg/d wk1 5.0 mg/kg/d b.i.d. wks 2-4	ABC-CV, CGI-I	Reduced hyperactivity and inappropriate speech according to clinician ratings (parent ratings do not reach significance).	Insomnia (4), somnolence (2).
	Mohammadi et al. (2013)	RCT, 10 wks add-on to RIS	40	4-12	AMA:100 or 150 mg/d by wt RIS: 1-2 mg/d	ABC-C, CGI-I	Reduced hyperactivity and irritability in children receiving AMA as add-on to RIS, vs PLA+RIS. No change in stereotypic behaviors, inappropriate speech and lethargy/social withdrawal.	No difference between AMA and PLA.
Clonidine	Fankhauser et al. (1992)	RCT, crossover, 4 wks	9	5-33	0.16-0.48 mg/d (transdermal)	RF-RLRS, CGI	Improving impulsivity, hyperarousal, self-stimulating behavior	Sedation, hypertension, fatigue (first 2 weeks), decreased activity
	Jaselskis et al. (1992)	RCT, crossover, 13 wks	8	5-11	0.15-0.20 mg/d	CPRS, CGI, ABC, CGAS	Modestly effective in the short-term treatment of irritability and hyperactivity	Increased drowsiness, decreased activity
Guanfacine	Handen et al. (2008)	RCT, crossover, 6 wks	11	5-9	1-3 mg/d	CGI-I, ABC-hyperactivity	Reduced hyperactivity. Responders: 5/11 (45%).	Sedation, irritability, enuresis,diarrhea, constipation, social withdrawal.
	RUPPAN Scahill et al. (2015)	RCT, 16 wks	62	5-14	1-4 mg/d ER (mode 3 mg/d)	ABC-hyperactivity, ADHDRS-IV, CGI-S/I, cognitive tests	Reduced hyperactivity and inattention, stereotypic behavior and inappropriate speech.	Sedation, fatigue, decreased appetite, dry mouth, emotional/tearful presentation, irritability, anxiety, hypotension.
	Politte et al. (2018)					HSQ-ASD, CASI, CSHQ, CYBOCS-ASD	Responders: 15/30 (50%). Reduced opposition and repetitive behaviors. No change in anxiety and sleep.	

tolerable (Table 4). Occasional serious adverse events with ATX, such as recurrent violence needing rehospitalization, were reported in other studies (Arnold et al., 2006). Most RCT and open-label/chart review studies administered dosages usually ranging from 1.2 to 1.4 mg/kg/d (Table 4). ATX was not associated with sleep disturbance in most (Hollway et al., 2018) though not all studies (Troost et al., 2006). Rare adverse events include Raynaud's phenomenon (Gülle et al., 2019) and a hypertensive crisis (Guldiken and Karayagmurlu, 2020).

Clonidine is a selective α2 adrenergic and imidazoline receptor agonist, approved by the FDA in 2010 for the treatment of ADHD in pediatric patients starting at the age of 6 years. This drug has been reported to be efficacious in treating ASD children with hyperactivity, hyperarousal, self stimulating behavior, aggressiveness, mood instability and irritability, according to two small RCTs (Jaselskis et al., 1992; Fankhauser et al., 1992), two open-label/chart review studies and several CRs (Table 4, Suppl. Table S10). Clonidine taken in the evening

may also be beneficial for sleep quality and to control nighttime awakenings (Ming et al., 2008). Dosage in most studies ranges from 0.1 to 0.2 mg/day and side effects include transient sedation and fatigue, hypotension, rarely hypertension, major depression with increased irritability and self-injurious behavior (Table 4, Suppl. Table S10).

Guanfacine was found to be well tolerated and especially effective on hyperactivity and inattention in two RCTs, two open-label/chart review studies and several CRs (Table 4 and Suppl. Table S10). Initially, a retrospective chart review of 80 ASD children and adolescents reported improvements in hyperactivity, inattention, insomnia and tics (Posey et al., 2004). An OL trial conducted on 25 ASD children who did not respond or did not tolerate MPH, found 12 (48%) of them to respond well to guanfacine (Scahill et al., 2006). The possible efficacy of this drug in improving hyperactivity and inattention in ASD children was then definitively proven by two RCTs, confirming 45%-50% response rates in 11 and 62 autistic children with comorbid ADHD, respectively (Handen et al., 2008; Scahill et al., 2015). Also stereotypic behaviors, inappropriate speech, and opposition displayed some improvement in the larger study (Scahill et al., 2015; Politte et al., 2018). Dosages raged between 0.25 and 9 mg/d, with 2-3 mg/d in divided doses as the most frequent dosing schedule. Side effects, usually transient or dose-dependent, included irritability, sedation, fatigue, sleep disturbance, constipation, headache and nocturnal enuresis (Table 4, Suppl. Table S10).

Amantadine increases dopamine in the synaptic cleft by stimulating its synthesis and release, while inhibiting dopamine reuptake; it also acts as a noncompetitive NMDA antagonist and nicotinic receptor antagonist. Two RCTs have assessed amantadine effects in ASD (Table 4). King et al. (2001) found a 4-week course of amantadine somewhat effective in reducing hyperactivity and inappropriate speech in 39 autistic children and adolescents, but only based on clinician ratings, whereas parent ratings did not reach statistical significance. Instead, a 10-week RCT assessing the effects of amantadine administered as add-on to 1-2 mg/d of risperidone demonstrated a measurable improvement in hyperactivity and irritability with the active compound compared to placebo (Mohammadi et al., 2013). Collectively, these studies suggest that the beneficial effects of amantadine may be real but relatively modest, possibly making this drug more appropriate for polypharmacy than for single-drug interventions.

4. Discussion

In this first review, we systematically searched for all published contributions concerning the past and the present of psychopharmacological interventions in ASD. In the past, for over two decades behavioral symptoms were treated with FGAs, TCAs, naltrexone and some mood stabilizers (mainly valproic acid and carbamazepine). Prescription of these drugs at the time represented the spontaneous extension of adult psychopharmacology targeting other psychiatric disorders onto pediatric ASD. For example, clomipramine was already well known to ameliorate anxiety and obsessive-compulsive behaviors; other TCAs, such as desipramine, imipramine, nortriptyline, amitriptyline, as well as the dopamine reuptake blocker bupropion, are still used as second-line therapies to treat depression or symptoms of Attention Deficit/Hyperactivity Disorder (ADHD) like inattention, impulsivity and hyperactivity in the non-autistic population. However, the administration of TCAs to treat these same symptoms in individuals with autism yielded variable clinical response and several side effects, whose frequency and occasional severity have limited their use (Peretti et al., 2000; Hurwitz et al., 2012). Similarly, some antipsychotics have proven very useful for autistic children with prominent hyperactivity, impulsivity, agitation, temper outbursts or aggression towards self or others. Often, once these behaviors were reduced, children could make better use of behavioral and educational interventions. However, drug sensitivity and side effect profiles were soon found to differ between children and adults, and between patients with schizophrenia and those with ASD, clearly indicating that "children are not small adults" and that the neurobiology of ASD and schizophrenia are sufficiently distinct to require very different starting doses and drug titration rates. Indeed, the frequently cited "overlap" between ASD and schizophrenia is primarly genetic (Kushima et al., 2018; Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017) and does not translate in an overlap in clinical and pharmacological management, which remains quite distinct.

The currently available second-generation psychopharmacology of ASD, involving SGAs, SSRIs, SNRIs, newer mood stabilizers and psychostimulants, partly suffers from similar limitations, but with some differences. In particular, starting in the mid-Nineties, the medical community began to perceive the need for preliminary testing of drug efficacy and safety specifically in pediatric age cohorts, before psychoactive drugs routinely prescribed to adults could also be prescribed to children and adolescents. This enhanced attention to the specificities of the pediatric population, paired with the exponential growth of the prevalence of ASD and of social interest in this disorder, have catalyzed a wealth of studies performed on pediatric cohorts of children diagnosed with autism according to DSM-IV or DSM-5 criteria (Table 2-4 and Suppl. Tables S6-S10). These studies have demonstrated that some atypical antipsychotics may be superior to neuroleptics, at least in terms of their perceived side effect profile. Risperidone and aripiprazole have obtained FDA indications for ASD treatment and, until now, represent the first main therapeutic options due to their relative efficacy and safety. Nonetheless, both risperidone and aripiprazole can produce side effects, especially promoting the development of a metabolic syndrome in predisposed individuals, although usually with different time courses and to a different extent. Hence potential alternatives, like loxapine and ziprasidone, well deserve to be tested in reasonably-sized RCTs targeting the pediatric ASD population. Indeed, these three drugs may benefit a subgroup of children and adolescents with aggressive behaviors, but no RCT has yet been published. Based on OL and CR studies, both their efficacy and tolerability profile seemingly displays great interindividual variability and it may be advisable to start at low doses especially with quetiapine, in order to minimize sedation and weight gain (Suppl. Table S6). Ziprasidone indeed deserves further scrutiny because, although the number of "responders" may be smaller compared to risperidone and aripiprazole, the absence of significant weight gain poses this drug as an interesting alternative to more effective SGAs, when these are either counterindicated or have been stopped due to side effects or lack of efficacy.

Naltrexone has a long track record of studies demonstrating lack of serious side effects and efficacy in a sizable minority of autistic children. It may thus well deserve a second-line therapeutic trial for drug-resistant self-injurious behavior and hyperactivity, initially prescribing a low dose (0.4-0.5 mg/kg/day) once every 2-3 days and then titrating up the dose to a daily 1.0-1.5 mg/kg/day in case of insufficient response. Unfortunately, in many countries the unavailability of liquid formulations and regulatory limitations to addictive disorders, in conjunction with the bitter taste of naltrexone tablets, may hamper its prescription to autistic children.

SSRIs and other antidepressants initially raised great expectations, but have subsequently yielded a partial disappointment, especially in reference to their lack of efficacy on RRBs consistently reported in several large-sized RCTs (Table 3). In some way, this outcome was anticipated by initial reports finding clomipramine comparable to placebo and significantly less effective than haloperidol on RRBs, irritability and hyperactivity (Remington et al., 2001). Nonetheless, some OL studies and case reports provide anecdotal and descriptive evidence of beneficial effects of SSRIs on social anxiety, obsessive-compulsive symptoms, and irritability/agitation, especially for fluoxetine and sertraline in adolescents (Suppl. Table S7). These symptom domains have been the object of a surprisingly small number of studies in pediatric cases with ASD. For example, sertraline has already been approved for use in pediatric patients with OCD starting at 6 years of age (Persico

et al., 2015). Yet, the only pediatric RCT performed to date (Potter et al., 2019) was primarily focused on expressive language, cognition and adaptive functioning, not on social anxiety, obsessive ideation, and irritability (Table 3). Furthermore, in this study unusually low doses of sertraline (2.5-5.0 mg/d) were administered, far from the 25-50 mg/d typically prescribed in clinical practice and also used in other OL and CR studies addressing pediatric ASD (compare Table 3 with Suppl. Table S7). Therefore, more research targeting symptoms other than RRBs (i.e., social anxiety, obsessive-compulsive symptoms and irritability) not only in children but also in adolescents is necessary, before SSRIs can be confidently dismissed as "ineffective in ASD" altogether. Similarly, it is not possible at this stage to conclusively evaluate the SNRI venlafaxine, because its efficacy and safety were investigated only in one OL, two CRs, and one RCT mainly involving adult ASD patients also receiving zuclopenthixol and clonazepam (Carminati et al., 2016). In general, its effects appear variable and may not largely differ from placebo. Furthermore, in the latter study, side effects, though minor, also include modest EPS signs which raise the question whether improvement, when observed, was really due to venlafaxine or to pharmacokinetic interactions raising zuclopenthixol blood levels, which were not measured (Carminati et al., 2016). Also tianeptine provided marginal, if any, evidence of efficacy on irritability and core symptoms of ASD (Niederhofer et al., 2003). Instead, mirtazapine is more consistently effective on sleep difficulties, compulsive masturbation and, to some extent, self-injurious behavior, according to several OL studies and CRs (Suppl. Table S7) and also to current clinical practice. These promising effects deserve to be conclusively demonstrated and quantified using standard RCT methodology. Also low (2.5 mg b.i.d.), but not higher doses of buspirone were proven effective on RRBs in combination with behavioral intervention (Chugani et al., 2016). These results again underscore the importance of "starting low" when dosing psychoactive drugs in pediatric cases with ASD.

Though rather popular in clinical practice, where they are frequently prescribed to ASD children for irritability and hyperactivity, traditional antiepileptic drugs, like valproic acid and carbamazepine, have yielded mixed results in RCTs and in OL studies, reporting great interindividual variability in efficacy and frequent side effects. Second-generation antiepileptics, like lamotrigine and levetiracetam, have been perhaps even more disappointing when prescribed for the control of behavioral symptoms in ASD (Table 4). Instead, positive results have been obtained in add-on protocols, whereby valproic acid was found to blunt fluoxetine-induced irritability (Anagnostou et al., 2006) and topiramate to boost the efficacy of risperidone on irritability, hyperactivity and stereotypic behaviors (Rezaei et al., 2010). This promising add-on approach may pave the path toward a more rational and synergistic use of these drugs.

In addition to newer mood stabilizers, "old" drugs like lithium have recently begun being tested in the pediatric ASD population with novel, unexpected scenarios. Preliminary reports indeed spur interest into the positive effects of lithium not only on mood symptoms, but possibly also on cognitive functions, at least in some genetic forms of intellectual disability like Phelan-McDermid syndrome (Serret et al., 2015; Egger et al., 2017).

Finally, the possibility granted by DSM-5 to diagnose also ADHD as co-morbid to ASD (American Psychiatric Association, 2013), which occurs in as many as 30-40% of autistic children (Visser et al., 2016), should prompt clinicians into treating ADHD symptoms with stimulants first. Methylphenidate is the gold standard treatment, an effective and safe drug to use in ASD, as it does not significantly worsen repetitive and oppositional-defiant behaviors, except at higher doses (i.e. >40 mg/d), nor does it increase the incidence of seizures (Posey et al., 2007). Atomoxetine represents a valid alternative (Sturman et al., 2017), which may at least partially benefit also some core ASD symptoms and executive function deficits, including stereotyped behaviors, inappropriate speech and lack of cognitive flexibility, though not social functioning altogether (Posey et al., 2006; Harfterkamp et al., 2014). Clonidine and guanfacine are additional second-line treatments endowed with evidence-based efficacy on a variety of problem behaviors (i.e., irritability, hyperactivity, hyperarousal, self-stimulating behavior, aggressiveness, mood instability, intermittent awakenings). Interestingly, about 50% of ASD children and adolescents respond to clonidine and guanfacine and these are often "non-responders" to MPH or drop-outs unable to tolerate psychostimulant side effects (Table 4). Evidence regarding the efficacy of other selective NRI or SNRI antidepressants, like reboxetine and duloxetine, respectively, is presently inconclusive (Suppl. Tab. S7), as RCTs are lacking. Some (Aman et al., 2003), though not all studies (Simonoff et al., 2013), support preferential use of atypical antipsychotics over stimulants in children with intellectual disability, which may be especially prone to developing irritability and aggressiveness with MPH: to what extent this also applies to low-functioning ASD remains to be determined. Indeed the efficacy of MPH is less stricking in comorbid ASD-ADHD compared to "pure" ADHD, so the many second-line drugs discussed above remain useful alternatives. Future studies will also have to test the validity of prescribing stimulants in add-on with an atypical antipsychotic, as seen at times in clinical practice to enhance efficacy and counterbalance SGAs' effect on body weight. Also amantadine seemingly exerts positive effects on hyperactivity and irritability, especially when administered add-on to 1-2 mg/d risperidone (Mohammadi et al., 2013) and a similar add-on effect has been described for buspirone (Ghanizadeh and Ayoobzadehshirazi, 2015). In general, polypharmacy is quite common in clinical practice, especially with LF-ASD cases, but a structured and evidence-based approach to polypharmacy remains a distant target and any attempt to test drug combinations using a controlled add-on RCT design should be encouraged.

5. Conclusions

The psychopharmacology of ASD represents a great medical challenge. This systematic survey of the existing Literature shall now be followed by another systematic search of published articles and ongoing projects listed in the "Clinical Trials.gov" web-site, regarding future, innovative, experimental and/or novel pharmacological treatments of ASD. These two systematic contributions, organized "by drug", shall be followed by a third and conclusive article, aimed to provide an overview of available pharmacological options "by symptom". The overarching aim of our effort is to help clinicians personalize the pharmacological therapies of their autistic patients, basing their prescription as much as possible on currently available scientific evidence, also considering that the vast majority of prescriptions of psychoactive drugs in child and adolescent neuropsychiatry occurs off-label (Persico et al., 2015; Sharma et al., 2016). The tremendous interindividual differences in ASD pathogenesis, clinical presentation and treatment response clearly imply that only evidence-based and individually tailored pharmacological therapies hold a real promise to improve the quality of life of autistic patients and of their family members.

Author's contributions

AMP, BV and CA designed the study. AMP, AR, ML, LT, FC and CB extracted the data, AMP and AR performed quality control. AMP, ML and CB drafted the manuscript. BV and CA revised the manuscript. All authors read and approved the final version of this manuscript.

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Declaration of Competing Interest

In the last two years, Dr. Vitiello was paid consultant for Medice Pharmaceuticals, Lundbeck Pharmaceuticals, Alkermes Co., and law-firms Goodwin & Procter, Haynes & Boone. Dr. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. The remaining authors have no financial or personal interest to declare.

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Appendix A. Supplementary data

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Auditory time thresholds in the range of milliseconds but not seconds are impaired in ADHD

Giovanni Anobile[1], Mariaelisa Bartoli[2], Chiara Pfanner[2], Gabriele Masi[2], Giovanni Cioni[2,3] & Francesca Tinelli[2]✉

The literature on time perception in individuals with ADHD is extensive but inconsistent, probably reflecting the use of different tasks and performances indexes. A sample of 40 children/adolescents (20 with ADHD, 20 neurotypical) was engaged in two identical psychophysical tasks measuring auditory time thresholds in the milliseconds (0.25–1 s) and seconds (0.75–3 s) ranges. Results showed a severe impairment in ADHD for milliseconds thresholds (Log10BF = 1.9). The deficit remained strong even when non-verbal IQ was regressed out and correlation with age suggests a developmental delay. In the seconds range, thresholds were indistinguishable between the two groups (Log10BF = – 0.5) and not correlated with milliseconds thresholds. Our results largely confirm previous evidence suggesting partially separate mechanisms for time perception in the ranges of milliseconds and seconds. Moreover, since the evidence suggests that time perception of milliseconds stimuli might load relatively less on cognitive control and working memory, compared to longer durations, the current results are consistent with a pure timing deficit in individuals with ADHD.

According to current diagnostic systems (DSM-5), attention deficit hyperactivity disorder (ADHD) is defined by pervasive and severe symptoms of inattention, hyperactivity, and impulsivity that have a direct negative impact on social, academic, or occupational functioning. ADHD children often show deficits in planning, organization and in executive functions, such as response inhibition, interference control, reasoning, hindsight, anticipation and working memory set-shifting[1].

Along with these deficits, findings suggest perceptual disfunctions related to time processing. Time perception in ADHD has been widely investigated but the results are mixed, probably reflecting the many different methods and performance parameters. Measures of time processing includes accuracy (how far from the target) and/or precision (response variability) measured by motor reproduction, verbal estimation, discrimination, and odd-ball tasks. Moreover, time processing has been investigated across different timing ranges (from a few milliseconds to several seconds) and across sensory modalities[2]. Even if the literature and the clinical practice indicate an impaired time processing in ADHD, the highly heterogeneous results make it difficult to draw firm conclusions.

A meta-analysis considering 27 studies on ADHD children and adolescents found a significant timing deficit in ADHD with impairments in both accuracy and precision and across visual and auditory stimuli[3]. Another recent meta-analysis considering 12 studies, despite generally confirming a time deficit in ADHD, suggested that there was a stronger effect size for tasks involving relatively long intervals (5 s) and for specific tasks such as estimation and reproduction[4]. An example of how the task and the timing range could affect the results comes from the study conducted by Smith et al.[5]. The authors measured time discrimination thresholds in a sample of ADHD children by asking participants to indicate which one of two audio-visual stimuli, ranging around 1 s, lasted longer. Results revealed higher thresholds (lower precision) in children with ADHD. In contrast, no group differences were found when time processing was measured with a reproduction task or with a verbal estimation task with longer (5 s–10 s) stimuli. Toplak and Tannock[6] also measured duration discrimination thresholds in a sample of ADHD adolescents for visual and auditory stimuli and for both short (around 200 ms) and longer (around 1 s) intervals. Results confirmed higher thresholds compared to controls, but across all the tasks. Similar impairments across vision and audition were later obtained by Rubia et al.[7] with younger ADHD children and

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by Dölek et al.[8] with adults. Plummer and Humphrey[9] measured ADHD children's timing performance with a motor reproduction task. Children were asked to reproduce, by key press, the duration of visual, auditory, or audio-visual stimuli ranging from 1 to 60 s. Results showed higher errors in ADHD across all the conditions. Radonovich and Mostofsky[10] measured ADHD duration discrimination thresholds for short (around 0.5 s) and longer (around 4 s) auditory stimuli. At odds with some of the previous studies, the results showed no deficits for the shorter stimuli but poorer performance for longer intervals. Gooch et al.[11] measured auditory time discrimination thresholds in ADHD by asking children to detect which of three sounds was different in duration (odd-one-out task) with stimuli ranging from 400 ms to 1 s. The results revealed higher thresholds (lower precision) in children with ADHD, compared to controls. The same results were obtained with a motor reproduction task for longer visual stimuli (from 2 to 10 s). Barkley[12] measured time perception with a verbal estimation and a reproduction task testing the same visual stimuli, lasting from 2 to 60 s. The results revealed poorer time perception (accuracy) for the reproduction, but not for the estimation, task. Two independent studies employing similar visual time intervals found the same pattern of results[13,14].

Interestingly, psychophysical and pharmacological studies indicate that the perception of relatively long stimuli requires and loads on cognitive control as well as working memory, while relatively shorter intervals (< 1 s) might be automatically processed and targeting a "pure" sense of time[15–17]. A more recent study using imaging techniques showed that although there are many brain areas encoding both short (milliseconds) and longer (seconds) durations, short durations elicit relatively more activation in the parietal cortex[18]. The authors suggest that this higher activation reflects a higher involvement of attentional resources when encoding short stimuli. However, the distinction between the use or non-use of attentional control as a function of stimulus duration is not clear-cut and there is also evidence for the involvement of cognitive resources in intervals in the millisecond range, leaving this issue largely open[19].

Overall, these and many other investigations suggest a time processing deficit in people with ADHD, with potentially relevant clinical and practical implications[20]. However, given the heterogeneity of results, further investigation is needed. To this aim, 20 children/adolescents with ADHD were engaged in a testing protocol in which we psychophysically measured auditory time thresholds in the milliseconds (0.5 s) and seconds (1.5 s) ranges. To avoid methodological confounds, the same psychophysical technique (categorization task, see methods) was used for both timing ranges. The performance on these tasks was compared to those obtained from 20 age-matched neurotypical controls. As many studies have found time perception deficits in children and adolescents with ADHD, we expected higher thresholds, on at least one of the timing ranges tested here. As perception of short stimuli has been suggested to depend relatively less on cognitive control and working memory, compared to longer durations, a specific deficit for short stimuli would suggest a pure time deficit.

Materials and methods

Participants. Forty children/adolescents participated in this study: 20 with ADHD (6 female, 14 males, mean age = 11.2 year old, age range 8–16) and 20 neurotypical (11 female, 9 males, mean = 11.2 year old, range 8.1–16.2). Individuals with ADHD were enrolled from the Stella Maris Foundation Institute in Pisa, a main center for ADHD care in Italy. ADHD inclusion criteria were: clinical diagnosis of ADHD based on DSM-5, a total intelligence quotient (TIQ), evaluated with the Wechsler Intelligence Scale for Children-IV[21] above 75, no neurological or sensory deficits, no psychiatric comorbidities, no current or past pharmacological treatment. Three children with ADHD met the criteria for a diagnosis of developmental dyslexia. Non-verbal reasoning skills were computed by a combined index of WISC-IV measuring Visual Perceptual Reasoning (IRP). The IQ of four ADHD participants was measured by an external independent institute and, for those participants, we were unable to calculate IRP. ADHD symptoms were measured by Conners Rating Scale (parent version). General clinical symptoms were measured by the Clinical Global Impression—Severity scale (CGI) and the Children Global Assessment Scale (CGAS). Detailed information about the group with ADHD is reported in Table 1.

The participants with ADHD were compared to a neurotypical group of age matched children/adolescents. The inclusion criteria for the control group were: no medical history, negative neuro-psychiatric exam and no learning difficulties (reported by parents) and IQ (evaluated with by Raven Colored Progressive Matrix-CPM or Progressive Matrix-PM, depending on chronological age) > 5° percentile. The study was approved by the Ethics Committee of the Meyer's Hospital (n. 248/2020 ID-DNATN "Attention, Time and Numeracy in children and adolescents with neurodevelopmental disorders"). Informed parental consent was obtained for each participant before the study. All experiments were performed in accordance with relevant guidelines and regulation.

Time perception. Time sensory thresholds were psychophysically measured with an auditory categorization task (Fig. 1A). On each trial, children listened to a single sound (500 Hz, 80 dB pure tone) and were asked to categorize it as "long" or "short". Before the testing phase, four initial "anchoring" trials were provided; the lower and longer time durations were played twice each and the children were told that those sounds corresponded to the range extremes (no responses were required). In separate sessions (lasting around 4 min each), we measured two different timing regimes, one centered (geometric mean) around 0.5 s containing stimuli in the milliseconds range (from 0.25 s to 1 s, milliseconds hereafter), and one centered (geometric mean) around 1.5 with most of the stimuli belonging to the seconds range (from 0.75 to 3 s, seconds hereafter). Each time range was divided into 11 equal steps spanning 1 octave above and one below the geometric mean of that specific range. The stimuli in the 1.5 s distribution were: 0.75, 0.86, 1, 1.13, 1.3, 1.5, 1.72, 1.98, 2.27, 2.61, 3 s. The stimuli in the 0.5 s distribution were: 0.25, 0.28, 0.33, 0.38, 0.43, 0.5, 0.57, 0.66, 0.75, 0.87, 1 s. In a single session, each duration was tested 4 times (randomly selected trial-by-trail) for a total of 44 trials for each range. Participants responded verbally ("long" or "short"), without any time pressure and the response was registered by the administrator with an appropriate key press. The proportion of "long" responses were plotted against the stimuli duration (in log scale)

Participants	Sex	Age	TIQ	IRP z-score	Subtype	CGI-S	CGAS	C1	C2	C3	C4
1	M	15 years 6 months	103	1.13	1	3	60–51	n.a	n.a	n.a	n.a
2	F	9 years 6 months	90	− 0.73	1	2	70–61	45	60	52	65
3	F	12 years 3 months	88	− 1.2	3	2	70–61	42	68	51	67
4	M	9 years 3 months	94	− 0.4	3	4	50–41	77	73	63	80
5	M	14 years 11 months	97	− 1.2	3 + dd	4	50–41	77	75	61	75
6	M	13 years 3 months	125	n.a	3	2	70–61	55	49	35	56
7	M	10 years 5 months	114	n.a	1	2	60–51	74	70	70	72
8	M	8 years 4 months	91	− 0.13	3	4	60–51	78	75	70	80
9	M	11 years	110	n.a	3	5	50–41	71	75	80	80
10	M	9 years 1 months	114	1.26	3	4	60–51	80	75	63	80
11	M	12 years 6 months	88	n.a	3	2	70–61	60	53	57	65
12	F	11 years 1 months	98	− 1.2	3	4	50–41	n.a	n.a	n.a	n.a
13	M	11 years 1 months	100	0	3	3	60–51	55	50	47	61
14	F	9 years 8 months	105	− 0.13	3	3	60–51	45	56	52	63
15	F	12 years 1 months	92	0.13	3 + dd	4	60–51	n.a	n.a	n.a	n.a
16	M	11 years 9 months	77	− 1	1	3	70–61	70	100	56	100
17	M	12 years 6 months	101	− 1.2	3	6	60–51	n.a	n.a	n.a	n.a
18	M	11 years 6 months	102	0.4	1	6	60–51	64	63	61	66
19	M	8 years 7 months	107	0.73	3	5	50–41	64	66	70	n.a
20	F	10 years	96	1.13	3 + dd	6	60–51	49	39	48	13

Table1. Descriptive characteristics of the ADHD group. *TIQ* Total Intelligence Quotient from WISC-IV, *IRP z-score* Visual Perceptual Reasoning from WISC-IV; *Subtype* 1 inattentive, 3 combined; *dd* developmental dyslexia, *CGI* Clinical Global Impression – Severity scale, *CGAS* Children Global Assessment Scale, *C1* Conners parents oppositivity, *C2* Conners parents inattanetion, *C3* Conners parents hyperactivity, *C4* Conners parents ADHD index, *n.a.* not available.

and fitted with a cumulative Gaussian error function. The 50% point of the fit provided an estimate of the point of subjective equality (PSE). The difference in duration between the 50% and 75% points gives the just notable difference (JND), which was used to estimate Weber Fractions (10^JND-1), a dimension free index of sensory precision.

Data analysis. Data were analyzed by Repeated Measures Analyses of Variance (RM-ANOVA), Analysis of covariance (ANCOVA), t-test and Pearson correlations and α values corrected for multiple comparisons when necessary (Bonferroni correction). Frequentist statistics were supplemented with Bayesian statistics, calculating Bayes Factors, the ratio of the likelihood of the alternative to the null hypothesis, and reporting them as base ten logarithms (Log10 Bayes Factors, LBF). For RM-ANOVA and ANCOVA with report $LBF_{inclusion}$ indicating how much the data are likely to occur from a model including that specific factor (or interaction), compared to models not including them. By convention, LBF > 0.5 is considered substantial evidence in favour of the alternative hypothesis (difference between groups in this case) and LBF < − 0.5 substantial evidence for the null hypothesis (no difference). Absolute values greater than 1 are considered strong evidence, and those greater than 2 as definitive evidence.

To make the ADHD Visual Perceptual Reasoning (IRP) index comparable to the non-verbal reasoning skills measured by Raven matrices on the control group, the indexes were both converted into z-scores (according to the normative age-standardized data provided by the tests manuals). For technical reasons we did not collect data for two participants (one control and one ADHD) in the seconds timing task. Missing data were left empty and excluded analysis by analysis. Effects sizes were reported as Cohen-d and η^2. Data were analyzed by JASP (Version 0.8.6), SPSS (Version 25) and R (Version 4.0.2) software.

Results

Demographical data. The ADHD and control groups did not differ in age ($t_{(38)} = 0.035$, $p = 0.97$, $d = 0.011$, $LBF = -0.52$) and male/female ratio ($X^2 = 0.93$, $p = 0.33$). Non-verbal reasoning skills were slightly lower in the group with ADHD ($t_{(32)} = 1.8$, $p = 0.083$, $d = 0.6$, $LBF = 0$).

Groups difference on time perception sensory precision. All participants were well able to perform the psychophysical timing task (depicted in Fig. 1A) producing ordered psychometric functions. Figure 1B,C shows psychometric functions obtained aggregating all the data together across participants. It is evident, even by inspection, that for the task measuring time perception in the milliseconds range (B), the psychometric function of the control participants (black) was steeper than that produced by the sample with ADHD (red). This difference indicates less precision (higher thresholds, Weber Fractions) in individuals with ADHD. Regarding

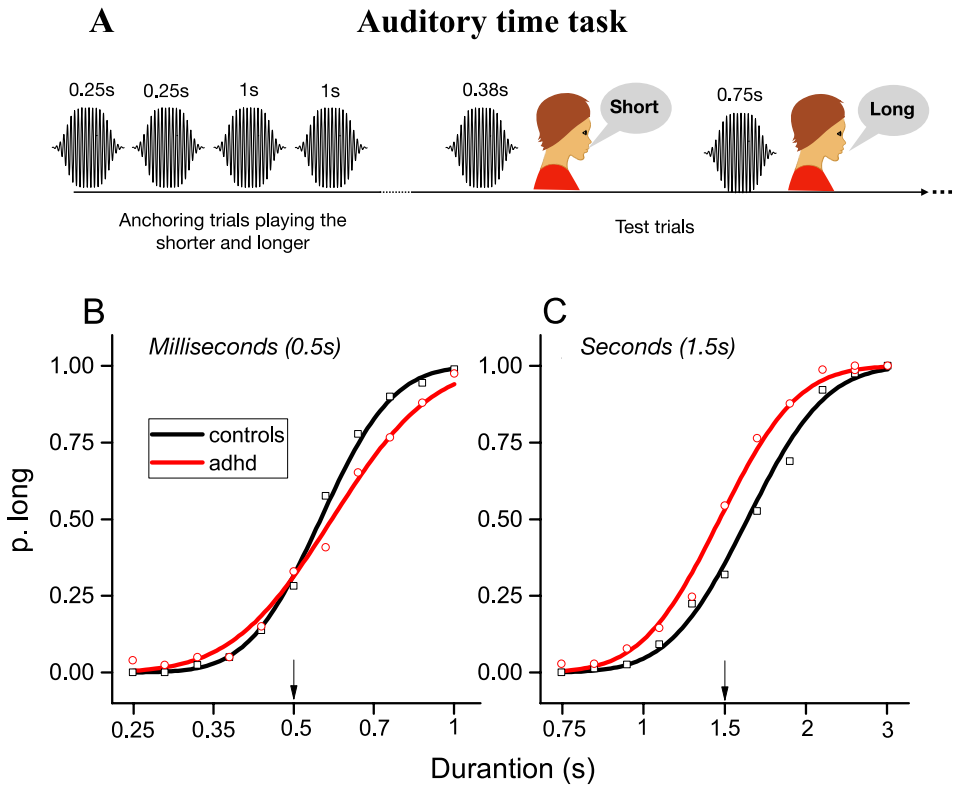

Figure 1. (**A**) A block consisted of four initial "anchoring" trials in which the shorter (0.25 s or 0.75 s depending on the condition) and the longer (1 s or 3 s depending on the condition) stimuli were presented (participants were told that those sounds correspond to the range extremes). After this phase, the testing phase started, and participants were asked to categorize as "long or short" a sound randomly drawn from a pre-defined distribution. (**B**,**C**) Psychometric functions (aggregate data) for controls (black, squares) and participants with ADHD (red, circles) for the milliseconds (**B**) and seconds (**C**) ranges.

Tasks	Groups	N	Mean (SD)	p-value	Cohen's d	LBF
Time milliseconds range (0.5 s)	ADHD	20	0.23 (0.1)	< 0.001***	1.26	1.9
	Controls	20	0.12 (0.05)			
Time seconds range (1.5 s)	ADHD	19	0.15 (0.07)	0.79	0.08	−0.5
	Controls	19	0.14 (0.06)			

Table 2. Descriptive Statistics on time thresholds (Weber Fraction). Two tailed t-tests, α Bonferroni corrected 0.05/2 = 0.025.

the seconds range (C) the psychometric functions have similar slopes between groups, indicating similar sensory precision levels.

The fitting procedure was applied to the data provided by each participant (see Table 2 for descriptive statistics). Figure 2 reports between participants average thresholds (Weber Fractions, Wf) separately for the two perceptual tasks, while single subject data are reported in Fig. 2B,C. From visual inspection, it is evident that only the time perceptual thresholds measured for short (0.5 s) auditory stimuli were impaired in participants with ADHD, with a clear interaction between tasks and groups.

A RM ANOVA with task (2 levels: Wf 0.5, Wf 1.5) as repeated measures factor and group (2 levels: ADHD, controls) as between participants factor, revealed a significant effect of task ($F_{(1,36)} = 7.38$, $p = 0.01$, $\eta^2 = 0.12$, $LBF_{incl} = 2.31$), suggesting different thresholds across tasks. Crucially the task*group interaction was highly statistically significant ($F_{(1,36)} = 18.04$, $p < 0.001$, $\eta^2 = 0.29$, $LBF_{incl} = 2.59$) indicating that the groups performed differently across the tasks. Post-hoc analyses confirmed that time thresholds for milliseconds (0.5 s) stimuli were higher in the ADHD group compared to controls ($t_{(38)} = 3.98$, $p < 0.001$, $d = 1.26$, $LBF = 1.9$). On this task, ADHD thresholds were, on average, almost double compared to controls (Wf = 0.23 and 0.12 for ADHD and controls respectively), indicating a severe impairment. Time thresholds for seconds (1.5 s) stimuli ($t_{(36)} = 0.26$, $p = 0.79$, $d = 0.08$, $LBF = -0.5$) were statistically indistinguishable between the groups.

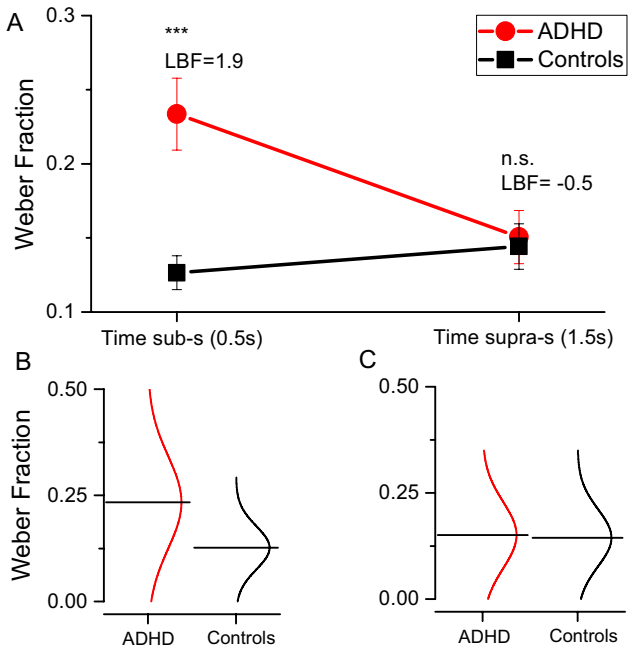

Figure 2. (**A**) Between participants average time thresholds divided by the two groups (ADHD: red circles and Controls: black squares). Error bars are standard errors of the mean; ***$p < 0.001$; n.s. not statistically different. (**B**–**D**) Individual data reporting time thresholds distributions. Horizontal lines report data average.

To explore the specificity of the impairment found for the time perception task in the milliseconds range, we ran a separate ANCOVA with time thresholds as the dependent variable, groups (ADHD, controls) as the fixed factor and age, non-verbal reasoning, and sex as covariates. Even when partialling out the effect of these covariates, the result remained unchanged with a significant effect of the group ($F_{(1,29)} = 20.11$, $p < 0.001$, $\eta^2 = 0.33$, $LBF_{incl} = 2.78$).

To check the discriminant power of the milliseconds auditory time thresholds, we ran a linear discriminant analysis with the group as the dependent variable and time thresholds (0.5 s Wf) as independent variable. The results revealed 72.5% of cases correctly classified. The sensitivity was 60% while specificity was 85%. As a sanity check, the same analysis on seconds stimuli thresholds (Wf) provides a near to chance level (53%) classification.

Developmental trajectories. To investigate whether the deficit was stable across the age range, we studied the developmental trajectories. Time thresholds for seconds stimuli had a similar and not significant dependency with age across both groups (ADHD: $r = -0.43$, $p = 0.062$, $LBF = 0.15$, controls: $r = -0.42$, $p = 0.068$, $LBF = 0.12$), suggesting that both were near to a developmental plateau. The developmental trajectories of time thresholds in the milliseconds range were, in contrast, different between the groups. While the controls had reached an almost full developmental stage ($r = -0.34$, $p = 0.14$, $LBF = -0.11$), the age dependence for participants with ADHD was steeper ($r = -0.62$, $p = 0.003$, $LBF = 1.2$), suggesting a different developmental trend (Fig. 3). Confirming partially independent mechanisms, regressing out age, thresholds for milliseconds and seconds stimuli were not correlated with each other (ADHD: $r_{partial} = 0.367$, $p = 0.134$, $LBF = 0.09$; controls: $r_{partial} = 0.287$, $p = 0.25$, $LBF = -0.07$).

Correlations with clinical symptoms. Within the sample with ADHD, we ran correlations and between time thresholds (milliseconds and seconds) and both general (CGI, CGAS, see Table 1) and specific clinical symptoms (the four parents Conners indexes, see Table 1 for details). For the CGAS test, which provides range scores, we transformed the ranges into categorical values reflecting the symptoms severity (following the test manual: from 1 to 10 with one indicating no symptoms and 10 indicating very severe symptoms). The analyses revealed no meaningful correlations (all $p > 0.05$, min $LBF = -0.55$, max $LBF = 0.3$).

Perceptual task reliability. It is theoretically possible that the different pattern of results provided by the two time tasks results from different reliability levels. To test this possibility, we measured and compared the reliability of the two psychophysical tasks. Following previous studies[22], we used a "sample-with-replacement" bootstrap technique[23]. For each participant, we calculated two separate thresholds in each task (0.5 s or 1.5 s), using a random sample of the data (44 trials, sampled with replacement), and then computed the correlation between those two measures, across participants. The process was reiterated 1,000 times. We found that mean correlations for milliseconds (0.5 s) and seconds (1.5 s) stimuli were very similar (Pearson's $r = 0.68$, $r = 0.64$, respectively) and not statistically different (bootstrap sign-test $p = 0.4$). This last control rules out the possibility that the different pattern of results was generated by different reliability levels.

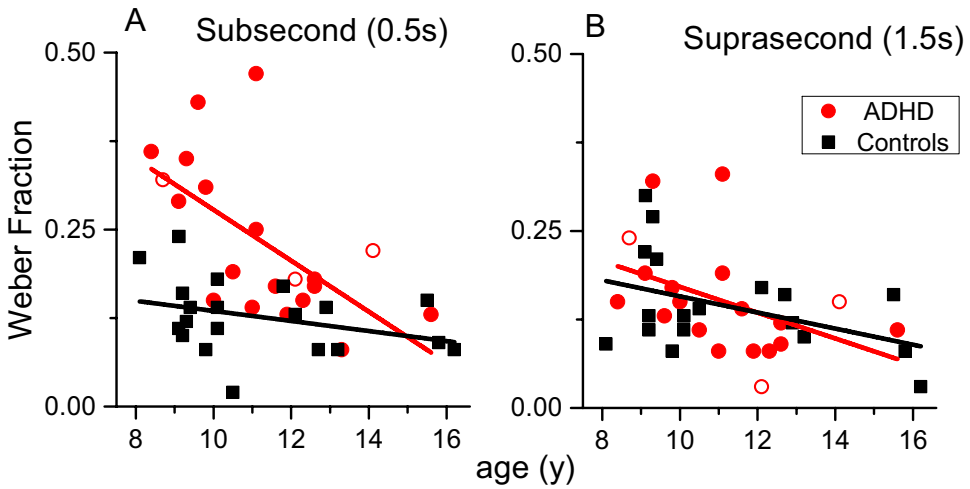

Figure 3. Auditory time thresholds for stimuli in the milliseconds (**A**) and seconds (**B**) ranges as a function of age divided by the two groups (ADHD: red filled circles, ADHD + dyslexia: red open circles, Controls: black squares).

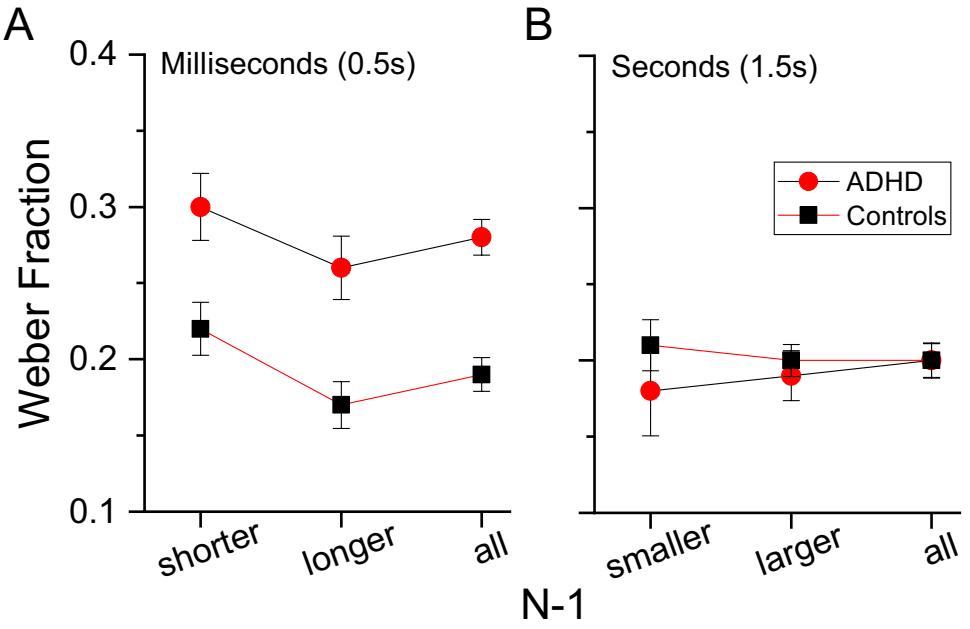

Figure 4. Auditory time thresholds for stimuli in the milliseconds (**A**) and seconds (**B**) ranges measured on all trials (all) or on data sorted as a function of the preceding stimulus duration (N-1) that could be shorter or longer compared to the stimulus judged in the current trial.

Contextual effects. The paradigm used to measure time thresholds requires the ability to perceive both the stimuli mean and range extremes of the set. The group with ADHD could have had excessive contextual effects, which would have inflated thresholds. To check for this possibility, we measured (on aggregate data) the PSEs and thresholds as a function of the magnitude of the preceding stimulus (N-1). To this aim, separately for the two groups and the two tasks, we sorted the aggregated data into two categories in which the preceding stimulus (N-1) was shorter or longer than the stimulus tested in the current trial. The data were then fitted by psychometric functions providing PSEs and thresholds (Weber fraction). The analyses releveled very small effects on PSEs for both groups (ADHD 1.5 s = shorter 1.4 s, longer 1.5 s; ADHD 0.5 s = shorter 0.56 s, longer 0.61 s; controls 1.5 s = shorter 1.6 s, longer 1.6 s; controls 0.5 s = shorter 0.55 s, longer 0.56 s), suggesting similar contextual effects. More importantly, for both subdivisions (shorter, longer), the difference between groups for thresholds in the milliseconds condition remained evident and constant (Fig. 4) confirming similar contextual effects.

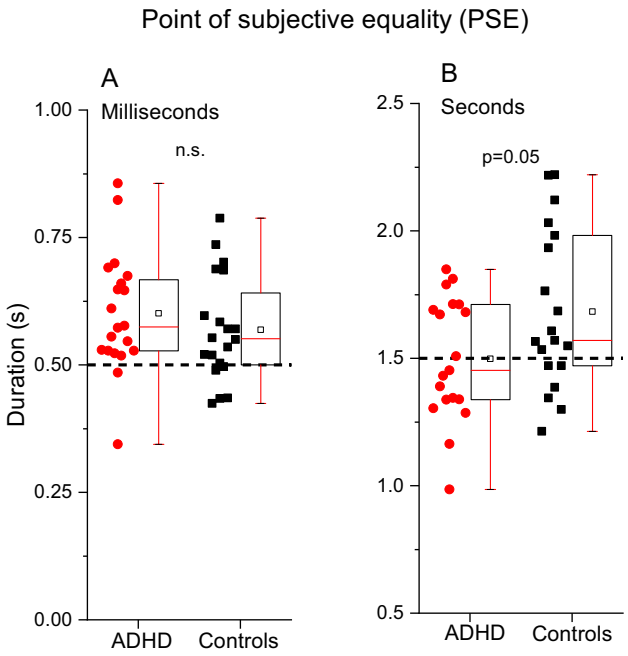

Figure 5. Box plots reporting point of subjective equality (PSEs) for the auditory time task in the millisecond (**A**) and seconds (**B**) ranges for the two groups of participants. Dotted lines report the physical value of the reference stimuli (0.5 s and 1.5 s). Symbols within the boxes reports median (line) and mean (open square) values.

Tasks	Groups	N	Mean (SD)	p-value	Cohen's d
Time milliseconds range (reference: 0.5 s)	ADHD	19	0.6 (0.12)	0.37	0.28
	Controls	19	0.57 (0.1)		
Time seconds range (reference: 1.5 s)	ADHD	20	1.49 (0.24)	0.05	0.66
	Controls	20	1.68 (0.31)		

Table 3. Descriptive statistics: point of subjective equality (PSEs). Two tailed t-tests, α Bonferroni corrected 0.05/2 = 0.025.

Time perception accuracy. After exploring the differences between groups in terms of sensory precision, we then analyzed estimations accuracy (PSE: Point of Subjective Equality, see Fig. 5 and Table 3). A RM ANOVA with task (PSEs time 0.5 s, PSEs time 1.5 s) as repeated measures factor and group (ADHD, controls) as between participants factor revealed an obvious significant effect of task ($F_{(2,36)} = 420.7$, $p < 0.01$, $\eta^2 = 0.91$) suggesting that PSEs change as a function of the task. Importantly, the task*group interaction was statistically significant ($F_{(2,36)} = 5.03$, $p = 0.031$, $\eta^2 = 0.01$) indicating that the groups performed differently across the tasks. The between factor "group" was not statistically significant ($F_{(1,36)} = 2.3$, $p = 0.13$, $\eta^2 = 0.06$) suggesting that, on average, the two groups performed similarly. To explore the interaction, we ran a series of post-hoc t-tests (α Bonferroni corrected = 0.025). In the range of milliseconds, the analysis revealed no differences between groups ($t(38) = 0.91$, $p = 0.37$, Cohen's $d = 0.28$). In the range of seconds the group with ADHD, compared to the controls, showed a tendency to overestimate durations ($t(36) = 2.03$, $p = 0.05$, Cohen's $d = 0.65$).

Discussion

We found that children/adolescents with ADHD, compared to neurotypicals, had a severe sensory precision deficit in perceiving auditory stimuli in the milliseconds range (0.25-1 s). Time thresholds for relatively longer stimuli (0.75-3 s) were unimpaired. Thresholds did not correlate between each other, and only thresholds for milliseconds durations showed a different developmental trajectory between groups, suggesting a developmental delay in participants with ADHD. Two control analyses ruled out the possibility that the pattern of results was driven by different tasks reliability levels and different use of contextual effects between groups. Consistent with previous studies[24], time processing abnormalities were equally reported in the various presentations of ADHD.

Time is not a unitary concept but encompasses many measurement scales, from a few milliseconds to several days. Even if there is not a defined boundary classifying a duration as "short" or "long", one of the most classic distinctions is that between milliseconds and seconds stimuli. Clear dissociations have been previously found

by pharmacological studies. Rammsayer et al.[25] found that administering ethanol impaired auditory temporal discrimination thresholds for long (1 s) but not shorter (50 ms) intervals. A similar pharmacological dissociation was later found by Rammsayer[17] showing that auditory temporal processing of long durations (1 s) was significantly impaired by administration of haloperiodol (a dopamine receptor antagonist) and midazolam (benzodiazepine), whereas processing of extremely brief intervals (50 ms) was only affected by haloperidol. The authors suggested that temporal processing of longer intervals is mediated by working-memory functions, while temporal processing of intervals in the range of milliseconds is more dependent on the effective level of dopaminergic activity in the basal ganglia. Psychophysical experiments also supported this differentiation. For example, it has been demonstrated that increasing cognitive load by dual-task procedures deteriorates discrimination thresholds for relatively long (1 s), but not short (50 ms) auditory stimuli, suggesting that the encoding of longer intervals requires cognitive control and working memory, while relatively shorter intervals are automatically processed[15,16]. However, is worth mentioning that the link between time perception and cognition remains poorly understood and there is also evidence challenging whether or not cognitive control and working memory play a role merely based on stimulus length. For example, Holm et al.[19] found that task cognitive and working memory loads both worsened repetitive motor timing (tapping) for durations in the millisecond range, more than in the seconds range. By a factor analyses approach Rammsayer et al. demonstrated that, while the model assuming two mechanisms underlying the processing of intervals in the seconds and the milliseconds ranges might be more appropriate, these two mechanisms are functionally overlapped, sharing 77% common variance[26]. Moreover, imaging studies suggest that, in addition to the duration of the stimuli, other factors such as the use of movement to define a temporal estimate and the continuity and predictability of the task may influence the engagement of different timing mechanisms, making the picture more complex than previously thought[27].

By showing a specific impairment of auditory time thresholds for relatively short (0.5 s) but not longer (1.5 s) intervals in ADHD, the current results fit well with the idea of different mechanisms for those regimes. The null correlation between thresholds across the two-timing regimes is also consistent with this hypothesis. Given that ADHD is often associated with deficits in cognitive control and working memory, it seems counterintuitive that timing thresholds for automatic, but not those under cognitive control, were impaired in our sample with ADHD, suggesting a pure time perception deficit. Leaving aside whether or not cognitive resources are engaged depending on the duration of the stimuli, an issue that has not been directly tested here, the current results (together with much previous evidence) are difficult to explain, suggesting a unique system for timing perception.

It is worth noting that our results are opposite to those found by Radonovich et al.[10]. In that study the authors measured auditory discrimination thresholds in controls and in children/adolescents with ADHD with short (550 ms) and longer (4 s) intervals and their results demonstrated worse thresholds for long but not short intervals. Although we do not have a definitive explanation to account for this difference, the different tasks could, even partially, account for that. The paradigm used by Radonovich et al. presented two pairs of tones, one with fixed delay and the other with variable delays, and participants were asked to report whether the second delay was shorter or longer than the first. Our paradigm required the presentation and categorization of a single tone. We find it reasonable to speculate that the Radonovich et al. task, compared to the task used here, would charge relatively more additional resources such as working memory and/or attention, which may account for the different pattern of results.

Regarding brain areas involved in the perception of milliseconds and seconds intervals, the literature, despite suggesting different networks, is not definitive. Mangles et al.[28] compared auditory time discrimination thresholds between controls and patients with focal lesions in the frontal cortex or in the cerebellum. The results indicate that frontal lesions impaired timing thresholds for long (4 s) but not short (0.4 s) intervals, while cerebellar lesions impaired both. Harrington et al.[29], however, cast doubts on the involvement of the cerebellum in the auditory time perception of milliseconds intervals (0.3 s, 0.6 s), with patients with cerebellar lesions showing similar thresholds compared to controls. On the other hand, cerebellar lesions have been demonstrated to have detrimental effects on visual time thresholds for longer (8–21 s) stimuli[30]. As mentioned before, basal ganglia have also been found to play a role in time perception. Gouvêa et al.[31] trained rats to categorize sounds as belonging to a long or short category. Animals made few errors when categorizing the shortest and longest intervals (the extremes), but performance become worse for intervals near to the 1.5 s categorical boundary (range: 0.6–2.4 s). Recording from populations of single striatal neurons, the authors found cells firing at different times within the interval period, suggesting the existence of short and long preferring neurons. The causal role of striatal neurons was also demonstrated by injecting muscimol. As a result, the duration thresholds worsened significantly, compared to the control group injected with saline. The parietal cortex has also been shown to play a critical role in time perception[32–35]. Hayashi et al.[36] correlated time discrimination thresholds measured in a sample of neurotypical adults, with gray matter (GM) volume in different parts of cortical and subcortical areas. Results showed that GM volume in the cerebellum but not in the parietal cortex correlated with milliseconds stimuli thresholds whilst, contrarily, GM volume in the parietal cortex but not in the cerebellum correlated with seconds stimuli thresholds. Moreover (as in the current study) threshold for milliseconds and seconds stimuli did not correlate with each other. In the same line, a meta-analysis of imaging studies also suggests that the parietal cortex, compared to the cerebellum, is more likely activated by seconds stimuli[27]. With the current psychophysical data, we cannot say much about the brain networks involved in milliseconds and seconds timing, but our findings are largely in line with the idea that those two functions engage distinct neural mechanisms.

Another interesting point emerges from the current results. The analysis of developmental trajectories (Fig. 3A) suggests that, rather than a generalized deficit across all ages, there could be a developmental delay for milliseconds thresholds in ADHD. Despite having few participants in the higher age range, the results seem to suggest that above 12/13 years old, the difference between groups would gradually decrease. Future studies might replicate this finding and expand the age range to quantitatively define the magnitude of such a possible developmental delay.

Together with a sensory precision deficit, the existing literature has also shown that people with ADHD are more likely, compared to neurotypicals, to commit overestimation errors, suggesting a faster "internal clock"[37,38]. Our results are in line with this idea. In the task testing durations in the seconds range, participants with ADHD provided more "long" judgements compared to controls, leading to a leftward shift of the psychometric curve. This bias indicates a duration overestimation, probably arising from a faster internal clock. In the task testing durations in the milliseconds range, there was no difference between groups, reinforcing the idea of partially independent mechanisms for short (ms) and longer (secs) intervals and replicating previous evidence[37].

Conclusions

A precise timing perception in the millisecond scale is crucial in perceiving and acting on the continuously changing environment. It has been suggested that this ability is automatic and allows complex human behaviours including speech perception and speech performance, music, driving, and many sports. The results of this study showed that children and adolescents with ADHD have a severe precision (thresholds) deficit in the duration perception of milliseconds (around 0.5 s) auditory stimuli. Time perception for relatively longer and more cognitively controlled stimuli was unimpaired. Although, with the current results, we cannot explain why the temporal perception of short stimuli is impaired in our sample with ADHD, it is surprising how such a simple and fast (4-min) psychophysical test succeeds in differentiating the two groups (LBF = 1.9). Moreover, while timing thresholds had a relatively low sensitivity power (60%), they turned out to have a good specificity (85%) level and were able to correctly classify 72.5% of cases. Finally, the timing thresholds deficit was resistant to the statistical controls of general but important covariates such as age, sex and non-verbal IQ, promoting it as a potential easy-to-administer tool for future studies. A better comprehension of time perception abnormalities in ADHD may give new insights in the neurological bases of the disorder. Furthermore, it may have relevant diagnostic and treatment implications. Understanding the functional consequences of these specific deficits in everyday life, in combination with other ADHD symptoms (i.e. impulsivity), may help to focus interventions on more specific goals, improving the clinical care of youth with ADHD. Moreover, as ADHD and autism might represent a continuum, sharing many pathophysiological features[39], it would be interesting and potentially relevant to test whether both clinical conditions also share a similar pattern of deficits in time perception.

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Additional information

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La psicosi e i disturbi psicotici nei bambini e negli adolescenti

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Avere sintomi psicotici non equivale ad avere un disturbo psicotico. Molto spesso i sintomi sono transitori e privi di impatto sul funzionamento; altre volte sono indicativi di forme secondarie (encefaliti autoimmuni, uso di sostanze) o parte di altre problematiche come i disturbi dell'umore. Ma è anche vero che può esserci un esordio schizofrenico già in epoca adolescenziale che richiede un alto indice di sospetto. L'articolo riporta in modo semplice e allo stesso tempo approfondito quelle che sono le evidenze disponibili, passo dopo passo. Una cultura e una pratica che devono essere sempre più parte delle conoscenze (anche) del pediatra.

PSYCHOSIS AND PSYCHOTIC SYMPTOMS IN CHILDREN AND ADOLESCENTS
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Key words
Psychosis, schizophrenia, children, adolescents

Summary
Psychosis can present a variety of symptoms such as hallucinations, delusions, catatonia, thought and speech disorganization, alogia, avolition and general functional decline. Transient psychotic symptoms are not uncommon during development and are not always indicative of psychopathology. Psychosis can be a manifestation of a schizophrenia spectrum disorder, or occur in the context of a mood disorder, such as major depression or bipolar mania. It can also be due to substance abuse or certain medical conditions, such as the NMDA encephalitis. Most cases of schizophrenia start between 15 and 25 years of age, while an onset under age 13 is rare. Schizophrenia tends to have an insidious onset with many months of subsyndromal and non-specific symptoms prior to the first openly psychotic episode. Repeated use of cannabis in youth increases the risk of psychosis, since the developing brain is especially sensitive to the psychoactive effects of tetrahydrocannabinol. As the duration of untreated psychosis predicts worse functional outcomes over time, a prompt recognition and early treatment of psychotic disorders has high clinical relevance. To this end, a close collaboration between paediatricians and child and adolescent neuropsychiatrists is crucial.

Il termine psicosi si riferisce a una grave compromissione del funzionamento del pensiero che altera l'esame di realtà della persona, cioè la capacità di distinguere ciò che è reale da ciò che non lo è. I sintomi principali caratteristici della psicosi includono i **deliri**, che consistono di convinzioni contrarie alla realtà, non condivise dal gruppo sociale e mantenute malgrado le evidenze che chiaramente le contraddicono, e le **allucinazioni**, che sono percezioni sensoriali false, come il sentire voci o avere visioni, esperite in assenza di stimoli ambientali reali. Questi sono solo i sintomi psicotici più eclatanti (anche detti **sintomi positivi**), che, nel caso di disturbo psicotico dello spettro schizofrenico, si inseriscono in un quadro clinico complesso che comprende anche **sintomi negativi** di tipo affettivo (affettività piatta o incongruente, anedonia, povertà di linguaggio, blocco del pensiero), disorganizzazione comportamentale con deficit funzionali (ad esempio, scarsa igiene personale) e, alle volte, anomalie di postura e movimento[1].

È importante sottolineare che la presenza di sintomi psicotici isolati o durante un periodo limitato (quello che viene chiamato un episodio psicotico) non indica necessariamente la presenza di un disturbo psicotico. Tuttavia, sembra esserci un'associazione tra sintomi psicotici in infanzia e adolescenza e il rischio di sviluppare successivamente un disturbo psicotico o altre forme di psicopatologia[2,3]. Sintomi psicotici possono anche essere infatti presenti in altre condizioni, come ad esempio nelle fasi depressive o maniacali dei disturbi dell'umore, o possono essere dovuti ad abuso di sostanze o condizioni mediche[4]. Risulta quindi molto importante valutare attentamente il quadro clinico di bambini e adolescenti con questi sintomi al fine di porre una diagnosi accurata, che è fondamentale per guidare correttamente il trattamento e migliorare l'esito funzionale.

L'eziopatogenesi dei disturbi psicotici è complessa e multifattoriale e, in accordo con il modello biopsicosociale dei disturbi mentali, comprende fattori di tipo genetico che interagiscono con fattori di tipo ambientale e sociale[5].

Il pediatra è spesso il primo professionista medico a entrare in contatto con bambini e adolescenti che presentano sintomi psicotici. In generale, l'identificazione e l'interpretazione della sintomatologia psicotica in età pediatrica è più complessa che nell'adulto, in quanto i sintomi sono spesso riportati con più difficoltà dal paziente e dalla famiglia e possono essere ascritti ad altre condizioni mediche o di sviluppo confondenti. Non meraviglia quindi che passino spesso molti mesi, e a volte anni, tra l'insorgenza dei primi segni di psicosi e la diagnosi di disturbo psicotico. L'inizio del trattamento antipsicotico è pertanto spesso ritardato. È stato rilevato che la prognosi a distanza è tanto peggiore quanto più lungo è il periodo di psicosi non trattata[6]. Per questo, la pronta identificazione del disturbo psicotico è di notevole rilevanza clinica. Fondamentale è pertanto instaurare una collaborazione tra il pediatra e i Servizi di Neuropsichiatria infantile a cui inviare tempestivamente il bambino o il ragazzo per svolgere appropriati approfondimenti diagnostici[7].

1. EPIDEMIOLOGIA

I sintomi psicotici sono relativamente comuni in età pediatrica, con una frequenza maggiore nei bambini rispetto agli adolescenti. Si stima che circa il 17% dei bambini di età compresa tra i 9 e i 12 anni e il 7,5% degli adolescenti tra i 13 e i 18 anni abbia avuto isolati sintomi psicotici, di solito transitori e privi di significativo impatto sul funzionamento[8]. Molto meno frequente, ma ben più grave, è il disturbo psicotico dello spettro schizofrenico. La schizofrenia che esordisce prima dei 18 anni viene considerata schizofrenia a esordio precoce (*Early Onset Schizophrenia* o EOS). Se si manifesta al di sotto dei 13 anni, viene considerata schizofrenia a esordio molto precoce (*Very-Early Onset Schizophrenia* o VEOS). Nella popolazione generale la prevalenza della schizofrenia è tra lo 0,3% e lo 0,7%[1]. Si stima che circa il 12% dei casi di schizofrenia insorga prima dei 18 anni, e il 3% prima dei 14 anni[9].

Nonostante una diagnosi di schizofrenia sia meno frequente in età pediatrica che nell'età adulta, la VEOS e la EOS tendono a essere più gravi e disabilitanti rispetto alla schizofrenia che esordisce nell'adulto[10]. Tipicamente, il primo episodio psicotico (*First Episode Psychosis* o FEP) consiste in una crisi acuta con sintomi psicotici floridi (deliri, allucinazioni, agitazione psicomotoria, comportamento bizzarro) della durata almeno di 4 settimane e una fase di recupero nei 6-12 mesi successivi[11]. Il picco di esordio del primo episodio psicotico si colloca tipicamente tra i 15 e i 25 anni[12]. Circa l'11-19% dei pazienti con FEP e il 23-25% dei soggetti ad alto rischio clinico per psicosi hanno sperimentato i primi sintomi psicotici attenuati prima dei 13 anni[13]. I disturbi psicotici rappresentano la terza causa di disabilità funzionale nei giovani di età compresa tra i 10 e i 24 anni[14]. Risulta quindi fondamentale identificare precocemente le persone ad alto rischio clinico per la psicosi e attivare strategie di prevenzione e trattamento precoce[15].

3. SINTOMI PSICOTICI

I sintomi psicotici vengono tradizionalmente suddivisi in tre principali categorie: **a)** i sintomi positivi, **b)** negativi e **c)** disorganizzati[16]. Ci possono essere anomalie del comportamento motorio, come la catatonia con immobilità, posture bizzarre, o peculiarità della deambulazione[1]. Inoltre, i soggetti con disturbi psicotici spesso presentano sintomi cognitivi e comportamentali che influenzano il funzionamento adattivo nella vita quotidiana[17,18]. I sintomi positivi sono considerati più specifici dei sintomi negativi, disorganizzati e cognitivi, che quindi sono più difficili da interpretare in quanto non caratteristici della psicosi e presenti anche in altri disturbi, come ad esempio la depressione maggiore. I sintomi positivi sono quelli che hanno una risposta migliore al trattamento farmacologico, che invece ha impatto più modesto sui sintomi negativi e cognitivi.

La gamma di sintomi che possono condurre a una diagnosi di disturbo dello spettro della schizofrenia è molto ampia, e ciascun soggetto può manifestare un suo quadro clinico particolare. È importante ricordare che la sola presenza di alcuni sintomi psicotici in bambini e adolescenti non è necessariamente indice della presenza di un disturbo psicotico, per il quale devono essere soddisfatti una serie di criteri diagnostici specificati dall'attuale nosologia psichiatrica, che fa in genere riferimento al *Diagnostic and Statistical Manual of Mental Disorders* attualmente alla 5ª edizione (DSM-5)[1]. Devono essere escluse altre possibili diagnosi differenziali e condizioni mediche.

3.1. Sintomi positivi

I sintomi positivi vengono denominati in questo modo in quanto sintomi inusuali caratterizzati da eccessi e distorsioni che sono assenti nel soggetto non psicotico. Essi comprendono:

Deliri - I deliri sono convinzioni false e contrarie alla realtà, che implicano delle interpretazioni e deduzioni errate relative alla realtà esterna, non condivise dal contesto socioculturale del soggetto e che vengono mantenute malgrado le evidenze che le contraddicono. Il DMS-5 classifica i deliri come *bizzarri*, se convinzioni assolutamente non plausibili e non riconducibili alle comuni esperienze di vita e al contesto culturale, e come *non bizzarri*, se invece in parte plausibili[1]. Un esempio di delirio bizzarro può essere la convinzione che una persona estranea abbia rimosso i propri organi vitali sostituendoli con gli organi di qualcun altro. Inoltre, i deliri possono essere distinti e classificati sulla base del loro contenuto nelle seguenti categorie principali[1,7]:

- *di persecuzione:* convinzione di essere il bersaglio di attacchi ostili da altri o vittima di un complotto;
- *di riferimento:* interpretazione errata di eventi o comportamenti altrui come riferimenti rivolti a sé;
- *di grandiosità:* convinzione di essere avere una missione speciale e/o talenti straordinari che non sono giustificati e chiaramente sproporzionati alla realtà;

- *di gelosia:* convinzione che il proprio *partner* sia infedele, in assenza di prove reali;
- *di controllo:* credenza che i sentimenti e comportamenti siano controllati da forze o volontà esterne;
- *di inserzione del pensiero:* credenza che i pensieri vengano posti nella sua mente da fonti esterne come altre persone o apparecchiature;
- *erotomanico:* convinzione che una persona, generalmente sconosciuta, sia innamorata di lui/lei;
- *somatico:* convinzioni e preoccupazioni intense rispetto all'aspetto, al funzionamento del proprio corpo e alla salute.

Nei bambini e adolescenti i deliri sono tipicamente meno frequenti rispetto ad altri sintomi psicotici, come le allucinazioni, e si manifestano diversamente dall'adulto. Tendono a essere più vaghi e imprecisi, a volte difficili da distinguere dalla realtà. Difficilmente si riscontrano al di sotto dei 16 anni deliri altamente complessi e specifici come quelli di tipo persecutorio o religioso che si manifestano nell'adulto[19].

Allucinazioni - Le allucinazioni sono esperienze percettive che vengono riferite in assenza di stimoli ambientali che le giustifichino. Possono riguardare diverse modalità sensoriali, ed essere uditive, le più frequenti, o visive, olfattive o tattili[20]. Le allucinazioni uditive tipicamente possono manifestarsi come voci che commentano e impartiscono comandi e che vengono percepite come esterne e non frutto del flusso interno del pensiero. Tipicamente sono vissute come esperienze intrusive, spaventose ed estremamente sgradevoli, e interferiscono con la capacità del soggetto di prestare attenzione a quanto accade intorno a lui. Nei bambini e adolescenti spesso le allucinazioni possono essere multimodali coinvolgendo diverse modalità sensoriali contemporaneamente. I bambini spesso danno un nome alle allucinazioni personalizzandole utilizzando caratteristiche fisiche o riferimenti a fenomeni culturali. Può quindi risultare complesso distinguerle dal fenomeno degli amici immaginari, che non è usualmente patologico in età evolutiva. Le allucinazioni devono essere anche distinte dai fenomeni ipnagogici e ipnopompici, dispercezioni che si verificano, rispettivamente, nella fase di addormentamento e nella fase di risveglio dal sonno, e che non hanno significato patologico[7,19].

3.2. Sintomi negativi

I sintomi negativi sono caratterizzati da una diminuzione o perdita delle normali risposte emotive e della motivazione. Essi consistono in un insieme di deficit comportamentali che comprendono abulia, anedonia, asocialità, appiattimento dell'affettività e alogia[21]. Questi sintomi tendono a perdurare anche oltre all'episodio psicotico acuto e la loro presenza nelle manifestazioni cliniche iniziali ha un impatto importante rispetto alla prognosi, in quanto associata a esito e qualità di vita peggiori a lungo termine[22].

Abulia - L'abulia, o apatia, si manifesta come uno stato caratterizzato da una mancanza di motivazione e un'incapacità a iniziare e portare a termine attività funzionali. Bambini e ragazzi con abulia possono avere difficoltà a svolgere le normali attività quotidiane (scolastiche o domestiche), trascorrendo la maggior parte del tempo senza fare nulla di finalizzato.

Anedonia - Riduzione o assenza della capacità di sentire piacere e anticipare il piacere futuro, potenzialmente attribuibili a sottostanti deficit motivazionali o cognitivi relativi alla memoria episodica di esperienze piacevoli passate[21,23]. Di conseguenza, si verifica perdita di interesse per attività piacevoli e ritiro sociale.

Appiattimento dell'affettività - Difficoltà nella capacità di esprimere ed esteriorizzare le emozioni. Una persona con questo sintomo tipicamente può avere uno sguardo vacuo e fisso nel vuoto, una mimica del viso ridotta, un linguaggio del corpo inespressivo, e tono di voce piatto. Sembra tuttavia che in persone con schizofrenia quella a essere compromessa sia esclusivamente la capacità di esprimere esternamente le emozioni, mentre la capacità di esperire le emozioni risulta essere preservata e addirittura aumentata[24].

Asocialità - È una riduzione nell'iniziativa sociale dovuta a una diminuzione dell'interesse nello stabilire relazioni profonde con gli altri. La riduzione della motivazione al contatto sociale può essere in parte dovuta alla presenza di deliri e/o allucinazioni o a umore deflesso. Viene tipicamente considerata una delle prime manifestazioni di un esordio di schizofrenia[21].

Alogia - È una riduzione della fluidità e quantità dell'eloquio che è facilmente identificabile durante il colloquio clinico. Il linguaggio si impoverisce, con risposte telegrafiche a domande che richiederebbero una risposta verbale più elaborata[21].

3.3. Sintomi disorganizzati

Eloquio disorganizzato - Un eloquio disorganizzato riflette un disturbo formale del pensiero e consiste in un'incapacità di organizzare le idee e pianificare l'espressione verbale. Persone con questo tipo di sintomo tipicamente saltano da un argomento all'altro senza nessi associativi (deragliamento), o non riescono a rispondere in maniera appropriata e finalizzata a specifiche domande (pensiero tangenziale), fino ad arrivare a una situazione di eloquio così compromesso da risultare totalmente incomprensibile agli altri come con la cosiddetta "insalata di parole", che è un insieme di parole o frasi sconnesse e prive di qualsiasi significato[1,7]. Questo sintomo sembra essere associato a problemi nelle funzioni esecutive e nella pianificazione del discorso più che a problemi formali di linguaggio[25]. È importante notare che nella psicosi queste manifestazioni rappresentano un sostanziale cambiamento dal precedente funzionamento del paziente e sono pertanto da distinguersi dalle difficoltà del pensiero e del linguaggio che si riscontrano nella disabilità intellettiva e nei disturbi del neurosviluppo.

Comportamento disorganizzato - È una compromissione nella capacità di organizzare ed eseguire comportamenti finalizzati a uno scopo specifico. Comporta difficoltà a svolgere attività quotidiane. Si possono verificare comportamenti infantili, inappropriati alla fase di sviluppo, non conformi al contesto sociale, alle volte chiaramente bizzarri, come abbigliarsi in modo inusuale. Ci possono essere episodi di agitazione.

3.4. Sintomi motori

Possono essere presenti anche delle anomalie del comportamento motorio e un comportamento psicomotorio grossolanamente disorganizzato, come la catatonia.

Catatonia - Comprende una gamma di diversi comportamenti e alterazioni motorie, tra cui: *stupor* (assenza di attività psicomotoria e reattività all'ambiente), *catalessia* (induzione passiva di una postura mantenuta contro la gravità), *mutismo* (assenza di risposte verbali), *flessibilità cerea* (mantenimento di posture inconsuete indotte da altri per lunghi periodi di tempo), *negativismo* (nessuna risposta a istruzioni), *manierismo* (caricature stravaganti di azioni normali), *stereotipie* (movimenti ripetitivi afinalistici), *agitazione*, *ecolalia* ed *ecoprassia* (imitazione dell'eloquio e dei movimenti altrui)[1,7]. La catatonia non è specifica dei disturbi psicotici e può essere presente anche in altre condizioni, come nel disturbo dello spettro autistico e negli episodi depressivi.

3.5. Sintomi cognitivi

Disturbi cognitivi sono spesso presenti nei disturbi psicotici e sono predittivi degli associati deficit funzionali[17,18,26,27]. Tra le funzioni compromesse vi sono:

- L'*attenzione*: nella psicosi ci sono difficoltà a focalizzare l'attenzione (attenzione selettiva) e nel mantenerla per lungo tempo (attenzione sostenuta).
- Le *funzioni esecutive*, che regolano e modulano i processi cognitivi e il comportamento. Si possono notare deficit della memoria temporanea di lavoro *(working memory)* e delle capacità di pianificazione e di risoluzione dei problemi. Queste difficoltà iniziano a manifestarsi tipicamente in concomitanza con il primo episodio psicotico e tendono a persistere.
- La *velocità di elaborazione delle informazioni*, con conseguente rallentamento dei processi cognitivi.
- Le capacità di apprendimento e di *memoria verbale a lungo termine* sono spesso compromesse nel disturbo psicotico. Difficoltà di memoria si manifestano ancora prima dell'esordio della psicosi, persistono anche dopo la stabilizzazione clinica e hanno un impatto negativo importante sul funzionamento quotidiano.
- La *cognizione sociale*, che include l'abilità di processamento, memorizzazione e analisi delle informazioni provenienti dalle altre persone e situazioni sociali. Ci possono essere difficoltà a riconoscere le espressioni emotive degli altri, a comprendere le intenzioni e gli stati mentali altrui e a mostrare empatia[27]. Questi deficit contribuiscono significativamente alle difficoltà nelle interazioni socio-relazionali che sono tipiche del disturbo psicotico.

Le caratteristiche dei principali sintomi psicotici sono riportate nella *Tabella I*.

ALCUNE CARATTERISTICHE DEI SINTOMI PSICOTICI IN ETÀ PEDIATRICA

Sintomo	Manifestazioni
Deliri	Il contenuto è spesso vago e poco elaborato
Allucinazioni	Spesso anche visive e tattili oltre che uditive
Disorganizzazione del linguaggio	Può essere difficile distinguerlo da quello di disturbo dello sviluppo
Comportamento disorganizzato	Può esporre il ragazzo a rischi di vario genere e richiede aumentata supervisione dalla famiglia
Sintomi negativi	Possono essere confusi con depressione o comportamento oppositivo
Frequenti comorbidità	Disturbo dello spettro autistico Disturbo di inattenzione/iperattività (ADHD) Disturbo oppositivo e provocatorio Disturbi d'ansia Disturbo depressivo

Tabella I

4. DISTURBI PSICOTICI

L'esordio acuto del disturbo psicotico con agitazione e comportamento chiaramente anormale è di solito preceduto da un lungo periodo, di diversi mesi e a volte anni, di sintomi sottosoglia o non specifici, come ritiro sociale, deterioramento del funzionamento a scuola e trascuratezza dell'igiene personale. Questa fase, detta *prodromica* o *ad alto rischio psicotico*, è difficile da riconoscere data la sua non specificità, e non sfocia inevitabilmente in psicosi conclamata. Uno studio longitudinale multicentrico (*North American Prodrome Longitudinal Study* - NAPLS) ha cercato di descrivere i meccanismi della conversione in disturbi psicotici in soggetti con rischio clinico che presentavano alcuni sintomi psicotici. In una valutazione di follow-up dopo 2 anni e mezzo dalla presentazione dei primi sintomi, circa un terzo dei soggetti a rischio clinico ha sviluppato successivamente un disturbo psicotico vero e proprio, mentre un altro terzo ha mostrato una remissione dei sintomi e il restante terzo ha continuato a mostrare sintomi positivi attenuati e un funzionamento globale povero[28]. Le variabili che sembrano maggiormente incrementare la probabilità di conversione verso un disturbo psicotico sono: un elevato declino nel funzionamento sociale, elevata sospettosità e contenuto di pen-

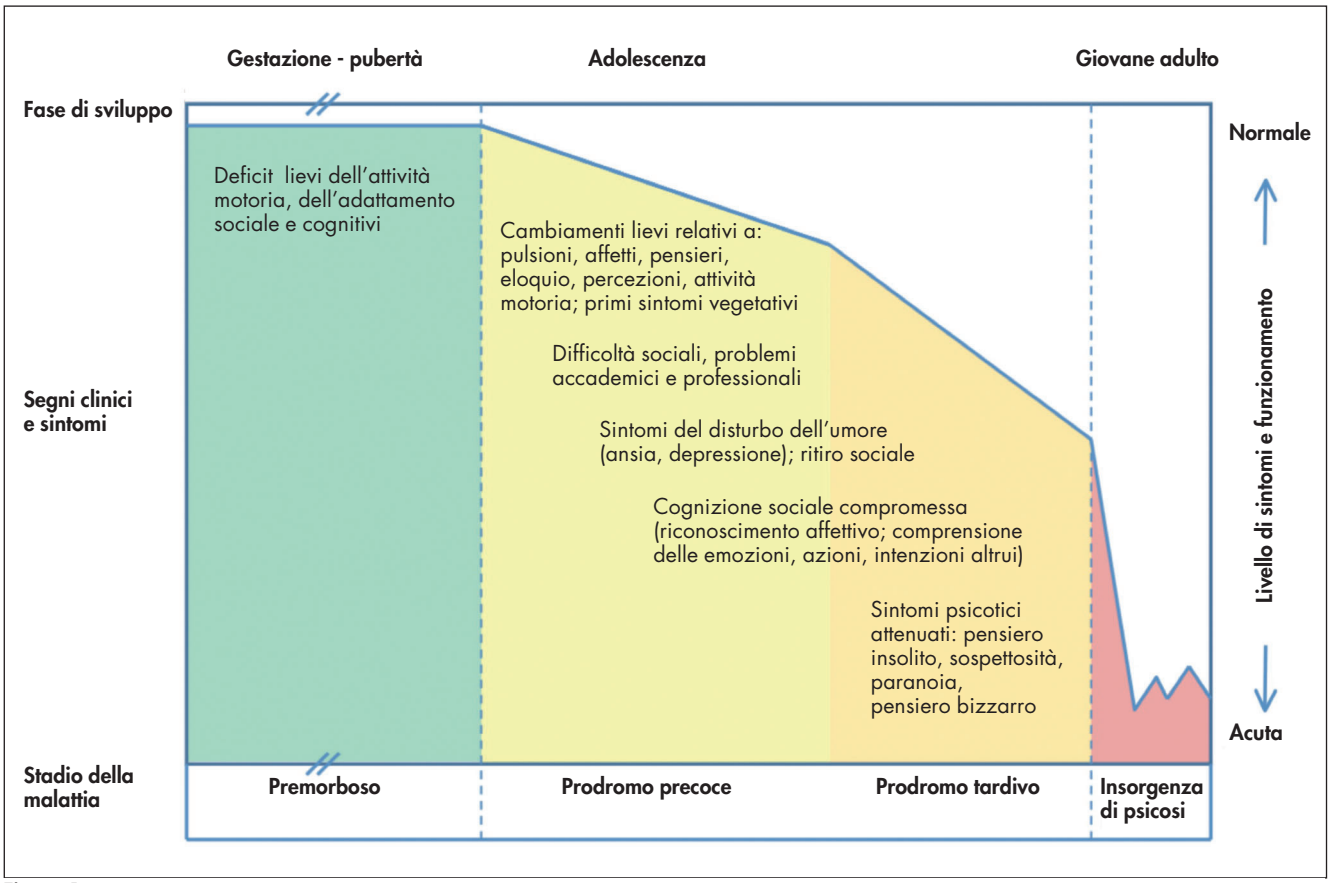

Figura 1. *Fasi e decorso clinico dei prodromi della psicosi (da voce bibliografica 31, modificata).*

siero insolito, una maggiore severità dei primi sintomi, peggiori abilità di apprendimento, memoria e velocità di elaborazione, e un'età inferiore alla prima manifestazione clinica[29].

Diversi studi volti a descrivere il decorso e i fattori di rischio dei disturbi psicotici hanno quindi identificato una fase precedente all'esordio del disturbo chiamata **fase prodromica**, un periodo caratterizzato da iniziali cambiamenti rispetto al funzionamento premorboso nel pensiero e nel funzionamento fino all'emergere di franchi sintomi psicotici. Circa l'80-90% di persone con schizofrenia riportano una varietà di sintomi subacuti nei mesi e negli anni precedenti all'esordio psicotico, che comprendono sintomi psicotici attenuati o intermittenti e cambiamenti nella motivazione, nella cognizione, nell'affettività e nel comportamento[30-32]. Si ritiene che la disabilità che si associa tipicamente ai disturbi psicotici inizi a svilupparsi a partire già dal periodo prodromico, nel quale il ritiro sociale e i sintomi negativi emergenti costituiscono la base sulla quale la psicosi si svilupperà successivamente[33]. Queste evidenze hanno determinato l'introduzione nella nosografia psichiatrica dei concetti di **stati mentali a rischio** (ARMS, *At Risk Mental States*), di alto rischio clinico (CHR, *Clinical High Risk*) e di altissimo rischio (UHR, *Ultra-High Risk*), condizioni con un'aumentata vulnerabilità allo sviluppo di un disturbo psicotico e/o un disturbo psichiatrico maggiore *(Figura 1)*[31]. Queste condizioni cliniche a rischio delle fasi prodromiche sono importanti da identificare tempestivamente, tramite anche l'utilizzo di specifici strumenti di screening, per poter intervenire precocemente e ridurre il rischio di sviluppo di disturbi psicotici futuri[31].

Nel DSM-5 vengono riportati e descritti i diversi disturbi psicotici, che nel manuale rientrano nella categoria chiamata "disturbi dello spettro della schizofrenia e altri disturbi psicotici" e che comprendono i seguenti disturbi principali: disturbo delirante, disturbo psicotico breve, disturbo schizofreniforme, schizofrenia, disturbo schizoaffettivo e disturbo psicotico dovuto ad altra condizione medica. Inoltre il DSM-5 include anche un'ulteriore condizione clinica volta a descrivere le fasi pre-morbose del disturbo, chiamata **sindrome psicotica attenuata**. Per una breve descrizione delle caratteristiche dei principali disturbi psicotici vedi la *Tabella II*[1].

5. DIFFICOLTÀ DIAGNOSTICHE SPECIFICHE NELL'ETÀ EVOLUTIVA

Il riconoscimento dei sintomi psicotici in età evolutiva può risultare complesso. Le manifestazioni vanno innanzitutto contestualizzate sulla base del livello di maturazione cognitiva,

CARATTERISTICHE E SINTOMI DEI PRINCIPALI DISTURBI DELLO SPETTRO DELLA SCHIZOFRENIA

Schizofrenia
- Due o più dei seguenti sintomi per almeno un mese: allucinazioni, deliri, eloquio disorganizzato, comportamento disorganizzato o catatonico, sintomi negativi.
- Compromissione in una o più aree di funzionamento (sociale, scolastica/lavorativa, cura personale) per un periodo di tempo significativo.
- Segni continui del disturbo per almeno 6 mesi (comprensivi di sintomi prodromici o residui).

Disturbo schizofreniforme
- Stessi criteri per la schizofrenia ma con sintomi presenti almeno per 1 mese e meno di 6 mesi.

Disturbo schizo-affettivo
- Presenza di sintomi che soddisfano i criteri per la schizofrenia ma che si manifestano insieme a un episodio maniacale o depressivo maggiore.
- La persona sperimenta allucinazioni o deliri per almeno 2 settimane quando non è in corso un episodio maniacale/depressivo.
- I sintomi che soddisfano i criteri per un episodio maniacale o depressivo sono presenti per almeno la metà della durata dei segni del disturbo.

Disturbo delirante
- Presenza di almeno un delirio per almeno 1 mese.
- La persona non ha mai soddisfatto i criteri per la schizofrenia.
- Il funzionamento della persona non è compromesso al di fuori dell'impatto specifico dei deliri.
- La durata di eventuali episodi maniacali/depressivi è stata breve in confronto alla durata dei deliri.

Disturbo psicotico breve
- Uno o più dei seguenti sintomi presenti per almeno 1 giorno e per meno di 1 mese: deliri, allucinazioni, eloquio disorganizzato, comportamento disorganizzato o catatonico.

Disturbo psicotico attenuato
- Uno o più dei seguenti sintomi presenti in forma attenuata: deliri, allucinazioni, eloquio disorganizzato.
- I sintomi devono essersi manifestati almeno 1 volta alla settimana per il mese precedente e devono essere cominciati o peggiorati nell'ultimo anno.
- I sintomi devono essere sufficientemente severi da causare distress o disabilità o da far sì che le altre persone ritengano che il soggetto abbia necessità di aiuto clinico.
- La persona non ha mai soddisfatto i criteri diagnostici per un disturbo psicotico e i sintomi non sono meglio riconducibili ad altri disturbi, all'uso di sostanze o ad altra condizione medica.

Tabella II. Da voce bibliografica 1, modificata.

dell'età e del contesto culturale di appartenenza[4]. I fenomeni psicotici possono infatti essere confusi con esperienze che in età evolutiva rientrano nell'ambito fisiologico: una vivida immaginazione, così come l'avere un "amico immaginario", possono essere mal interpretati come manifestazioni di natura psicotica[19]. Altri fenomeni che possono essere erroneamente interpretati come patologici sono le cosiddette allucinazioni ipnagogiche e ipnopompiche, tipiche rispettivamente dell'addormentamento e del risveglio. Inoltre, è importante considerare che, in età pediatrica, esperienze stressanti o vissute come traumatiche possono riemergere sotto forma di voci o immagini intrusive[34]. I sintomi positivi hanno infatti una prevalenza maggiore in età evolutiva che in età adulta, e sembrano costituire un fattore di rischio di psicopatologia[35]. Va inoltre considerato che la presenza di sintomi psicotici attenuati in età evolutiva, pur costituendo un fattore di rischio per lo sviluppo di un disturbo dello spettro schizofrenico, sembra associarsi a un minor tasso di conversione verso una forma conclamata che in età adulta[10]. Sintomi psicotici che si presentano solo in contesti specifici, come in alcuni momenti della giornata o in situazioni di stress, e in assenza di altre manifestazioni quali pensiero disorganizzato e sintomi negativi, sono considerati poco predittivi di schizofrenia e rientrano nel fenomeno delle cosiddette pseudo-allucinazioni, che sono manifestazioni di natura ansioso-conversiva[19,36].

Un altro fattore che rende complicata la diagnosi di psicosi in età pediatrica risiede nella minore capacità di introspezione e descrizione verbale dei sintomi esperiti[35]. Questo elemento è particolarmente rilevante in caso di comorbidità con disabilità intellettiva, disturbo dello spettro autistico o altri disturbi del neurosviluppo.

6. DIAGNOSI DIFFERENZIALE

6.1. Disturbi dell'umore

Sono, insieme a quelli dello spettro schizofrenico, le condizioni psichiatriche che più comunemente si associano ai sintomi psicotici. La corretta diagnosi e distinzione tra psicosi affettiva e schizofrenica può essere complessa. Nei disturbi dell'umore, i sintomi psicotici si presentano in concomitanza con un episodio maniacale o depressivo e sono tendenzialmente congrui al tono dell'umore[37].

I **deliri tipici della mania** consistono, ad esempio, in idee di grandiosità, nella percezione di essere dotati di poteri straordinari o di essere in contatto con una divinità. Inoltre, tra i sintomi tipici degli stati maniacali acuti, così come della schizofrenia, rientrano le allucinazioni, la disorganizzazione del pensiero e dell'eloquio[34]. Ciò che aiuta a discriminare tra la schizofrenia e la mania è la presenza dei sintomi negativi, più tipici dei disturbi schizofrenici. Inoltre, nella mania i sintomi psicotici spesso sono caratterizzati da deliri floridi, ben strutturati, e da un pensiero elaborato, contrariamente a quanto avviene nella schizofrenia, connotata da una povertà di pensiero e di eloquio. Una marcata in-

sonnia è tipica del disturbo bipolare, sebbene una disorganizzazione del sonno venga spesso osservata anche nella schizofrenia[4]. Negli **episodi depressivi**, i sintomi psicotici tipici sono invece i deliri di colpa, di fallimento e i deliri nichilistici. Sono inoltre di comune riscontro allucinazioni uditive consistenti in voci autosvalutanti e colpevolizzanti[1]. Altre manifestazioni tipiche sono l'isolamento relazionale, il rallentamento ideo-motorio e la catatonia, che possono essere difficilmente distinguibili dai sintomi negativi della schizofrenia[38]. I sintomi psicotici generalmente costituiscono un fattore prognostico negativo, in quanto si associano a maggiori tassi di ospedalizzazione e suicidalità[39].

Un follow-up a lungo termine con periodiche rivalutazioni nel tempo è necessario per poter confermare l'ipotesi diagnostica iniziale, la persistenza di sintomi psicotici in assenza di rilevanti alterazioni del tono dell'umore, infatti, è maggiormente suggestiva di un disturbo schizoaffettivo[1].

Per la corretta diagnosi differenziale, è necessario effettuare un'accurata anamnesi familiare e di sviluppo, con particolare attenzione alla presenza di un ritardo nell'acquisizione delle tappe neuro-psicomotorie, che spesso è associato alla schizofrenia a esordio precoce[40]. Precoci esperienze traumatiche costituiscono invece un fattore di rischio comune a entrambi i disturbi[41,42].

6.2. Disturbo dello spettro autistico

Mentre la schizofrenia a esordio precoce è rara, l'autismo è un disturbo diagnosticato frequentemente in età infantile (nel 2020 il CDC - *Centers for Disease Control and Prevention* - ha riportato una prevalenza in età infantile di circa 1 su 54, con una frequenza quattro volte maggiore nei maschi) e la sua prevalenza è in aumento[43]. Entrambi i disturbi hanno alla base un'alterazione precoce dello sviluppo del sistema nervoso centrale e condividono numerosi fattori genetici e neuropatologici[44,45]. Inoltre, entrambe le condizioni presentano in anamnesi un ritardo nell'acquisizione del linguaggio e un deficit nelle relazioni sociali[40]. Dal punto di vista epidemiologico, autismo e schizofrenia precoce si presentano spesso in comorbidità[46]. Circa il 30% dei soggetti con schizofrenia precoce presenta i criteri per la diagnosi di un disturbo dello spettro autistico prima dell'esordio dei sintomi psicotici[47]. Inoltre, l'esordio dei sintomi psicotici sembra essere più precoce nei soggetti con diagnosi di disturbo dello spettro autistico[48].

Anche sul piano clinico autismo e schizofrenia presentano una sovrapposizione sintomatologica che ne rende complessa la diagnosi differenziale. I sintomi caratteristici dell'autismo, quali la mancanza di reciprocità socio-emotiva, l'utilizzo di un linguaggio stereotipato, la presenza di comportamenti ripetitivi e non finalistici possono confondersi con i sintomi negativi e i comportamenti disorganizzati tipici della schizofrenia[49]. Gli interessi peculiari, i comportamenti e i pensieri bizzarri possono essere interpretati come deliri, sebbene il fatto di approfondire in modo particolare uno specifico argomento, con una minuziosa attenzione per i dettagli, sia un comportamento più caratteristico dell'autismo.

Per distinguere le due entità è importante effettuare un'accurata raccolta anamnestica; infatti, se nell'autismo gli interessi peculiari e le difficoltà cognitive rappresentano il *pattern* di funzionamento basale, nei pazienti con schizofrenia i sintomi determinano un cambiamento significativo del funzionamento psicosociale e cognitivo[50]. Un'altra differenza risiede nel fatto che nell'autismo i sintomi psicotici vengono spesso elicitati da eccessivo stress conseguente a elevate richieste sociali[51].

6.3. Disabilità intellettiva

Mentre la disabilità intellettiva di grado severo o moderata è facilmente identificata e diagnosticata in età pediatrica, le disabilità di grado lieve possono rimanere a lungo misconosciute[52]. Difficoltà in ambito scolastico possono non essere ricondotte a un deficit intellettivo fino a che le differenze rispetto ai pari non raggiungono un'entità significativa. In tali situazioni, l'aumento delle richieste psicosociali in adolescenza può determinare un incremento dell'irritabilità e difficoltà di adattamento, sino a sfociare in episodi psicotici transitori, che non di rado costituiscono la presentazione clinica iniziale delle disabilità intellettive lievi[53]. I sintomi psicotici tipici dei soggetti con disabilità intellettiva sono tendenzialmente poveri di dettagli e poco strutturati[52]. Le allucinazioni uditive non sono comuni e possono indicare la presenza di un disturbo schizofrenico in comorbidità[54]. Anche in questo caso, un'accurata anamnesi di sviluppo può aiutare a diagnosticare correttamente i sintomi psicotici, la presenza di difficoltà nel funzionamento scolastico e sociale di lunga data possono essere suggestive di una disabilità intellettiva sottostante[50].

6.4. Psicosi secondaria ad altre condizioni mediche

I sintomi psicotici possono anche svilupparsi in conseguenza di altre condizioni mediche, raggruppabili a seconda del fattore eziologico nelle seguenti categorie: psicosi secondarie a cause genetiche, disturbi neurologici, endocrinologici, metabolici, scompensi elettrolitici, patologie infettive del SNC, disordini autoimmuni e deficit nutrizionali *(Box 1)*[1,7,50-62]. La diagnosi differenziale è importante ai fini del trattamento, infatti, mentre nella psicosi da cause psichiatriche il trattamento si basa principalmente su interventi farmacologici e psicoeducazionali, nella psicosi secondaria ad altre condizioni mediche il trattamento ha come *target* il fattore eziologico sottostante.

6.5. Psicosi iatrogena e indotta da sostanze

Tra le sostanze associate a sintomi psicotici vi sono alcuni farmaci (corticosteroidi, derivati della morfina, isoniazide, farmaci antimalarici, antibiotici, tra cui i chinolonici), alcol, *Cannabis*, allucinogeni e sostanze psicostimolanti (amfetamine, cocaina)[63]. Inoltre, alcuni studi hanno osservato una correlazione tra l'utilizzo di *Cannabis* in giovane età e la schizofrenia[64]. Anche l'intossicazione acuta da metalli pesanti, quali rame e piombo, va considerata in diagnosi differenziale[65].

Box 1 - PSICOSI SECONDARIE A SPECIFICHE CONDIZIONI MEDICHE

Tra i disordini genetici, quelli più frequentemente associati ai disturbi psicotici sono la sindrome dell'X-fragile e la sindrome velocardiofaciale o di DiGeorge. In tali condizioni, i sintomi psicotici si associano a dismorfismi facciali, anomalie del palato o cardiache, così come ad altri disturbi del neurosviluppo (disabilità intellettiva, autismo o ADHD)[50]. Altre condizioni genetiche che possono essere associate a sintomi psicotici sono la sindrome di Turner, la sindrome di Prader-Willi e la sindrome di Klinefelter[55].

Tra i disturbi neurologici, quelli che in età pediatrica si associano più comunemente alla psicosi sono l'epilessia (in particolare modo quella del lobo frontale e temporale), l'emicrania, il trauma cranico e le neoplasie[1,56,57]. Sono suggestivi di un disturbo neurologico i *pattern* sintomatologici atipici quali allucinazioni miste e in prevalenza visive, stato confusionale o fluttuazione dello stato di coscienza, tipici del *delirium*, deficit neurologici focali e stati catatonici[55]. Nel sospetto di un disturbo neurologico è necessario effettuare un approfondimento diagnostico mediante l'esecuzione di esami strumentali, quali l'EEG, la RM o la TAC dell'encefalo[7].

I sintomi psicotici possono anche essere secondari ad alcuni disturbi del metabolismo. Deficit metabolici congeniti vanno sospettati qualora i sintomi psicotici siano associati ad anomalie del neuro-sviluppo (ipotonia, microcefalia, disabilità intellettiva), convulsioni, atassia, dismorfismi e anomalie multisistemiche[58]. Alcuni segni e sintomi sono di aiuto per la diagnosi differenziale: epatosplenomegalia e ittero sono tipici della malattia di Wilson o quella di Niemann-Pick; quest'ultima si associa anche ad altre manifestazioni neurologiche, tra cui atassia, disartria, disfagia e paralisi sopra-nucleare dello sguardo verticale. Dolori addominali e neuropatia periferica sono tipici della porfiria, alterazioni oculari e scheletriche sono suggestive per omocistinuria da deficit di cistationina beta-sintetasi[59]. Anche gli scompensi elettrolitici, come alterazioni repentine dei livelli di calcio, fosfato, sodio e magnesio, possono generare scompensi psicotici acuti sotto forma di *delirium*.

La psicosi può anche essere secondaria ad alcune encefaliti autoimmuni, che tipicamente si presentano con un esordio subacuto di sintomi psichiatrici (tra cui deliri, allucinazioni, insonnia e agitazione) associati a sintomi neurologici (convulsioni, discinesia, atassia, coreoatetosi, tremori, distonia e instabilità autonomica). L'encefalite autoimmune più comune è l'encefalite anti-recettori per l'N-metil D-aspartato (NMDA), causata da autoanticorpi IgG contro la subunità GluN1 del recettore NMDA. I sintomi osservati sono anomalie del comportamento e del pensiero (deliri, allucinazioni, aggressività, catatonia), con irritabilità e insonnia, successivamente seguiti da alterazione dell'eloquio, discinesia, deficit di memoria, instabilità autonomica e alterazione dello stato di coscienza[60]. Le convulsioni possono verificarsi durante qualsiasi momento del decorso, presentando generalmente un esordio più precoce nei maschi. La prevalenza dell'encefalite anti-recettori NMDA è maggiore nelle femmine, con un rapporto di 4:1. In età adulta è frequentemente associata alla presenza di una neoplasia sottostante, che nelle donne, nella maggior parte dei casi, è il teratoma ovarico[61].

Altri disordini autoimmuni che possono associarsi a manifestazioni di tipo psicotico sono il lupus eritematoso sistemico, la sindrome da anticorpi anti-fosfolipidi e l'encefalomielite acuta disseminata (ADEM). Nella diagnosi differenziale dei disturbi psicotici vanno considerati anche alcuni disturbi endocrinologici quali il morbo di Cushing, le alterazioni della funzionalità tiroidea, così come stai di ipoglicemia e, meno frequentemente, di iperglicemia[55].

Anche alcuni deficit nutrizionali, come i deficit vitaminici (vitamina B12, B9, D, A), di micronutrienti (iodio, ferro, zinco) e di acidi grassi polinsaturi a catena lunga rientrano nella diagnosi differenziale[62].

7. IDENTIFICAZIONE PRECOCE, PROGNOSI E *OUTCOME*

I disturbi psicotici rappresentano una delle prime cause di disabilità funzionale nei giovani di età compresa tra i 10 e i 24 anni e hanno un impatto importante in diverse aree di funzionamento, come quello socio-relazionale, familiare, scolastico o lavorativo, e delle autonomie personali, con una compromissione generale della qualità di vita[14,32]. Purtroppo è stato stimato che solamente una persona con schizofrenia su due riceve cure adeguate per la sua condizione[32]. Inoltre, solo una persona su sette mostra un recupero funzionale, e negli ultimi decenni l'*outcome* di queste persone non sembra essere migliorato significativamente dalla pratica clinica di *routine*[66]. Rispetto alla popolazione generale, le persone con disturbi psicotici hanno un rischio globale di mortalità doppio[67]. In particolare, soggetti con esperienze psicotiche hanno un rischio significativamente maggiore di sperimentare idee suicidarie, di tentare il suicidio e di morte per suicidio[68]. In uno studio longitudinale è emerso come la presenza di sintomi psicotici in adolescenti di età compresa tra i 13 e i 16 anni rappresenti un importante fattore di rischio clinico per comportamenti suicidari futuri[69]. Risulta quindi fondamentale identificare correttamente e tempestivamente le prime manifestazioni dei sintomi psicotici in bambini e adolescenti, al fine di attuare interventi di prevenzione e trattamento adeguati e precoci, mirati a massimizzare l'*outcome* funzionale[32]. Interventi specifici implementati fin dalle prime fasi prodromiche del disturbo sembrano infatti avere un impatto importante sull'*outcome*[70]. La durata della psicosi non trattata (*Duration of Untreated Psychosis*, DUP), definita come il periodo che intercorre tra la prima presentazione dei sintomi e l'inizio di un trattamento, è infatti correlata alla prognosi e alla risposta al trattamento: persone con una DUP minore hanno infatti una prognosi migliore e una risposta maggiore ai trattamenti[71].

8. TRATTAMENTO

8.1. Farmacologico

Gli antipsicotici di seconda generazione, come risperidone, olanzapina, aripiprazolo o quetiapina, sono considerati il trattamento farmacologico di prima scelta nella schizofrenia a esordio precoce[4]. Numerosi studi hanno dimostrato una maggiore efficacia di questi ultimi rispetto al placebo nella riduzione dei sintomi positivi della schizofrenia, con un effetto meno marcato sui sintomi negativi. Una terapia precoce è fondamentale poiché permette di ridurre l'impatto dei sintomi sullo sviluppo cognitivo e sul funzionamento sociale[72]. L'antipsicotico che ha dimostrato maggiore efficacia rispetto agli altri è la clozapina, che tuttavia è associata al rischio di sviluppare gravi, anche se rari, effetti collaterali come agranulocitosi e miocardite, e viene pertanto utilizzata nei casi che non abbiano risposto ad almeno due monoterapie con gli altri antipsicotici[34]. Oltre alla clozapina, tutti gli al-

tri antipsicotici di seconda generazione usati nell'adulto (con l'eccezione dello ziprasidone) hanno dimostrato efficacia anche nell'adolescente, senza mostrare differenze significative in efficacia tra di loro. La scelta del farmaco è pertanto dettata dal profilo di rischio[72]. Rispetto agli adulti, bambini e adolescenti sembrano essere più a rischio di sviluppare effetti collaterali quali sedazione, sintomi extrapiramidali, innalzamento dei livelli di prolattina, aumento di peso e alterazioni metaboliche[73]. L'obiettivo è quello di mantenere la dose minima efficace in modo da minimizzare i possibili effetti collaterali. Al *baseline* e durante il trattamento andranno monitorati l'indice di massa corporea (BMI), la circonferenza alla vita, la glicemia, il profilo lipidico e la pressione arteriosa, con maggiore frequenza nei pazienti con diabete o incremento > 5% del loro peso iniziale. È necessario inoltre monitorare l'eventuale insorgenza di effetti extrapiramidali quali distonia, acatisia e discinesia tardiva, che possono essere trattati mediante l'utilizzo di farmaci anti-parkinsoniani. Un altro possibile effetto collaterale da monitorare è l'allungamento del QTc[7]. In caso di ipertermia, rigidità, alterazioni dello stato mentale e aumento dei livelli di creatinchinasi (CK) va sospettata la sindrome maligna da neurolettici, che necessita l'immediata interruzione della terapia[7]. Nei pazienti in terapia con clozapina si rende anche necessario il monitoraggio periodico della conta dei globuli bianchi e del numero assoluto dei neutrofili secondo un preciso protocollo[34]. La maggior parte dei casi di schizofrenia precoce necessita di trattamenti a lungo termine e la sospensione causa frequentemente ricadute. Nonostante il trattamento, la condizione è spesso causa di regressione e deficit cronici nel funzionamento sociale[74].

8.2. Interventi psicosociali

Nonostante i trattamenti farmacologici siano in grado di ridurre alcuni sintomi, soprattutto quelli positivi, da soli hanno un impatto limitato sull'*outcome* globale del disturbo[32]. Per raggiungere la sua massima efficacia, infatti, il trattamento deve essere combinato e comprendere sia trattamenti farmacologici che interventi psicosociali adeguati e tempestivi.

Terapia cognitivo-comportamentale

La terapia cognitivo-comportamentale (*Cognitive-Behavioral Therapy*, CBT) è un tipo di trattamento psicologico *evidence-based* considerato a livello internazionale uno dei più efficaci e affidabili per il trattamento dei disturbi psicopatologici e per la loro comprensione. La Psicoterapia cognitiva spiega i disturbi emotivi e psicologici attraverso l'analisi delle relazioni esistenti tra pensiero e schemi cognitivi, emozioni e comportamento. Si propone di aiutare la persona a identificare i pensieri ricorrenti e gli schemi disfunzionali di ragionamento e interpretazione della realtà al fine di sostituirli e integrarli con schemi cognitivi più funzionali. Nel caso di persone che soffrono di disturbi psicotici, la CBT si propone di ridurre il distress e la disabilità attraverso un lavoro sulle distorsioni cognitive (deliri), sulle allucinazioni e sui sintomi negativi tipici. Si pone l'obiettivo di identificare spiegazioni alternative per i sintomi psicotici che siano accettabili per il soggetto, in modo da ridurre il distress associato ai sintomi vissuti[75]. Questo tipo di trattamento, in combinazione con quello farmacologico, sembra essere utile nel ridurre i sintomi psicotici e incrementare il funzionamento di persone con disturbi psicotici[76]. Inoltre, il trattamento CBT si è dimostrato efficace anche fin dalle prime fasi prodromiche del disturbo e, se implementato tempestivamente, sembra ridurre i sintomi psicotici e le possibilità di progressione verso un disturbo psicotico vero e proprio[77,78]. Le evidenze rispetto all'efficacia della CBT in bambini e adolescenti con sintomi e disturbi psicotici sono ancora limitate rispetto a quelle nella popolazione adulta, e a oggi i trattamenti CBT vengono adattati a partire dalle evidenze sull'adulto[10]. Le linee guida dello *UK National Institute for Health and Care Excellence* (NICE) raccomandano l'implementazione di trattamenti cognitivo-comportamentali, combinati o meno anche con interventi familiari, sia nel momento della diagnosi di un disturbo psicotico sia nella fase prodromica[11].

Riabilitazione cognitiva

Le tecniche di riabilitazione cognitiva comprendono un'ampia gamma di trattamenti *evidence-based* che hanno l'obiettivo di riabilitare o potenziare il funzionamento cognitivo di soggetti con difficoltà cognitive dovute a lesioni cerebrali o ad altre condizioni, o di fornire strategie per compensare i deficit cognitivi persistenti. Poiché in persone con sintomi e disturbi psicotici sono spesso presenti delle difficoltà cognitive che hanno un impatto importante sul funzionamento globale, è importante che nel trattamento siano compresi anche interventi specifici di riabilitazione cognitiva per il potenziamento dei deficit presenti. Due recenti metanalisi hanno mostrato come la riabilitazione cognitiva sia in grado di migliorare il funzionamento di queste persone, specialmente in alcune aree cognitive quali l'attenzione, la velocità di elaborazione, la memoria verbale, il *problem solving*, la memoria di lavoro verbale e la cognizione sociale. Questi interventi risultano essere più efficaci nel migliorare i sintomi e in grado di avere un impatto maggiore sull'*outcome* e sul funzionamento quotidiano se vengono implementati in un trattamento psichiatrico integrato e insieme ad altri tipi di trattamenti psicosociali, quali per esempio dei *training* per le abilità sociali[79,80]. Alcuni studi di riabilitazione cognitiva in bambini e adolescenti con EOS o VEOS hanno mostrato come anche in questa popolazione questo tipo di interventi siano efficaci nel migliorare il funzionamento in diversi domini cognitivi, soprattutto in quelli delle funzioni esecutive attentive e della memoria verbale, domini che risultano predittivi di quello che sarà l'esito clinico e funzionale. Queste prime evidenze di efficacia suggeriscono come sia importante fornire interventi precoci che si focalizzano sul potenziamento dei deficit cognitivi e delle abilità sociali anche nella popolazione pediatrica. In que-

sta età molte funzioni (cognitive e sociali) sono ancora in via di sviluppo e interventi di questo tipo a sostegno di queste abilità risultano essere particolarmente importanti in ragazzi con disturbi psicotici[10].

Altri interventi psicosociali

Tra gli altri possibili interventi psicosociali utili in questa popolazione rientrano dei *training* per le abilità sociali e interventi di terapia familiare e psicoeducazione. I *training* per le abilità sociali si propongono di far apprendere come gestire con successo diverse situazioni socio-relazionali quotidiane. Vengono attuati attraverso *role-playing* e altri esercizi e attività in gruppo. Gli interventi familiari comprendono tipicamente programmi psicoeducativi mirati a incrementare la conoscenza e la consapevolezza del disturbo della famiglia e provvedimenti volti a migliorare la comunicazione nel nucleo familiare e a ridurre l'emotività espressa. Questi trattamenti descritti, insieme ad altre possibili azioni scolastiche, educative o residenziali, sono complementari al trattamento farmacologico e sono fondamentali per migliorare il livello funzionale e la qualità di vita di questi ragazzi[10,11,81,82].

9. CONCLUSIONI

La psicosi si può manifestare con una sintomatologia ampia che comprende sintomi positivi, negativi, disorganizzati e cognitivi-comportamentali che possono avere un impatto rilevante sul funzionamento quotidiano e sulla qualità di vita. È importante tenere a mente che la presenza di alcuni sintomi psicotici per un periodo di tempo ridotto o in forma attenuata non necessariamente deve condurre a una diagnosi di disturbo psicotico vero e proprio. Una diagnosi corretta e tempestiva, specialmente in età pediatrica, rappresenta sicuramente una sfida complessa per il clinico: è necessario infatti considerare possibili diagnosi differenziali, condizioni mediche sottostanti e la specifica fase di sviluppo in cui il bambino o ragazzo si trova. Un'identificazione precoce dei primi sintomi fin dalle fasi prodromiche, una diagnosi accurata e l'implementazione di trattamenti combinati e tempestivi sono tutti elementi fondamentali per poter migliorare la prognosi e il funzionamento a lungo termine.

Spesso il pediatra è il primo professionista a incontrare bambini e adolescenti che manifestano e/o riportano sintomi di tipo psicotico. In queste situazioni il pediatra dovrebbe procedere con una valutazione cauta e completa della situazione, tenendo a mente quelle che possono essere le possibili diagnosi differenziali e le condizioni mediche che possono essere associate a sintomi psicotici in età pediatrica. Risulta molto importante indagare la presenza di eventuali problematiche di sicurezza del minore, in particolare la possibile presenza di comportamenti autolesivi, pensieri suicidari o tentativi suicidari veri e propri. Poiché la presentazione dei sintomi psicotici e la loro corretta comprensione possono essere complesse, è importante che si instaurino fin da subito una stretta collaborazione e un confronto con gli specialisti e i servizi di Neuropsichiatria infantile. Se un bambino o ragazzo manifesta sintomi psicotici è indicato infatti richiedere una visita neuropsichiatrica infantile per effettuare una valutazione specialistica completa e approfondita. Il periodo tra la prima presentazione di sintomi psicotici spesso attenuati e l'esordio di un disturbo psicotico vero e proprio è estremamente importante per il monitoraggio clinico e l'implementazione di interventi precoci. In situazioni acute in cui si rilevano delle problematiche di sicurezza del minore o delle altre persone intorno a lui, è importante inviare tempestivamente il minore presso i servizi di Pronto Soccorso. Un invio tempestivo presso i servizi di Neuropsichiatria infantile è fondamentale per far sì che sia possibile identificare minori con rischio clinico o con disturbi psicotici e cominciare la presa in carico e il trattamento il prima possibile in modo da massimizzare la risposta al trattamento, la prognosi a distanza e in generale la loro qualità di vita[7,11].

CASO CLINICO

Tommaso è un ragazzo di 12 anni che è arrivato in Pronto Soccorso su invio della psicologa per sospetto esordio psicotico. I primi cambiamenti nel pattern comportamentale sono stati osservati alcuni mesi prima del ricovero, durante il primo lockdown: la mamma era stata contattata dai professori poiché durante la didattica a distanza non appariva mai connesso. Aveva inoltre iniziato a parlare in maniera ossessiva di argomenti bizzarri o macabri, raccontando ad esempio al fratello minore che la mamma sarebbe presto deceduta. Il giorno prima del ricovero, Tommaso si era avvicinato alla mamma in lacrime, impugnando un coltello nascosto dietro la schiena. A fronte di tali comportamenti, su consiglio della psicologa da cui Tommaso era in carico da circa un anno per isolamento sociale e difficoltà relazionali, la mamma lo ha condotto in Pronto Soccorso con urgenza. Al colloquio neuropsichiatrico il pensiero appariva incoerente, disorganizzato nella forma, con tangenzialità e allentamento dei nessi associativi, e polarizzato su tematiche bizzarre, con compromissione dell'esame di realtà. Non si evidenziavano franche allucinazioni, sebbene, in certi momenti, Tommaso tendesse a parlare tra sé e sé, apparendo quasi assente. Il comportamento appariva altrettanto bizzarro e stereotipato (camminava tastando le pareti, affermando di essere attratto dalla forza di gravità), con un'importante iperattività motoria. L'esame obiettivo neurologico risultava nella norma. Durante la degenza sono stati effettuati esami del sangue e delle urine, così come esami strumentali (elettroencefalogramma e risonanza magnetica dell'encefalo), tutti risultati nella norma. Dall'anamnesi effettuata non si evidenziavano ritardi nell'acquisizione delle tappe di sviluppo, né familiarità per patologie di natura psichiatrica; emergevano tuttavia difficoltà relazionali sin dall'infanzia, accentuatesi con l'inizio delle scuole medie, associate a interessi selettivi e stereotipati. A partire dalla scuola secondaria, si segnalava inoltre un calo nel rendimento scolastico, sebbene il quoziente intellettivo risultasse nel range di norma.

In regime di ricovero, veniva avviata una terapia farmacologica con risperi-

done alla posologia di 0,5 mg, gradualmente aumentata fino a 2 mg. Con l'avvio della terapia il pensiero appariva più coerente e organizzato, non si verificavano episodi di auto o eteroaggressività e si osservava una marcata riduzione dell'iperattività. Veniva dimesso con diagnosi di disturbo schizofreniforme e inviato al servizio Neuropsichiatria infantile di pertinenza territoriale per la presa in carico e la prosecuzione delle cure, con monitoraggio periodico dei sintomi rispetto a una possibile evoluzione verso una schizofrenia a esordio precoce. È stato inoltre avviato un intervento educativo individuale, con supporto anche in ambito scolastico. A seguito delle dimissioni persistevano difficoltà nell'interazione con i pari, così come l'interesse assorbente per tematiche bizzarre (quali leggende e storie sul ritrovamento di pietre preziose). Tommaso è stato pertanto rivalutato in regime ambulatoriale nel sospetto di un disturbo dello spettro autistico mediante ADOS-2 (Autism Diagnostic Observation Schedule-Second Edition) e ADI-R (Autism Diagnostic Interview-Revised), considerati i gold standard per la diagnosi di autismo, risultati entrambi positivi. È stata pertanto posta anche diagnosi di disturbo dello spettro autistico in aggiunta a quella di disturbo schizofreniforme. Tommaso continua il trattamento con risperidone ed è monitorato nel tempo per valutare se svilupperà tutti i criteri della schizofrenia.

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MESSAGGI CHIAVE

- ❏ Avere sintomi psicotici non equivale ad avere un disturbo psicotico.
- ❏ Nel bambino sintomi psicotici isolati e transitori non sempre hanno un significato patologico.
- ❏ La psicosi può essere una manifestazione di un disturbo dello spettro schizofrenico, ma anche di altre problematiche, come i disturbi dell'umore, l'abuso di sostanze o l'encefalite con anticorpi anti-recettore NMDA.
- ❏ La schizofrenia ha di solito esordio tra i 15 e i 25 anni (in circa il 12% prima del 18° anno), mentre è molto rara prima dei 13 anni.
- ❏ L'esordio schizofrenico è insidioso, con mesi e a volte anni di sintomi sottosoglia o non specifici.
- ❏ Una pronta identificazione della schizofrenia può consentire un trattamento precoce che potrebbe migliorare la prognosi.

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Un bambino adottato che ha un difetto di attenzione con iperattività. Una presa in carico amorevole può tutto. Il secondo caso distingue una candidosi di un neonato nella forma congenita rispetto a quella acquisita. Per la forma congenita vale un binomio: neonato prematuro rosso come il fuoco entro pochi giorni dalla nascita? Dare l'antifungino sistemico. Di fronte a una ipertransaminasemia il ruolo della biopsia è spesso determinante per la diagnosi, in questo caso per una rara condizione di sclerosi epatorenale.

ADOZIONI E ADHD: QUANDO SI APRONO LE PORTE

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International adoption and ADHD

Key words *ADHD, International adoption*

The troubled story of a young Russian boy adopted by an Italian couple is presented. Lights and shadows of the international adoption are discussed.

Mi chiama un mio amico avvocato, mi chiede se posso vedere un ragazzino, appena adottato da una coppia di suoi clienti che sono in grave difficoltà. Dopo pochi giorni sono già pentiti della loro scelta e "non sanno se tenerlo". Vasja è stato adottato in Russia, è figlio di una sedicenne, gli era stata diagnosticata una lue congenita (cosa che si rivelerà poi falsa). Il ragazzino ha passato gli ultimi quattro anni in orfanotrofio dove è stata posta diagnosi di ADHD. Non ha superato il primo anno delle elementari del suo Paese. Nei primissimi giorni nella nuova famiglia il ragazzino, che ovviamente non parla l'italiano, di fronte a una piccola frustrazione ha minacciato la figlia naturale della coppia (più grande di lui) con un oggetto, ha avuto alcuni atteggiamenti "sessualizzati" nei suoi confronti e avrebbe tentato di fuggire. In altri momenti Vasja ha cercato di ingraziarsi i nuovi genitori, ad esempio lavando i piatti. Quando vengono da me, a meno di due settimane dall'adozione, i genitori adottivi dicono di "sentirsi minacciati" e mi informano del fatto che hanno già avviato le pratiche per non occuparsi più del bambino.

In sede di visita, all'inizio Vasja si comporta bene. Non ci possiamo capire ma produce un bel disegno. Nel corso dell'incontro diventa sempre più vivace e disinibito. Infine cambia nettamente il proprio comportamento, con un atteggiamento fortemente angosciato e aggressivo, quando tento di visitarlo. L'atteggiamento dei genitori adottivi è sorprendente, ma a me interessa solo il futuro del bambino: spiego che la diagnosi di ADHD è verosimile e che a ciò si associano i comportamenti tipici di un disturbo dell'attaccamento. Pensando che forse la coppia tornerà sulle proprie decisioni, propongo immediatamente una terapia con risperidone e fornisco i primi consigli. Mi metto a disposizione per rivedere Vasja a breve. Evito accuratamente di commentare le decisioni della coppia. Ho visto diverse situazioni in cui i genitori adottivi non credevano nel futuro del loro bambino e che hanno visto puntualmente avverarsi le loro profezie: l'affetto non può essere forzato. Ai controlli successivi persiste (e ti pareva) una forte gelosia nei confronti della figlia della coppia. Alle dosi adeguate il risperidone si dimostra utile. Il bambino ha ancora esplosioni di aggressività ma solo nei confronti degli oggetti. In un'occasione se l'è presa con il cane. Tutto si svolge repentinamente.

A un mese dall'ingresso del bambino in famiglia, i genitori adottivi hanno già una prima udienza in Tribunale per le "opportune decisioni". Cerco di tirare fuori il meglio dal ragazzino, la cui aggressività si riduce ulteriormente, ipotizzo un tentativo terapeutico con il metilfenidato.

A un mese e mezzo dall'arrivo di Vasja in Italia, il Tribunale per i Minorenni si pronuncia iscrivendo il bambino nel Registro dello stato civile. Contemporaneamente sospende la responsabilità genitoriale e apre un procedimento relativo allo stato di abbandono, affidando Vasja al Servizio sociale. Viene deciso un collocamento in comunità, nel frattempo il bambino rimane in "famiglia". Vengo a sapere che, nonostante non conosca la nostra lingua, Vasja ha identificato perfettamente il ruolo delle assistenti sociali che incontra e in quelle occasioni "fa di tutto" con plateali manifestazioni di affetto nei confronti della madre, per rassicurare gli adulti sul fatto che sta bene dove sta. Diventa letteralmente "un bravo bambino" e, a due mesi dall'adozione non esprime quasi più aggressività: impara velocemente l'italiano, non ha più problemi di addormentamento, si propone sempre per alcune faccende domestiche, aiuta a cucinare… spiega che da grande vorrebbe diventare poliziotto. In questo periodo l'unico a cambiare atteggiamento è stato Vasja, gli adulti restano fermi sulle loro decisioni. I genitori adottivi attendono il momento del passaggio in comunità che avviene, improvvisamente per il bambino, a quattro mesi dal suo arrivo in Italia. Pagheranno una specie di "penale" e usciranno definitivamente dalla storia. Contro tutte le premesse, il passaggio avviene senza troppi problemi, tanto che un mese dopo l'inserimento in comunità viene decisa la progressiva riduzione e infine la sospensione della terapia farmacologica. Inizia una presa in carico da parte del Servizio territoriale di competenza. La descrizione dei colleghi è la seguente: "*nel corso dei colloqui conoscitivi con la psicologa, Vasja è parso un bambino incapace di raccontare e ricostruire la sua storia e spesso dimostra atteggiamenti di chiusura se gli si pongono domande relative al suo passato. Nomina spesso i genitori e la sorella e sembra aver compreso ma non accettato il loro abbandono e manifesta con insistenza il desiderio di poter avere una famiglia. Si è osservato che spesso il bambino ricerca in maniera indifferenziata diverse figure di riferimento, sempre femminili, a cui si rivolge cercando accudimento fisico e calore affettivo, chiedendo talvolta di far parte della loro famiglia. Sul piano comportamentale si è osservato un quadro di iperattività e impulsività associato a un persistente stato di allerta*".

Il livello cognitivo è del tutto adeguato. Le difficoltà attentive si confermano, in particolare a livello scolastico, dove Vasja fa davvero fatica.

Rivedo il ragazzino dopo un anno, in quanto i colleghi del Servizio territoriale ipotizzano un aiuto farmacologico con psicostimolanti ed è necessario per questo afferire al nostro Centro di riferimento. Questa volta, Vasja e io possiamo parlare tranquillamente in italiano (il bambino ha appreso la lingua in maniera impeccabile). Un certo nervosismo, nel ritrovarsi negli stessi luoghi dove ci eravamo visti con la famiglia, è evidente. Il ragazzino sfoga la propria aggressività con un disegno, che completa con la scritta "stupido" (evidentemente indirizzata a me).

Mi conferma che vuole sempre diventare un poliziotto "per dare la multa a tutti". Meno di questo, onestamente, non potevo aspettarmi…
Ma in questo periodo è successo qualcosa: una nuova coppia si è proposta per l'adozione. Vasja ritorna, in seguito, con la nuova famiglia: è raggiante. Dopo pochi mesi affronta la classe successiva in una nuova scuola, in una terza città. È ben voluto, viene aiutato. Le prestazioni scolastiche migliorano drasticamente. È passato un anno: Vasja, i suoi nuovi genitori e i suoi nuovi nonni si vogliono bene e hanno fiducia nel futuro. Il ragazzino è bravo a scuola ed è bravissimo a calcio. Ha moltissimi amici. Si è aperto il portone.

UN NEONATO CHE BRUCIA

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A newborn on fire

Key words *Candidiasis, Cutaneous congenital candidiasis*

A case of Cutaneous Congenital Candidiasis (CCC) in a preterm newborn is described. The diagnostic and therapeutic implications of CCC are discussed.

Il neonato è un pretermine di 29 settimane di età gestazionale con PN 1,570 kg, nato da parto vaginale per rottura prematura delle membrane e travaglio inarrestabile. Alla 20ª settimana di età gestazionale la madre aveva ricevuto un cerchiaggio cervicale per minaccia di parto pretermine e aveva assunto terapia antibiotica per un tampone vaginale positivo per *Serratia*. Inoltre aveva una storia di frequenti candidiasi vaginali.
Il bambino nasce bene, ma al terzo giorno di vita presenta un'eruzione cutanea eritematosa "rosso fuoco" su collo, ascelle, tronco, dorso ed estremità con esfoliazione e desquamazione cutanea. Non presentava febbre o altri sintomi sistemici. I parametri vitali sono stabili e il piccolo era in respiro spontaneo in aria ambiente con N-CPAP *(Nasal-Continuous Positive Airway Pressure)*. Vengono eseguiti tamponi cutanei e mucosali che risulteranno positivi per *Candida albicans*, ma non viene riscontrato alcun coinvolgimento sistemico della candidiasi, in particolare esame urine ed emocoltura risulteranno negativi. Viene eseguita anche un'ecografia transfontanellare che risulta nella norma. Non viene eseguita una puntura lombare in considerazione della presenza del *rash* sul dorso. Viene subito avviata terapia sistemica con fluconazolo ev per 14 giorni, come da letteratura, portando alla risoluzione del *rash* in pochi giorni.

La **candidiasi cutanea congenita** è un'infezione fungina invasiva di pelle ed epidermide che compare entro i 6 giorni dalla nascita, tipicamente entro 72 ore dal parto. È dovuta a un'infezione da *Candida* acquisita per via ascendente e i fattori di rischio sono il cerchiaggio cervicale o altri *device* endouterini, storia di candida vaginale ricorrente, la rottura prematura delle membrane. Colpisce più frequentemente i neonati pretermine per via dell'immaturità delle loro difese immunitarie e della loro barriera muco-cutanea. Nel neonato a termine ha di solito un decorso più benigno e autolimitantesi. Si differenzia dalla candidiasi neonatale perchè risparmia le mucose e la zona del pannolino e perché compare precocemente, mentre la candidiasi neonatale compare di solito dopo la prima settimana di vita. La presentazione con un rash definito *burn-like*, e cioè rosso come il fuoco, è associato a una malattia più invasiva con rischio di mortalità del 40%; per tale motivo va subito avviata una terapia antifungina sistemica con amfotericina B o fluconazolo per almeno 14 giorni. Terapie ritardate o troppo brevi sono associate a *outcome* sfavorevoli.

Take home message

Neonato prematuro rosso come il fuoco entro sei giorni dalla nascita: dagli di antifungino sistemico.

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SCLEROSI EPATOPORTALE

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Hepatoportal sclerosis

Key words *Hepatoportal sclerosis, Noncirrhotic portal hypertension*

Hepatoportal sclerosis (HS) is a syndrome of obscure aetiology that may evolve in noncirrhotic portal hypertension. The paper reports the case of a 3-month-old infant presenting with HS and isolated liver enzymes elevation.

Una bambina di 3 mesi, in occasione di esami ematochimici eseguiti in corso di un'infezione cutanea da stafilococco, presenta un quadro di ipertransaminasemia (AST 146 U/l, ALT 101 U/l) in assenza di altri indici di danno epatico. Nei mesi successivi i controlli hanno confermato un persistente e asintomatico aumento delle transaminasi con valori di gGT normali. Per tale motivo all'età di 11 mesi la bambina viene ricoverata per eseguire accertamenti di primo e secondo livello che sono risultati tutti negativi. All'età di 13 mesi giunge alla nostra attenzione in Pronto Soccorso per un quadro di infezione delle alte vie respiratorie. Agli esami ematochimici si conferma ancora il quadro di ipertansaminasemia con AST 383 U/l e ALT 577 U/l! Visto il quadro di ipertransaminasemia cronica persistente e di entità moderata (durata superiore ai 6 mesi e valori tra 2-10 volte il valore massimo di normalità) la bambina viene ricoverata per eseguire ulteriori accertamenti.

All'esame obiettivo il peso e l'altezza sono sul 25° percentile, assenti l'epatosplenomegalia e altri segni di malattia epatica cronica. Emocromo, indici di flogosi e funzionalità epatica (assetto coagulativo, protidemia e protidogramma) nella norma. Il dosaggio degli indici di colestasi (gGT e bilirubina totale e frazionata) è risultato nei limiti, quadro compatibile con una sindrome citolitica pura. Eseguito dosaggio di CPK che ha permesso di escludere una miopatia pauci-asintomatica.
Sono state escluse infezioni croniche da virus epatotropi (HAV, HBV, HCV, EBV, CMV), malattia celiaca, tiroidopatia e malattie metaboliche. Assente ipergammaglobulinemia, ANA, ASMA, ANCA, LKM e LC1 negativi. Eseguita un'ecografia addominale che non ha evidenziato epatosplenomegalia, alterazioni dell'ecogenicità o in presenza di noduli o masse.
Che altro ci resta da fare? Una biopsia epatica!
L'esame istologico ha mostrato un quadro microscopico caratterizzato da "modesto infiltrato infiammatorio di tipo cronico, si apprezza uno spazio portale con plurimi rami della vena porta a pareti sottili e in alcuni tratti rami estroflessi nel parenchima come da erniazione, note di polimorfismo epatocellulare come da rigenerazione e minima capillarizzazione sinusoidale a livello della lamina limitante". Dilemma risolto! Il quadro istologico è compatibile con la diagnosi di sclerosi epatoportale.

Nella pratica ambulatoriale pediatrica quadri di moderata e persistente ipertransaminasemia sono di frequente riscontro e riflettono generalmente un danno isolato e persistente dell'epatocita. Questo dato può accompagnarsi a diversi segni e sintomi di malattia epatica oppure, più frequentemente, può essere un fortuito riscontro laboratoristico. Se l'ipertransaminasemia persiste bisogna sempre escludere una miopatia con dosaggio delle CPK nel siero. Per un miglior inquadramento del problema e per proseguire razionalmente nell'esecuzione di indagini di secondo livello è necessario dosare l'attività gGT per distinguere tra un danno citolitico puro e un danno misto citolitico-colestatico. Infine in caso di aumento persistente delle transaminasi di almeno 6 mesi, con negatività di tutte le indagini precedentemente eseguite, valutare la necessità di eseguire una biopsia epatica in quanto risulta l'esame *gold standard* per la diagnosi delle malattie epatiche croniche.
Le epatopatie croniche nei bambini, soprattutto nei primi anni di vita, possono essere asintomatiche e presentarsi solo con riscontro occasionale di ipertransaminasemia. Anche la sclerosi epatoportale, che più frequentemente esordisce con segni di ipertensione portale, può avere come prima e unica manifestazione una ipertransaminasemia isolata persistente.
Davanti a un quadro non chiaro non farti sfuggire una diagnosi, valuta sempre se fare una biopsia!

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