NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD MAGGIO 2021

Academic Emergency Medicine. 2021;28:S45.

DOES ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER INCREASE RISK OF MINOR BLUNT HEAD TRAUMA IN CHILDREN?
Pakyurek M, Nobari O, Badawy M, et al.

Background and Objectives: Children with attention-deficit hyperactivity disorder (ADHD) may be at increased risk of head trauma. We aimed to identify the rate of ADHD in children with minor blunt head trauma and if ADHD increases the risk of head trauma. We hypothesized that children with head trauma due to non-MVC mechanisms will have higher rates of ADHD than children with head trauma due to MVC mechanisms.

Methods: We conducted a prospective observational study of children with non-trivial blunt head trauma. In a planned substudy, guardians were queried, and medical records reviewed as to whether the patient had ever been diagnosed with ADHD. Enrolled patients were categorized based on their mechanism of injury. Patients injured in MVC mechanisms were considered to represent the prevalence of ADHD in the general population and the reference group for the study. The ADHD rate in the MVC cohort was then compared to the rate in the non-MVC cohort to identify mechanisms with a higher rate of ADHD. Data are described with simple descriptive statistics and 95% CIs and compared with relative risk ratios (RR).

Results: 3,410 (84%) enrolled children had data available on ADHD status, and 274 (8.0%; 95% CI 7.1, 9.0%) had previously been diagnosed with ADHD. Mean age was 9.2 -¦ 3.5 years and 64% were male. The rates of ADHD for specific mechanisms of injury were: assaults: 23/131 (17.6%; 95% CI 11.5, 25.2%), automobile vs pedestrian 23/173 (13.3%; 95% CI 8.6, 19.3%), bicycle crashes 26/148 (17.6%; 95% CI 11.8, 24.7%), falls 107/1,651 (6.5%; 95% 5.3, 7.8%), object struck head 31/421 (7.4%; 5.1, 10.3%), motorized vehicle crashes (e.g. motorcycle, motor scooter) 11/148 (7.4%; 3.8, 12.9%) and MVCs 46/704 (6.5%; 95% CI 4.8, 8.6%). Compared to patients with MVC mechanisms, patients with assault (RR=3.3, 95% CI 2.1-5.2), auto vs pedestrian (RR=2.0, 95% CI 1.3-3.3) and bicycle (RR=2.7, 95% CI 1.7-4.2) mechanisms had higher rates of ADHD. There was no increased risk of ADHD among patients with falls (RR=1.0, 95% CI 0.7-1.4).

Conclusion: Children with ADHD with non-trivial minor blunt head trauma appear to be at increased risk of certain mechanisms of injury including assaults, auto versus pedestrian, and bicycle crashes but are not at an increased risk for falls. Future studies are needed to evaluate interventions in children with ADHD to minimize the increased risk of head trauma from these mechanisms

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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.

Acad Pediatr. 2021.

EXAMINING THE RELATIONSHIP BETWEEN ADVERSE CHILDHOOD EXPERIENCES AND ADHD DIAGNOSIS AND SEVERITY.

Crouch E, Radcliff E, Bennett KJ, et al.

Objective: Although prior research has examined the prevalence of ACEs among children with attention deficit-hyperactivity disorder (ADHD), little is known about the household and family settings of children with ADHD. Our study utilizes a recent nationally representative dataset to examine the association between adverse childhood experiences (ACEs), child and household characteristics, and ADHD diagnosis and severity.

Methods: Using the 2017ΓÇô2018 National Survey of Children's Health (NSCH), our sample consisted of children three years of age or older, as this is the youngest age at which the NSCH begins to ask caregivers if a child has been diagnosed with ADHD (n = 42,068). Multivariable logistic regression was used to examine the association between ACE type, score, and ADHD and ADHD severity, controlling for child and household characteristics.

Results: Children exposed to four or more ACEs had higher odds of ADHD (aOR 2.16; 95% CI 1.72-2.71) and moderate to severe ADHD (aOR 1.89; 95% CI 1.31-2.72) than children exposed to fewer than four ACEs. Other child characteristics positively associated with ADHD included age and public insurance; other Non-Hispanic races compared to Non-Hispanic White had lower odds of ADHD. Of children reported with ADHD, public insurance was also associated with caregiver-reported moderate to severe ADHD.

Conclusions: Children with ADHD have a higher prevalence of ACEs, making this study important for understanding the relationship between ACEs and ADHD at the population level

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Acta Diabetol. 2021 May;58:623-31.

COELIAC DISEASE IS ASSOCIATED WITH DEPRESSION IN CHILDREN AND YOUNG ADULTS WITH TYPE 1 DIABETES: RESULTS FROM A MULTICENTRE DIABETES REGISTRY.

Tittel SR, Dunstheimer D, Hilgard D, et al.

Aims: To analyse the association between coeliac disease (CD) and depression in children, adolescents, and young adults with type 1 diabetes (T1D).

Methods: We included 79,067 T1D patients aged 6-20 years, with at least six months of diabetes duration, and treatment data between 1995 and 2019 were documented in the diabetes patient follow-up registry. We categorized patients into four groups: T1D only (n = 73,699), T1 + CD (n = 3379), T1D + depression (n = 1877), or T1D + CD + depression (n = 112).

Results: CD and depression were significantly associated (adjusted OR: 1.25 [1.03-1.53]). Females were more frequent in both the depression and the CD group compared with the T1D only group. Insulin pumps were used more frequently in T1D + CD and T1D + depression compared with T1D only (both $p < .001$). HbA1c was higher in T1D + depression (9.0% [8.9-9.0]), T1D + CD + depression (8.9% [8.6-9.2]), both compared with T1D only (8.2% [8.2-8.2], all $p < .001$). We found comorbid autism, attention deficit hyperactivity disorder, anxiety, schizophrenia, and eating disorders more frequently in the T1D + CD + depression group compared with T1D only (all $p < .001$).

Conclusions: CD and depression are associated in young T1D patients. The double load of T1D and CD may lead to an increased risk for depression. Depression was associated with additional psychological and neurological comorbidities. Aside from imperative CD screening after T1D diagnosis and regular intervals, depression screening might be helpful in routine care, especially in patients with diagnosed CD

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Acta Paediatr Int J Paediatr. 2021.

HALF OF THE CHILDREN WITH OVERWEIGHT OR OBESITY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER REACH NORMAL WEIGHT WITH STIMULANTS.

Fast K, et al.

Aim: Treatment of childhood obesity is often insufficient and may be aggravated by high co-occurrence of attention-deficit/hyperactivity disorder (ADHD). We aimed to investigate whether children with overweight or obesity normalised in weight when receiving stimulant treatment for ADHD.

Methods: Growth data of 118 children were obtained from medical records at outpatient paediatric and children's psychiatric services in the Gothenburg area, Sweden. The children were diagnosed with ADHD and were between 6 and 17 years at the start of stimulant treatment. The pre-treatment data act as an internal control where every child is their own control.
Results: At the start of treatment, 74 children had normal weight and 44 had either overweight or obesity. During the year with stimulants, the mean (SD) body mass index (BMI) in standard deviation score (SDS) decreased significantly: 0.72 (0.66) compared with 0.17 (0.43) during the year before treatment ($p<0.01$). After one year with treatment, 43% of those with overweight or obesity had reached normal weight.
Conclusions: Stimulant treatment for ADHD yields significant weight loss. In children with overweight or obesity and ADHD, this is an important finding showing additional benefit in terms of weight management

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Am Fam Physician. 2021 May;103:539-46.

THE PREPARTICIPATION PHYSICAL EVALUATION.

MacDonald J, Schaefer M, Stumph J.

The preparticipation physical evaluation (PPE) is a common reason for young athletes to see a primary care physician. An annual PPE is required by most state high school athletic associations for participation in school-based sports, although there is limited evidence to support its effectiveness for detecting conditions that predispose athletes to injury or illness. In 2019, the American Academy of Pediatrics, with representatives from the American Academy of Family Physicians and other organizations, published updated PPE recommendations (PPE5). According to the guideline, the general goals of the PPE are determining general physical and psychological health; evaluating for life-threatening or disabling conditions, including risk of sudden cardiac arrest and other conditions that may predispose the athlete to illness or injury; and serving as an entry point into the health care system for those without a medical home or primary care physician. The guideline recommends that the evaluation take place in the physician's office rather than in a group setting. The PPE should include a structured physical examination that focuses on the cardiovascular, musculoskeletal, and neurologic systems. Screening for depression, anxiety disorders, and attention-deficit/hyperactivity disorder is also recommended. Clinicians should recognize any findings suggestive of the relative energy deficiency in sport syndrome. Additional consideration is required to address the needs and concerns of transgender athletes and athletes with physical and intellectual disabilities. Finally, guidelines have been published regarding return to play for athletes who have had COVID-19

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Am J Orthod Dentofacial Orthop. 2021 May;159:653-59.

THE PREVALENCE OF MALOCCLUSION IS HIGHER IN SCHOOLCHILDREN WITH SIGNS OF HYPERACTIVITY.

Mota-Veloso I, Ramos-Jorge J, Freitas LRP, et al.

Introduction: Attention deficit-hyperactivity disorder is a behavioral disorder characterized by a lack of focus, impulsive behavior, and or excessive activity. This research aimed to evaluate the association between signs of attention deficit-hyperactivity disorder and malocclusion in schoolchildren.
Methods: A cross-sectional study was conducted with a representative sample of 633 children aged 7-12 years. The children were clinically examined for malocclusion using the Dental Aesthetic Index. The predominant breathing pattern was also determined. Parents answered a questionnaire addressing socioeconomic characteristics and the presence of nonnutritive sucking habits. The Swanson, Nolan, and Pelham Scale-IV was filled out by both parents and teachers to compare behavioral patterns. The children were submitted to a neuropsychological evaluation using the Raven's Colored Progressive Matrix Test. Data analysis involved the chi-square test and Poisson regression analysis.
Results: The prevalence of malocclusion was 42% higher among children with signs of hyperactivity reported by both parents and teachers (prevalence ratio [PR], 1.42; 95% confidence interval [CI], 1.11-1.81; P = 0.004). In the final Poisson regression model, the prevalence of malocclusion was lower among schoolchildren aged 11 and 12 years (PR, 0.62; 95% CI. 0.52-0.73; P <0.001) and higher among those who used a pacifier for at least 4 years (PR, 1.25; 95% CI, 1.02-1.54; P = 0.029) as well as those classified as mouth breathers (PR, 1.28; 95% CI, 1.09-1.51; P = 0.003).

Conclusions: The prevalence of malocclusion was higher among children with signs of hyperactivity independently of age, pacifier use, and mouth breathing

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Am Fam Phys. 2020;102:592-602.

ADHD IN CHILDREN: COMMON QUESTIONS AND ANSWERS.

Chang JG, Cimino FM, Gossa W.

Attention-deficit/hyperactivity disorder (ADHD) is a multidimensional chronic neurodevelopmental condition that affects 8.4% of U.S. children between two and 17 years of age and may pose long-term morbidity if untreated. The evaluation for ADHD begins when parents or caregivers present to primary care physicians with concerns about behavior problems or poor school or social function. A comprehensive history and physical examination should assess for comorbid or other conditions that can mimic ADHD. The combination of Diagnostic and Statistical Manual of Mental Disorders, 5th ed., criteria and validated screening tools completed by parents, teachers, or other adults can aid in establishing the diagnosis. The goals of treatment include symptom reduction and improved social and cognitive function. Psychosocial interventions are the recommended first-line treatment for preschool children (four to five years) and can improve overall function when used as an adjunct therapy in elementary school children (six to 11 years of age) and adolescents (12 to 17 years of age). Stimulant medications are well-established as an effective treatment for reducing symptoms of ADHD in elementary school children and adolescents. Nonstimulant medications are less effective but reasonable as adjunct or alternative therapy when stimulants are ineffective or not tolerated. Regular follow-up is key in the management of ADHD and should assess symptoms, overall function, presence of comorbidities, adverse effects of treatment, and medication use

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Anadolu Psikiyatr Derg. 2021;22:100-05.

DECREASED THEORY OF MIND ABILITIES AND INCREASED EMOTIONAL DYSREGULATION IN ADOLESCENTS WITH ASD AND ADHD.

Da-ƒdelen F.

Objective: The aim of this study is to evaluate the possible relationship theory of mind (ToM) and emotion regulation (ER) skills in adolescents diagnosed with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD).

Methods: This study comprised 60 individuals with ADHD and 60 individuals with ASD according to DSM-5 and between the ages of 12-16, and 60 adolescents without any psychiatric diagnosis. The Turkish version of the schedule for affective disorders and schizophrenia for school-age children, both present and lifetime versions, was applied to assess psychopathology and comorbidity. The intelligence level of the patients was assessed with the Wechsler Intelligence Scale for Children-Revised. Reading the mind in the eyes test, the Faux Pas Test, and the hinting task were given to patients to evaluate the ToM skills. The difficulties in ER Scale were also used to evaluate the skills of regulating emotions.

Results: Adolescent patients with ADHD and ASD have difficulties in ToM and ER skills. Adolescents diagnosed with ASD had more difficulty in ToM and ER than adolescents with ADHD.

Discussion: This study supports the idea that ADHD and ASD are related to deficits in ToM and ER skills. Therefore, further studies are required to confirm the findings of this study

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Arch Dis Child Educ Pract Ed. 2021;106:63.

ATTENTION DEFICIT HYPERACTIVITY DISORDER WAS ASSOCIATED WITH INCREASED RISK OF SUICIDAL BEHAVIOUR.

Friend AJ.

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Autism. 2021 Apr;25:705-18.

HEALTHCARE SERVICE UTILIZATION AND COST AMONG TRANSITION-AGE YOUTH WITH AUTISM SPECTRUM DISORDER AND OTHER SPECIAL HEALTHCARE NEEDS.

Ames JL, Massolo ML, Davignon MN, et al.

Youth with autism spectrum disorder often have complex medical needs. Disruptions of healthcare during the transition from pediatric to adult healthcare may put youth with autism spectrum disorder at higher risk of medical emergencies and high medical costs. To understand healthcare utilization during the transition years, we conducted a study among transition-age youth (14-25 years old) receiving healthcare at Kaiser Permanente Northern California during 2014-2015. We examined differences in healthcare utilization and costs among youth with autism spectrum disorder (n = 4123), attention deficit and hyperactivity disorder (n = 20,6015), diabetes mellitus (n = 2156), and general population controls (n = 20,615). Analyses were also stratified by age and sex. Youth with autism spectrum disorder had the highest utilization of outpatient primary care, mental health, and psychotropic medications and the lowest utilization of obstetrics/gynecology and urgent care. Costs for youth with autism spectrum disorder were higher than those for attention deficit and hyperactivity disorder and general population peers and lower than for diabetes mellitus. Healthcare utilization patterns varied by age. Transition-age youth with autism spectrum disorder generally used healthcare at higher rates relative to attention deficit and hyperactivity disorder and general population peers but at similar or lower rates than diabetes mellitus peers, indicating this group's complex combination of psychiatric and medical healthcare needs. The relatively high utilization of psychiatric services and low utilization of women's health services in transition-age youth with autism spectrum disorder may have implications for long-term health and warrants additional research

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Behav Ther. 2021 May;52:745-60.

PATTERNS OF PARENTAL ADHERENCE AND THE ASSOCIATION TO CHILD AND PARENTING OUTCOMES FOLLOWING A MULTICOMPONENT SCHOOL-HOME INTERVENTION FOR YOUTH WITH ADHD.

Dvorsky MR, Friedman LM, Spiess M, et al.

The goal of the present study was to evaluate the role of parent adherence in the Collaborative Life Skills (CLS) program, a multicomponent school-home intervention, for predicting child and parenting outcomes. A sample of 129 children (63% male; M age = 8.22, SD = 1.10; grades 2–5) with attention-deficit/hyperactivity disorder (ADHD) and their parents participated in CLS, which included 10 weekly behavioral parent training group sessions. Each week, parents provided information on their CLS skill use between sessions (at home) as part of the intervention. Outcome measures included parent and teacher ratings of child behavior and parenting at post-intervention and 6 months follow-up. Growth mixture models examining weekly parent skill use trajectories throughout the intervention significantly predicted parent- and teacher-reported outcomes including parent-rated child behavior, teacher-rated academic competence, and positive parenting behaviors. Fifty-two percent of parents displayed moderate skill use throughout the intervention, whereas the remaining parents had either low (20%) or high (28%) initial levels of use but demonstrated high skill utilization by the middle of the intervention. Results highlight the importance of examining individual differences in parents between session strategy use for behavioral parent training interventions targeting child and parenting outcomes

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Biochemical and Cellular Archives. 2021;21:1687-91.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PRIMARY SCHOOL CHILDREN IN RAMADI CITY.

Al-Ani MM, Shitran RF, Rajab YA.

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurobehavioral disorders of childhood, which interferes with the social and educational development. The aim and objective of the study was designed for detection of ADHD symptoms among primary school children in Ramadi city. Across sectional study done for students in 10 primary schools for boys and girls from 18 of October 2018 to 6th of December 2018, the criteria of diagnosis done according to the American Psychiatric Association, students who fill in the criteria are studied for age, sex, family history, mother education, socioeconomic status of the family and school performance. The prevalence of ADHD was 9.45, male was found in 55% of cases,most

cases were from 6-8 years of old, inattention ADHD was found in 47% of cases. 62% of cases had positive family history.38% of cases were from low educated mothers. Most of cases were from middle socioeconomic status families 59%. Poor school performance were present in 73% of cases. In conclusions, ADHD is a big problem among children of primary school in Ramadi city with a significant effect on the academic state

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Biomedical Optics Express. 2021;12:3037-49.

DISRUPTED SIGNAL VARIABILITY OF SPONTANEOUS NEURAL ACTIVITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hu Z, Liu L, Wang M, et al.

Brain signal variability (BSV) has shown to be powerful in characterizing human brain development and neuropsychiatric disorders. Multiscale entropy (MSE) is a novel method for quantifying the variability of brain signal, and helps elucidate complex dynamic pathological mechanisms in children with attention-deficit/hyperactivity disorder (ADHD). Here, multiplechannel resting-state functional near-infrared spectroscopy (fNIRS) imaging data were acquired from 42 children with ADHD and 41 healthy controls (HCs) and then BSV was calculated for each participant based on the MSE analysis. Compared with HCs, ADHD group exhibited reduced BSV in both high-order and primary brain functional networks, e.g., the default mode, frontoparietal, attention and visual networks. Intriguingly, the BSV aberrations negatively correlated with ADHD symptoms in the frontoparietal network and negatively correlated with reaction time variability in the frontoparietal, default mode, somatomotor and attention networks. This study demonstrates a wide alternation in the moment-to-moment variability of spontaneous brain signal in children with ADHD, and highlights the potential for using MSE metric as a disease biomarker

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BMC Psychiatry. 2021;21.

COGNITIVE CONTROL AND EMOTIONAL RESPONSE IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER COMORBIDITY WITH DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS.

Zhu Y, Liu L, Yang D, et al.

Background: This study investigated cognitive and emotional functioning in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and disruptive, impulse-control, and conduct disorders (DICCD).

Methods: Thirty patients with ADHD, 26 with DICCD, 22 with ADHD+DICCD were recruited from the outpatient department of Shanghai Changning Mental Health Center, plus 20 healthy controls (HC). Differences between the groups in cognitive and emotional functioning were examined using Golden's Stroop and Emotional Stroop tests. For Emotional Stroop Mean reaction time (RT) of positive word (POS) and negative word (NEG) with color congruence (C) or incongruence (I) were recorded as POS-C, POS-I, NEG-C and NEG-I, respectively.

Results: For Golden's interference scores (IGs), both errors and RTs in the ADHD group were higher than in the other groups. Longer mean RTs of POS-C, POS-I, NEG-C and neural word (NEU) of the ADHD group, and NEG-I of ADHD+DICCD and DICCD groups were observed compared to HC. After 12 weeks of methylphenidate treatment, differences between ADHD subgroups and HC on Golden's Stroop RT disappeared, but differences in Golden's Stroop errors and Emotional Stroop mean RTs remained. The ADHD+DICCD group showed longer mean RTs in NEG-C, NEG-I and NEU of the Emotional Stroop test than the ADHD group.

Conclusions: Our study shows that regardless of emotional responding, deficit in cognitive control is the core symptom of ADHD. However, emotionally biased stimuli may cause response inhibitory dysfunction among DICCD with callous-unemotional traits, and the comorbidity of ADHD and DICCD tends to account for the negative emotional response characteristic of DICCD. These deficits may be eliminated by medication treatment in ADHD, but not the ADHD with comorbid DICCD. Our results support the notion that ADHD with comorbid DICCD is more closely related to DICCD than to ADHD

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BMC Psychiatry. 2021 May;21.

TEMPORAL TRENDS IN ANNUAL INCIDENCE RATES FOR PSYCHIATRIC DISORDERS AND SELF-HARM AMONG CHILDREN AND ADOLESCENTS IN THE UK, 2003–2018.

Cybulski L, Ashcroft DM, Carr MJ, et al.

Background: There has been growing concern in the UK over recent years that a perceived mental health crisis is affecting children and adolescents, although published epidemiological evidence is limited.

Methods: Two population-based UK primary care cohorts were delineated in the Aurum and GOLD datasets of the Clinical Practice Research Datalink (CPRD). We included data from 9,133,246 individuals aged 1–20 who contributed 117,682,651 person-years of observation time. Sex- and age-stratified annual incidence rates were estimated for attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (age groups: 1–5, 6–9, 10–12, 13–16, 17–19), depression, anxiety disorders (6–9, 10–12, 13–16, 17–19), eating disorders and self-harm (10–12, 13–16, 17–19) during 2003–2018. We fitted negative binomial regressions to estimate incidence rate ratios (IRRs) to examine change in incidence between the first (2003) and final year (2018) year of observation and to examine sex-specific incidence.

Results: The results indicated that the overall incidence has increased substantially in both boys and girls in between 2003 and 2018 for anxiety disorders (IRR 3.51 95% CI 3.18–3.89), depression (2.37; 2.03–2.77), ASD (2.36; 1.72–3.26), ADHD (2.3; 1.73–3.25), and self-harm (2.25; 1.82–2.79). The incidence for eating disorders also increased (IRR 1.3 95% CI 1.06–1.61), but less sharply. The incidence of anxiety disorders, depression, self-harm and eating disorders was in absolute terms higher in girls, whereas the opposite was true for the incidence of ADHD and ASD, which were higher among boys. The largest relative increases in incidence were observed for neurodevelopmental disorders, particularly among girls diagnosed with ADHD or ASD. However, in absolute terms, the incidence was much higher for depression and anxiety disorders.

Conclusion: The number of young people seeking help for psychological distress appears to have increased in recent years. Changes to diagnostic criteria, reduced stigma, and increased awareness may partly explain our results, but we cannot rule out true increases in incidence occurring in the population. Whatever the explanation, the marked rise in demand for healthcare services means that it may be more challenging for affected young people to promptly access the care and support that they need

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BMC Psychol. 2021 May;9:72.

AN EEG INVESTIGATION OF ALPHA AND BETA ACTIVITY DURING RESTING STATES IN ADULTS WITH WILLIAMS SYNDROME.

Greer JMH, Riby DM, McMullon MEG, et al.

Background: Williams syndrome (WS) is neurodevelopmental disorder characterised by executive deficits of attention and inhibitory processing. The current study examined the neural mechanisms during resting states in adults with WS in order to investigate how this subserves the attention and inhibitory deficits associated with the syndrome.

Method: Adopting electroencephalography (EEG) methodology, cortical electrical activity was recorded from eleven adults with WS aged 35 + years during Eyes Closed (EC) and Eyes Open (EO) resting states, and compared to that of thirteen typically developing adults matched for chronological age (CA) and ten typically developing children matched for verbal mental ability (MA). Using mixed-design analyses of variance (ANOVA), analyses focused on the full alpha (8-12.5 Hz), low-alpha (8-10 Hz), upper-alpha (10-12.5 Hz), and beta (13-29.5 Hz) bands, as these are thought to have functional significance with attentional and inhibitory processes.

Results: No significant difference in alpha power were found between the WS and CA groups across all analyses, however a trend for numerically lower alpha power was observed in the WS group, consistent with other developmental disorders characterised by attentional/inhibitory deficits such as Attention Deficit Hyperactivity Disorder (ADHD). In contrast, comparable beta power between the WS and CA groups during both EC/EO conditions suggests that their baseline EEG signature is commensurate with successful attentional processing, though this needs to be interpreted with caution due to the small sample size. Analyses also revealed an unusual trend for low variability in the EEG signature of the WS group, which contradicts the heterogeneity typically observed behaviourally.

Conclusions: This novel finding of low variability in the EEG spectra in the WS group has been previously associated with poor behavioural performance in ADHD and is highly informative, highlighting future research

needs to also consider how the role of low variability in the EEG profile of WS manifests in relation to their behavioural and cognitive profiles

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Br J Clin Psychol. 2021 Jun;60:252-69.

THE EFFECT OF MEDICATION AND QUESTION WORDING ON SELF-REPORTED SYMPTOMS AND THEIR ACCURACY IN YOUNG ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lineweaver TT, Kercood S, Gabor AJ, et al.

OBJECTIVES: This study examined the effect of whether participants were on or off their medications and the effect of questionnaire wording on self-reported symptoms in young adults with ADHD. Additionally, this research evaluated the relationships between these self-reported symptoms and objective performance on measures of working memory.

DESIGN: This experimental study utilized a mixed factorial design with one between-subjects factor (whether participants were unmedicated or medicated at the time they completed their assessment) and one within-subjects factor (whether participants reported their on-medication or off-medication symptoms when describing their ADHD subjective symptomatology).

METHODS: Forty-five young adults with ADHD (ages 18-23) completed a brief neuropsychological evaluation and several self-report questionnaires. RESULTS: Although being medicated or unmedicated while completing the questionnaires did not directly affect self-reported symptoms or their accuracy, questionnaire wording exerted a statistically significant effect on subjective symptomatology; participants described themselves as substantially more symptomatic at times when they are off than at times when they are on their medications. More importantly, their general self-perceptions (symptoms when medication state was not specified) of their Inattention/Memory Problems and their Hyperactivity/Restlessness aligned with their descriptions of their off-medication symptoms, whereas their general self-perceptions of their Impulsivity/Emotional Lability and Problems with Self-Concept related to both their self-reported off-medication and on-medication symptoms.

CONCLUSIONS: These results highlight the necessity of specifying medication state when asking patients to report their current symptomatology. Failing to do so risks an over-reporting of symptoms from patients who are typically on medications as they may describe the extent of their unmedicated, rather than medicated, symptomatology.

PRACTITIONER POINTS: Being medicated or unmedicated while completing questionnaires about subjective symptomatology did not directly affect self-reported symptoms of young adults with ADHD or the accuracy of these self-reports. When medication state was not specified on a questionnaire, young adults with ADHD reported symptoms similar to those they experience when they are not medicated. These results highlight the importance of specifying medication state when asking young adults with ADHD to report their current symptomatology. Failing to do so risks an over-reporting of symptoms from patients who are typically on medications. These findings open the door for further research with larger and more diverse and representative samples of adults with ADHD to evaluate the accuracy of their subjective symptomatology relative to their objective abilities. Future studies should also examine whether gender affects subjective symptoms, their accuracy, or the influence of question wording and medications on self-reported symptomatology of adults with ADHD, as the current study was unable to address this important issue

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Brain Behav Immun. 2021 May;94:327-37.

GHRELIN MODULATES DOPAMINERGIC NEURON FORMATION AND ATTENTION DEFICIT HYPERACTIVITY DISORDER-LIKE BEHAVIORS: FROM ANIMALS TO HUMAN MODELS.

Shi X, Guan K, Peng X, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children. The orexigenic hormone ghrelin is important in neuroprotection and neurodevelopment, which may play an important role in psychopathogenesis of ADHD. This study aimed to systematically investigate the genomic and pharmacological manipulations of ghrelin functioning in ADHD-like symptoms in zebrafish models and validated the effects of ghrelin polymorphisms in human subjects with ADHD. We firstly generated ghrelin(Î”/Î”) zebrafish mutant, which displayed hyperactive, attention deficit-like and impulsive-like behaviors,

as well as endophenotypes, mimicking human ADHD. Ghrelin(Î”/Î”) zebrafish exhibited downregulated expression levels of wnt1, wnt3a, wnt5a that are critical for dopaminergic neuron development to possibly regulate their number and spatial organization. Pharmacological blockade of wnt signaling with XAV939 induced a reduced moving activity and less dopaminergic neurons; whereas, wnt agonist SB415286 rescued hyperactivity and dopaminergic neuron loss in ghrelin(Î”/Î”) zebrafish. In addition, we further identified and validated a SNP, rs696217, on orexigenic hormone preproghrelin/ghrelin (T408T, Met72Met) to be associated with a higher risk of ADHD in a case-controlled association study with 248 subjects with ADHD and 208 subjects of healthy controls. Together, our results reveal a novel endogenous role for orexigenic hormone ghrelin in ADHD, which provides insights into genetic regulation and drug screens for the identification of novel treatments of ADHD

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Brain Sciences. 2020;10:1-10.

OBJECTIVE ASSESSMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) USING AN INFINITE RUNNER-BASED COMPUTER GAME: A PILOT STUDY.

Delgado-Gomez D, et al.

In the last few years, several computerized tasks have been developed to increase the objectivity of the diagnosis of attention-deficit hyperactivity disorder (ADHD). This article proposes the running raccoon video game to assess the severity of inattention in patients diagnosed with ADHD. Unlike existing tests, the proposed tool is a genuine video game in which the patient must make a raccoon avatar jump to avoid falling into different gaps. The distance to the gap is recorded for each jump. To evaluate the proposed game, an experiment was conducted in which 32 children diagnosed with ADHD participated. For each participant, the median and interquartile range of these distances were calculated, along with the number of omissions. Experimental results showed a significant correlation between the participants inattention (measured by the Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior rating scale (SWAN) inattention subscale) with each of these three measures. In addition to its accuracy, other benefits are its short duration and the possibility of being run on both standard computers and mobile devices. These characteristics facilitate its acceptance in clinical environments or even its telematic use. The obtained results, together with the characteristics of the video game, make it an excellent tool to support clinicians in the diagnosis of ADHD

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Brain Sciences. 2021;11.

NEUROPSYCHOLOGICAL PROFILE, EMOTIONAL/BEHAVIORAL PROBLEMS, AND PARENTAL STRESS IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Operto FF, Smirni D, Scuoppo C, et al.

Background: The aim of our study was to trace a specific neuropsychological profile, to investigate emotional-behavioral problems and parental stress in children with Autism Spectrum Disorder Level 1/High functioning (ASD-HF), Specific Learning Disorders (SLD) and Attention Deficit/Hyperactivity Disorder (ADHD) disorders and to highlight similarities and differences among the three groups.

Methods: We retrospectively collected the data from a total of 62 subjects with ASD-HF (n = 19) ADHD (n = 21), SLD (n = 22) and 20 typical development. All the participants underwent neuropsychological standardized test for the evaluation of cognitive profile (Wechsler Intelligence Scale for Children Fourth Edition-WISC-IV), behavioral and emotional problems (Child Behavior CheckList CBCL), and parental stress (Parental Stress Index Short Form-PSI-SF). The scores of the ASD-HF, ADHD, and SLD groups were compared using non-parametric statistic methods (Kruskall-Wallis H test and U Mann-Whitney for post-hoc analysis).

Results: The ASD-HF group were significantly higher in all areas of the WISC-IV than the other two clinical groups. The SLD group performed significantly lower than ASD-HF in Working Memory Index. The SLD group showed lower scores on the somatic problems subscale than the other two groups. In the Difficult Child subscale of the PSI-SF, parents of ADHD children scored lower than the mothers of SLD subjects and higher than the fathers of SLD subjects. In all three groups there are specific deficiencies compared to the control group in the cognitive profile, behavioral and emotional problems, and parental stress.

Conclusions: Our comparative analysis highlighted similarities and differences in three groups of children with different neurodevelopmental disorders, helping to better define cognitive, behavioral, and emotional characteristics of these children and parental stress of their parents

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Brain Sciences. 2021;11.

THE ASSOCIATION BETWEEN PROSOCIAL BEHAVIOUR AND PEER RELATIONSHIPS WITH COMORBID EXTERNALIZING DISORDERS AND QUALITY OF LIFE IN TREATMENT-NA+»VE CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Velo S, Kereszteny A, Ferenczi-Dallos G, et al.

Several recent studies confirmed that Attention Deficit Hyperactivity Disorder (ADHD) has a negative influence on peer relationship and quality of life in children. The aim of the current study is to investigate the association between prosocial behaviour, peer relationships and quality of life in treatment naïve ADHD samples. The samples included 79 children with ADHD (64 boys and 15 girls, mean age = 10.24 years, SD = 2.51) and 54 healthy control children (30 boys and 23 girls, mean age = 9.66 years, SD = 1.73). Measurements included: The “Mini International Neuropsychiatric Interview Kid; Strengths and Difficulties Questionnaire” and the “Inventar zur Erfassung der Lebensqualität bei Kindern und Jugendlichen”. The ADHD group showed significantly lower levels of prosocial behaviour and more problems with peer relationships than the control group. Prosocial behaviour has a weak positive correlation with the rating of the child’s quality of life by the parents, both in the ADHD group and in the control group. The rating of quality of life and peer relationship problems by the parents also showed a significant negative moderate association in both groups. The rating of quality of life by the child showed a significant negative weak relationship with peer relationships in the ADHD group, but no significant relationship was found in the control group. Children with ADHD and comorbid externalizing disorders showed more problems in peer relationships than ADHD without comorbid externalizing disorders. Based on these results, we conclude that therapy for ADHD focused on improvement of prosocial behaviour and peer relationships as well as comorbid externalizing disorders could have a favourable effect on the quality of life of these children

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Brain Sciences. 2021;11.

BEHAVIOURAL MEASURES OF INFANT ACTIVITY BUT NOT ATTENTION ASSOCIATE WITH LATER PRESCHOOL ADHD TRAITS.

Goodwin A, Hendry A, Mason L, et al .

Mapping infant neurocognitive differences that precede later ADHD-related behaviours is critical for designing early interventions. In this study, we investigated (1) group differences in a battery of measures assessing aspects of attention and activity level in infants with and without a family history of ADHD or related conditions (ASD), and (2) longitudinal associations between the infant measures and preschool ADHD traits at 3 years. Participants (N = 151) were infants with or without an elevated likelihood for ADHD (due to a family history of ADHD and/or ASD). A multi-method assessment protocol was used to assess infant attention and activity level at 10 months of age that included behavioural, cognitive, physiological and neural measures. Preschool ADHD traits were measured at 3 years of age using the Child Behaviour Checklist (CBCL) and the Child Behaviour Questionnaire (CBQ). Across a broad range of measures, we found no significant group differences in attention or activity level at 10 months between infants with and without a family history of ADHD or ASD. However, parent and observer ratings of infant activity level at 10 months were positively associated with later preschool ADHD traits at 3 years. Observable behavioural differences in activity level (but not attention) may be apparent from infancy in children who later develop elevated preschool ADHD traits

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Br J Psychiatry. 2021;218:64-65.

LONG-TERM OUTCOMES OF FEMALES WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: INCREASED RISK FOR SELF-HARM.

O'Grady SM, Hinshaw SP .

Although long-term outcomes of girls with attention-deficit hyperactivity disorder are understudied, high risk for adolescent and young-adult self-harm is salient. We present data on predictors and mediators of such risk, highlighting a recent dual-process model involving trait impulsivity plus family- and peer-related contributors. We conclude with recommendations for assessment and preventive intervention

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Br J Psychiatry. 2021;218:43-50.

THE NEURODEVELOPMENTAL NATURE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN ADULTS.

Breda V, Rohde LA, Menezes AMB, et al.

Background Population studies have suggested that most adults with attention-deficit hyperactivity disorder (ADHD) did not have the disorder in childhood, challenging the neurodevelopmental conceptualisation of ADHD. Arbitrary definitions of age at onset and lack of defined trajectories were accounted for the findings. Aims The objective of this study was to assess the proportion of individuals presenting with either a neurodevelopmental trajectory or late-onset disorder, and to assess risk factors associated with them.

Method Data of 4676 individuals from the 1993 Pelotas birth cohort at 11, 15, 18 and 22 years of age were used. Polythetic and latent class mixed model analyses were performed to define ADHD trajectories from childhood to adulthood, and characterise the neurodevelopmental or late-onset courses. Regression models were applied to assess factors associated with different trajectories.

Results Classical polythetic analyses showed that 67% of those with ADHD at 22 years of age had a neurodevelopmental course of the disorder. Latent class mixed model analysis indicated that 78% of adults with ADHD had a trajectory of persistent symptoms, more common in males. The remaining adults with ADHD had an ascending symptom trajectory that occurred after puberty, with late-onset ADHD associated with female gender and higher IQ.

Conclusions Both polythetic and latent trajectories analyses provided empirical evidence supporting that the large majority of adults with ADHD had a neurodevelopmental disorder

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Child Neuropsychol. 2021.

CLINICAL PRESENTATIONS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS: COMPARISON OF NEUROCOGNITIVE PERFORMANCE.

Krieger V, Amador-Campos JA.

This study aimed to compare performance in working memory (WM), processing speed (PRS), and attention measures in children and adolescents with typical development (TD) and with Attention deficit hyperactivity disorder (inattentive [ADHD-I] or combined [ADHD-C]) presentations, and to determine the predictive ability of the measures mentioned to discriminate between ADHD presentations and TD. 260 children and adolescents, 138 with ADHD (70 ADHD-I and 68 ADHD-C) and 122 TD in two age cohorts (8ΓÇô12-áyears; 13ΓÇô16-áyears), were assessed with WM and PRS indexes of Wechsler Intelligence Scale for Children (WISC-IV) and the d2 attention test. Significant differences between ADHD and TD groups in the WISC-IV GAI scores were found in children but not in adolescents. Children and adolescents with both ADHD presentations performed poorly on the PRS index, while on the WM index only children exhibited difficulties. In the attention test, children with ADHD-C showed more impulsivity and more difficulties for processing speed, concentration and accuracy than ADHD-I and TD. In addition, both ADHD presentations had higher inattention scores than TD. ADHD adolescents performed worse than TD in processing speed, concentration and accuracy. ADHD groups showed more impulsivity and inattention than TD. Digit Span and Symbol Search (WISC-IV) and processing speed and accuracy (d2) successfully classified ADHD and TD in children, but in adolescents, only coding (WISC-IV) and accuracy (d2) successfully classified ADHD presentations and TD. The WISC-IV and d2 yield neuropsychological profiles which reflect age-related cognitive changes and may allow the adaptation of more tailored early interventions for ADHD

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Child Neuropsychol. 2021.

THE CONTRIBUTION OF SLUGGISH COGNITIVE TEMPO TO PROCESSING SPEED IN SURVIVORS OF PEDIATRIC BRAIN TUMORS.

Peterson RK, Jones K, Jacobson LA.

Sluggish Cognitive Tempo (SCT) describes a pattern of under-activity, poor initiation, and slowness. It was first reported within the Attention Deficit Hyperactivity Disorder (ADHD) literature and found to be positively associated with the inattentive symptoms of ADHD and negatively or not significantly associated with the hyperactivity/impulsivity symptoms of ADHD. SCT has since been considered applicable to the pediatric oncology population given the emergence of inattentive, sluggish symptoms secondary to cancer treatment. The present study examined the unique contribution of SCT to various processing speed skills in a clinical sample of pediatric brain tumor (BT) survivors in order to determine the degree to which SCT explained timed cognitive processing components. Measures included speeded naming, graphomotor speed, and speeded inhibition. Hierarchical linear regression analyses were used to predict performance-based measures of processing speed. After controlling for verbal ability and inattention, SCT, particularly Daydreamy SCT (+¦=0.698, p =0.023), explained 28% of variance in speeded inhibition. SCT did not add significantly to the prediction of speeded naming or graphomotor speed. Findings suggest that the ΓÇ£daydreamyΓÇØ aspect of SCT, rather than sluggishness per se, may be related to more complex, cognitively-demanding tasks with greater executive functioning burdens in BT survivors. Implications for intervention for oncology survivors as well as future research directions are discussed

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Child Neuropsychol. 2021.

NEUROPSYCHOLOGICAL PREDICTORS OF DRIVING HAZARD DETECTION IN AUTISM SPECTRUM DISORDER AND ADHD.

Bednarz HM, Kana RK, Svancara AM, et al.

Driving is a neuropsychologically complex task; this can present challenges for individuals with neurodevelopmental disorders (NDDs) such asautism spectrum disorder (ASD) and attentionΓÇôdeficit/hyperactivity disorder (ADHD). Deficits in theory of mind (ToM) and executive function (EF) are common features of ASD and ADHD, respectively, and may influence driving processes such as hazard perception. No studies have directly examined the neuropsychological contributions to hazard detection among drivers with ASD compared to ADHD.In the current study, 48 participants ages 16-30-áyears (13 ASD, 17 ADHD, 18 typically developing (TD)) completed a driving simulator task in which they encountered hazards in the driving environment. Hazards varied in whether they were social (contained a human component) or nonsocial (were physical objects) to examine the contribution of ToM and social processing to hazard response. Additionally, participants completed a neuropsychological battery targeting ToM and EF/attention skills (cognitive tasks and self-report measures).Within the ASD group, participants responded relatively slower to social compared to nonsocial hazards; no effect of hazard type was observed in the ADHD or TD groups. Additionally, measures of ToM and EF were correlated with driving performanceamong ASD participants; within the ADHD group, only self-reported behavior regulation was associated with driving performance. Broadly, this suggests that cognitive factors such as ToM and EF impact driving hazard performance in ASD and ADHD. The results of the study have implications for developing driving intervention programs for individuals with NDDs

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Child Neuropsychol. 2021.

THE ACTIVATE TEST OF EMBODIED COGNITION (ATEC): RELIABILITY, CONCURRENT VALIDITY AND DISCRIMINANT VALIDITY IN A COMMUNITY SAMPLE OF CHILDREN USING COGNITIVELY DEMANDING PHYSICAL TASKS RELATED TO EXECUTIVE FUNCTIONING.

Bell MD, Weinstein AJ, Pittman B, et al.

Embodied cognition assessment may be more closely related to how children function than standard measures of executive functioning (EF) that require little body movement. Activate Test of Embodied Cognition (ATEC) measures cognitive functioning based on cognitively demanding physical tasks assessed using an automated administration with motion capture technology. This study evaluated the psychometrics of ATEC. Children ages 5–11 years were recruited from the community (N = 55). ATEC was performed twice

for a subsample, approximately 2 weeks apart. Motion capture data were collected and converted into ATEC Total Score. Concurrent measures included scores from NIH Toolbox for EF (Flanker, Working Memory, Go/No-Go task, Balloon Analogue Risk Task (BART)), and parent reports (Child Behavior Checklist (CBCL), Behavioral Rating Inventory of Executive Function (BRIEF-2) and Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) for ADHD). ATEC Total Score was significantly correlated with concurrent measures of EF and showed significant discriminant validity between At-Risk children and Normal Range children on CBCL Competency, CBCL ADHD Combined score, BRIEF-2 Global Executive Composite, BRIEF-2 Cognitive Regulation Index and SNAP-IV ADHD Combined Score. Regression analyses showed that ATEC Total score was a better predictor of CBCL Competency than any of the standard EF assessments. ATEC Total Score had excellent test–retest reliability, (ICC = .945, df = 27, p < .001) with a small practice effect (Cohen's d = 0.33). ATEC Total Score correlated with age (r = .42, p < .003) suggesting improvement with normal development. ATEC produces reliable scores that may identify children at risk for EF impairments

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Clinical Journal of Sport Medicine. 2021;31:207.

COMPARISON OF CONCUSSION SYMPTOMS IN ADOLESCENTS WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Rizk C, Ferderber M, Hadadi N.

Purpose: Prior studies have shown those with ADHD are more likely to report post-concussion symptoms at baseline. This study aims to evaluate differences in PCSS scores as part of SCAT5 and subsequent development of post-concussion syndrome in those diagnosed with a current concussion with and without ADHD.

Methods: A retrospective chart review was performed on adolescents ages 13 to 19 presenting to the sports medicine clinic between January 1, 2016 and December 31, 2019. Inclusion criteria for the study included: (1) PCSS/SCAT completion at the first clinic appointment following concussion; (2) documentation of presence or absence of ADHD; (3) documented date of start of return-to-play protocol.

Results: 108 charts meet the criteria. 17.5% (n = 19) were individuals with documented ADHD, while the remaining 89 comprised the non-ADHD control group. The average number of days from the time of injury to the time of SCAT evaluation was 7.67611.46. Within the ADHD cohort, 73% were males and the mean age was 15.84 -¦ 1.06. The mean number of days to recovery (or return to play protocol initiation) was 21.78 -¦ 21 in the ADHD group, compared with 23.17631.02 in the control group. In the ADHD group, the mean number of symptoms was 10.44 -¦ 7.96, mean symptom severity score was 31.58633.19, overall SAC score was 24.24 -¦ 3.13 and mean concentration score was 1.86 -¦ 2.23. The mean scores obtained in the control group were 9.97 -¦ 5.90 number of symptoms, 28.34 -¦ 24.73 symptom severity, 24.70 -¦ 3.25 overall SAC score and 1.94 -¦ 1.87 concentration score. T-tests comparing the 2 groups for days to recovery, symptom number, symptom severity, SAC and concentration scores had P-values >0.05.

Conclusions: There was no significant difference in number of symptoms, symptom severity scores and cognitive screening (SAC scores) between those with ADHD and those without upon initial presentation of concussion. There is no significant difference in the percentage of adolescents who developed post-concussion syndrome based on diagnosis of ADHD. There is no significant difference in difficulty concentrating following concussion between the cohorts.

Significance: SCAT5 still a good tool to assess for concussion in those with ADHD. While the etiology of prolonged recovery from concussion is multifactorial, ADHD does not appear to increase risk of developing post-concussion syndrome in this cohort

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Clin Neuropharmacol. 2021;44:104-05.

EXCESSIVE MASTURBATION SUCCESSFULLY TREATED WITH METHYLPHENIDATE IN A 6-YEAR-OLD CHILD WITH AUTISM SPECTRUM DISORDER ACCOMPANIED BY ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ferahkaya H, Bilgi A.

Children with autism spectrum disorder frequently exhibit inappropriate sexual behaviors, such as excessive masturbation. However, research on the control and management of excessive masturbation in these children is very limited. In this presentation, excessive masturbation that responded to treatment with

methylphenidate is described in a young boy diagnosed with autism spectrum disorder and comorbid attention deficit hyperactivity disorder

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Clin Neuropharmacol. 2021;44:101-03.

ACTIVATION SYNDROME IN A PATIENT WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH ATOMOXETINE: A CASE REPORT.

Karakaya SEK, Yektas , Tufan AE.

"Activation syndrome"represents a cluster of symptoms of excessive emotional arousal or behavioral activation, which emerges after the first few weeks of antidepressant treatment or a dose increase and resolves with dose reduction or cessation of treatment. It was reported after treatment with selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor group of agents, but no case of activation syndrome has been reported with the norepinephrine reuptake inhibitor group. Atomoxetine is a norepinephrine reuptake inhibitor and nonstimulant and is used to manage symptoms of attention-deficit/hyperactivity disorder (ADHD). Atomoxetine-related symptoms of mania and hypomania were reported in literature previously. Here, we report a case of activation syndrome arising after atomoxetine (ATX) dose titration in a prepubertal male child with ADHD. Differentiation of activation symptoms from mania/hypomania symptoms after treatment with ATX may be important for the clinicians to manage the adverse effects and understand the risk factors behind activation syndrome with use of ATX in children and adolescents diagnosed with ADHD

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Clin Pharmacol Drug Dev. 2021.

IMPACT OF PAROXETINE, A STRONG CYP2D6 INHIBITOR, ON SPN-812 (VILOXAZINE EXTENDED-RELEASE) PHARMACOKINETICS IN HEALTHY ADULTS.

Wang Z, Kosheleff AR, Adeojo LW, et al.

SPN-812 (viloxazine extended-release) is a novel nonstimulant recently approved as a treatment for attention-deficit/hyperactivity disorder in children and adolescents. Given that SPN-812 is metabolized by CYP2D6 and may be coadministered with CYP2D6 inhibitors, this trial investigated the pharmacokinetics and safety of SPN-812 coadministered with the potent CYP2D6 inhibitor paroxetine. In this single-sequence, 3-treatment period study in healthy volunteers, subjects received a single oral dose of 700 mg SPN-812 alone (period 1), 20 mg daily paroxetine (10 days, period 2), followed by concurrent administration of SPN-812 and paroxetine (period 3). Blood samples were collected for 72 hours post-SPN-812 dosing and analyzed for viloxazine and its primary metabolite, 5-HVLX-gluc. Twenty-two healthy adults were enrolled; all completed the trial. The potential for drug interaction between SPN-812 and paroxetine was assessed using analysis of variance on the log-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUCinf. The least-squares geometric mean ratios for viloxazine were (reported as the ratio of combination/SPN-812 alone) Cmax, 116.04%; 90%CI, 109.49%-122.99%; AUC0-t, 134.65%; 90%CI, 127.65-142.03; and AUCinf, 134.80%; 90%CI, 127.94%-142.03%. CYP2D6 inhibition resulted in a modest change (<35%) on viloxazine AUCs with no change in Cmax. All adverse events were mild in severity

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Clin Psychol Rev. 2021;87.

A SYSTEMATIC REVIEW OF TRANSDIAGNOSTIC RISK AND PROTECTIVE FACTORS FOR GENERAL AND SPECIFIC PSYCHOPATHOLOGY IN YOUNG PEOPLE.

Lynch SJ, Sunderland M, Newton NC, et al.

A large body of research has emerged over the last decade examining empirical models of general and specific psychopathology, which take into account comorbidity among psychiatric disorders and enable investigation of risk and protective factors that are common across disorders. This systematic review presents findings from studies of empirical models of psychopathology and transdiagnostic risk and protective factors for psychopathology among young people (10-24 years). PsycInfo, Medline and EMBASE were searched from inception to November 2020, and 41 studies were identified that examined at least one risk or protective factor in relation to broad, empirically derived, psychopathology outcomes. Results revealed

several biological (executive functioning deficits, earlier pubertal timing, genetic risk for ADHD and schizophrenia, reduced gray matter volume), socio-environmental (stressful life events, maternal depression) and psychological (low effortful control, high neuroticism, negative affectivity) transdiagnostic risk factors for broad psychopathology outcomes, including general psychopathology, internalising and externalising. Methodological complexities are discussed and recommendations for future studies of empirical models of psychopathology are presented. These results contribute to a growing body of support for transdiagnostic approaches to prevention and intervention for psychiatric disorders and highlight several promising avenues for future research

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Clin Psychol Rev. 2021;87.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND RISK-TAKING: A THREE-LEVEL META-ANALYTIC REVIEW OF BEHAVIORAL, SELF-REPORT, AND VIRTUAL REALITY METRICS.

Roberts DK, Alderson RM, Betancourt JL, et al.

Meta-analytic methods were used to examine ADHD-related risk-taking in children and adults, and to compare the magnitude of risk taking across behavioral, self-report, and virtual reality metrics. Potential moderators of effect size heterogeneity were also examined via a three-level multi-level approach and a hybrid meta-analytic/systematic review approach. Aggregated effect sizes obtained from 56 behavioral-task studies (82 effect sizes; ADHDN = 2577; TDN = 2606), 51 self-report studies (130 effect sizes; ADHDN = 18,641; TDN = 113,163), and 8 virtual reality studies (16 effect sizes; ADHDN = 382; TDN = 436) suggest that children and adults with ADHD exhibit moderately more risk-taking compared to children and adults without the disorder. Notably, the aggregated effect size obtained from virtual reality simulations (Hedges', g = 0.43) was 30–40% larger than effect sizes obtained from self-report and behavioral task metrics (Hedges' g = 0.31 and 0.27), respectively. Suboptimal Decision Making was the only significant moderator identified via multi-level modeling; however, comparison of subgroup effect sizes revealed potential moderating effects of ADHD presentation and trial-by-trial feedback on behavioral tasks. Collectively, findings suggest that ADHD is reliably associated with small to moderate magnitude greater risk-taking behavior and virtual reality simulations appear be the most sensitive currently available metric

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Clin Psychopharmacol Neurosci. 2021;19:262-68.

MIR-132 AND MIR-942 EXPRESSION LEVELS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: A CONTROLLED STUDY.

Coskun S, Karadag M, Gokcen C, et al.

Objective: Although attention deficit hyperactivity disorder (ADHD) is a disease with high genetic transition, our knowledge about the mechanism of the disease is limited. In this study, it was aimed to evaluate the levels of miR-132-3p and miR-942-5p that are associated with the dopamine carrier protein gene (DAT1) and dopamine receptor 5 (DRD5) genes, which have been shown to play a role in the development of ADHD.

Methods: According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition, 50 children diagnosed with ADHD and 48 healthy controls were included in the study. Affective Disorders and Schizophrenia Interview Schedule-Now and Lifetime Version-Turkish Adaptation was used to evaluate ADHD and the diagnoses accompanying ADHD. Quantitative Real-Time Polymerase Chain Reaction was used to evaluate miR-132-3p and miR-942-5p expression levels.

Results: It was observed that miR-132-3p level (p = 0.001) was significantly higher with children with ADHD compared to the control group, and the level of miR-942-5p (p = 0.181) was higher in ADHD but did not reach statistically significant level.

Conclusion: In our study, we found that the increase in the miR-132-3p levels of children with ADHD may be a therapeutic target of the disease

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Clin Psychopharmacol Neurosci. 2021;19:334-40.

THE RELATIONSHIP BETWEEN PLASMA ERYTHROPOIETIN LEVELS AND SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Shim SH, Kim YK, Hwangbo Y, et al.

Objective: There are animal models associating dopamine dysfunction with behavioral impairments that model attention deficit hyperactivity disorder (ADHD). Erythropoietin (EPO) has trophic effects on dopaminergic neurons. The aim of this study was to examine the EPO plasma levels and determine whether there was any correlation between plasma EPO levels and clinical characteristics of ADHD.

Methods: Plasma EPO levels were measured in 78 drug-na+»ve children with ADHD and in 81 healthy children. The severity of ADHD symptoms was determined by scores on the Korean ADHD Rating Scale (K-ARS) in ADHD children and healthy controls.

Results: The difference between median plasma EPO levels in ADHD children and in healthy controls was not statistically significant. Adjusting for age and sex, a linear regression analysis showed that inattention score was significantly higher in the second highest tertile of plasma EPO compared to those in the lowest tertile. Hyperactivity-impulsivity score was significantly higher in the highest tertile of plasma EPO compared to those in the lowest tertile. Moreover, total K-ARS scores were significantly higher in the second highest tertile of plasma EPO compared to those in the lowest tertile.

Conclusion: These findings suggest that plasma EPO levels were related to some ADHD symptoms, which could be used in the monitoring of the disorder

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CNS Drugs. 2021;35:575-89.

DISRUPTION OF PHARMACOTHERAPY DURING THE TRANSITION FROM ADOLESCENCE TO EARLY ADULTHOOD IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CLAIMS DATABASE ANALYSIS ACROSS THE USA.

Farahbakhshian S, Ayyagari R, Barczak DS, et al.

Background and Objective: Attention-deficit/hyperactivity disorder (ADHD) treatment rates in adults are low, possibly owing to discontinuation of pediatric care due to various circumstances (including inadequate health insurance coverage, poor disease insight, and patient/family resistance, as well as those who manage their ADHD independent of pharmacologic intervention) during the transition from adolescence to adulthood. To improve the understanding of treatment patterns during this transition, this study characterized pharmacotherapy use in patients with ADHD aged 16ΓÇô21 years.

Methods: A retrospective claims analysis of the IBM-« MarketScan-« Commercial Databases, which represent all census regions of the USA, included patients aged 16ΓÇô21 years with two or more ADHD diagnoses between 1/1/2008 and 12/31/2017 (one or more diagnoses during the year of age 17) who were continuously enrolled from ages 16-21 years and prescribed ADHD medication for 6 months at age 17 years. Pharmacotherapy use was assessed longitudinally. Comparisons between ages were conducted using Wilcoxon signed-rank tests and McNemar tests. Treatment discontinuation was estimated using Kaplan-Meier analyses.

Results: The analysis included 10,292 patients. The overall percentage of patients receiving pharmacotherapy significantly decreased ($p < 0.001$, regardless of treatment type and presence of co-occurring psychiatric disorders) as patients aged, with a median time to treatment discontinuation of 2.94 years. Among patients using pharmacotherapy at the age of 17 years, more than 30% were no longer using pharmacotherapy at age 21 years. As patients aged, the percentage using long-acting amphetamines or methylphenidates decreased, and the percentage receiving no treatment increased. The percentage of patients with disrupted treatment from age 18 to 21 years ranged from 17.9 to 24.1%. After transitioning to disrupted treatment or no treatment, low percentages of patients returned to pharmacotherapy use (disrupted treatment: 15.7-21.5% per year; no treatment, 2.7-3.8% per year). Across all age groups, statistically significantly greater ($p < 0.05$) percentages of patients with co-occurring psychiatric disorders used lisdexamfetamine, dextroamphetamine-amphetamine mix short acting, and non-stimulants compared with patients without co-occurring psychiatric disorders. Patients with co-occurring psychiatric disorders remained on ADHD pharmacotherapy longer and switched or augmented their pharmacotherapy more frequently than patients without co-occurring psychiatric comorbidities.

Conclusions: Patients rarely reinitiated treatment after pharmacotherapy was disrupted or discontinued, emphasizing the need for increased focus on the management of ADHD as patients transition from adolescence to adulthood

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Cogn Behav Pract. 2021.

INTENSIVE BEHAVIOR THERAPY FOR TICS AND CO-OCCURRING ADHD: A CASE REPORT.

Dale C, Ramos M, Parent J.

Tic disorders (TDs) can substantially impact daily child functioning across social, familial, and academic domains, leading to a significant public health impact. Additionally, an overwhelming majority of children with a TD have at least one co-occurring disorder. In particular, over 60% of children with a TD also meet criteria for attention-deficit/hyperactivity disorder (ADHD). Comprehensive Behavioral Intervention for Tics (CBIT) is a first-line treatment for youth with TDs and has been shown to be effective in reducing the frequency, duration, and severity of tics in children and adolescents. Nonetheless, access to trained CBIT providers remains limited, and common comorbid conditions are not addressed in standard CBIT. Thus, there is a need for CBIT interventions that can incorporate treatment strategies for TDs and common comorbidities. To address the critical need to address TD and common comorbidities simultaneously, the current case study presents and evaluates a 2-week intensive approach to address tic and ADHD symptoms concurrently in a peripubertal male. The child's parents reported significant improvements in tic and ADHD symptoms following the end of treatment, which were maintained throughout three follow-up booster sessions. Clinical implications and future directions to modify and improve the proposed treatment are discussed

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Cognitive Neurodynamics. 2021.

DIRECTION OF INFORMATION FLOW BETWEEN BRAIN REGIONS IN ADHD AND HEALTHY CHILDREN BASED ON EEG BY USING DIRECTED PHASE TRANSFER ENTROPY.

Ekhlasi A, Nasrabadi AM, Mohammadi MR.

Directed information flow between brain regions might be disrupted in children with Attention Deficit Hyperactivity Disorder (ADHD) which is related to the behavioral characteristics of ADHD. This paper aims to investigate the different information pathways of brain networks in children with ADHD in comparison with healthy subjects. EEG recordings were obtained from 61 children with ADHD and 60 healthy children without neurological disorders during attentional visual task. Effective connectivity among all scalp channels was calculated using directed phase transfer entropy (dPTE) for delta, theta, alpha, beta, and lower-gamma frequency bands. Group differences were evaluated using permutation tests in connectivity between regions. Significant posterior to anterior patterns of information flow in theta frequency bands were found in healthy subjects (p-value < 0.05), while disrupted pattern flow, in an opposite way, was found in ADHD children. In the beta band, information flow in pathways between anterior regions was significantly higher in healthy individuals than in the ADHD group. These differences are more indicated in connectivity that leads from frontal and central regions to the right frontal regions of the brain (F8 electrode). Furthermore, connections from central and lateral parietal areas to Pz electrode areas are statistically significant and higher in healthy children in this band. In the delta band, internal connections in the anterior region show a significant difference between the two groups, as this amount is higher in the ADHD group. Our analysis may provide new insights into information flow in brain regions of ADHD children in comparison with healthy children

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Early Hum Dev. 2021;155.

COGNITIVE ACHIEVEMENTS IN SCHOOL-AGE CHILDREN BORN FOLLOWING ASSISTED REPRODUCTIVE TECHNOLOGY TREATMENTS: A PROSPECTIVE STUDY.

Farhi A, Gabis LV, Frank S, et al.

Background: While assisted reproductive technology is increasingly prevalent, there is concern amid conflicting findings reported regarding the long-term outcomes of children born following these treatments. The aim of this research was to investigate aspects of cognitive development in early school-age Israeli

children born following assisted reproductive technology (ART) treatments, compared to those spontaneously conceived (SC).
Method: This prospective follow-up study was based on an Israeli cohort recruited from June 2006 to December 2008, that included 561 women whose pregnancies were achieved by ART treatments and 600 women whose pregnancies were SC. When the children were 7–8 years old, 759 of their mothers were interviewed by telephone, and 294 were came for developmental assessment. The examination included: Kaufman Brief Intelligence Test; Kaufman Assessment Battery for Children (arithmetic only); Test of Everyday Attention for Children; Beery-Buktenica Developmental Test of Visual-Motor Integration and Supplemental Test for Visual Perception; Rey-Osterrieth Complex Figure Test; Aleph-ad-Tav Hebrew reading and writing; Tavor Picture Naming Expressive Vocabulary Test. Multivariable analyses were adjusted for maternal years of education (Γëñ12, 13+) at child's birth and child's sex.
Results: Cognitive function, visual-motor ability, attention, and verbal skills of children born after ART treatments were similar to those of SC children, upon both univariate and multivariable analysis.
Conclusion and implications: No significant differences were found between the ART and SC groups on any of the measures examined. This finding offers couples seeking ART treatments improved information regarding child development during the important and formative school years. What this paper adds: Increasing rates of ART treatments arouse concern about long-term outcomes for offspring, and conflicting findings have been reported with respect to the skills necessary to their academic success. This prospective follow-up study compared school-age children born following ART with spontaneously-conceived children. Children were examined by developmental psychologists, and cognitive function, visual-motor, attention, verbal, and performance skills were similar in both groups

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Egypt J Neurol , Psychiatr Neurosurg. 2021;57.
THE INTERICTAL ACTIVITIES LOAD AND COGNITIVE PERFORMANCE OF CHILDREN WITH TYPICAL ABSENCE EPILEPSY.
ELAhwal SA, El-Heneedy YAE, Bahnasy WS, et al.
Background: The description of childhood absence epilepsy (CAE) a benign self-limited generalized epilepsy has become a matter of debate. The objectives of this work were to evaluate the existence of psychiatric and cognitive impairments among patients with typical CAE and to correlate their possible relation to seizure frequency, duration of epilepsy, IISL, and valproate therapy.
Methods: The study was conducted on 19 typical CAE patients receiving valproate therapy, 11 newly diagnosed CAE patients not receiving AEDs, and 30 healthy control subjects (HCS). Participants were subjected to medical history taking, EEG monitoring, child behavior checklist (CBCL), Stanford Binet Intelligence Scale 5th edition, and computerized psychometric tests that assess cognitive domains and executive functions.
Results: The study revealed a high rate of cognitive and psychiatric dysfunctions in CAE patients. 53.3% of patients had psychiatric problems versus 16.6% in HCS. Attention deficit hyperactive disorder (ADHD) (26.6%), anxiety (16.6%), and depression (6.6%) were the most common psychiatric disorders in the patient group. Withdrawn/depressed symptoms, thought problems, social problems, and attention problems in CAE patients were significantly increased compared to HCS. At the same time, CAE patients perform worse in cognitive scales than HCS with comparable intelligent quotient (IQ) scores.
Conclusion: Cognitive and psychiatric impairments in typical CAE patients appear multifactorial in origin with epilepsy-related factors including the duration of epilepsy and interictal spike load (IISL)

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Emot Behav Difficulties. 2021.
LOOKING BACK ON COMPULSORY SCHOOL: NARRATIVES OF YOUNG ADULTS WITH ADHD IN SWEDEN.
Taneja Johansson S.
Relegated to the margins of the large body of research on ADHD and school is individualsΓÇÖ own retrospective accounts of schooling. Drawing on multiple narrative interviews with nine young adults with ADHD in Sweden, the present study explores their experiences and reflections concerning their years in compulsory school. Despite variations in the gradient of decline, time in school was described as a slippery slope, with rapid deterioration in secondary school. Participation in sports and cultural activities outside

school emerged as strong supportive factors. The expectations placed on the individual in the school context and relationships with teachers were described as key hurdles. In hindsight, school was perceived as a meaningless phase of their lives. The present findings nuance the skewed diagnosis focus in contemporary research, raising questions about timing of support in school and offering important insights concerning girls with ADHD

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Encephale. 2021.

ADHD DURING CHILDHOOD AND SUBSEQUENT PSYCHOTIC DISORDER: A LINK?

Gering A, Fourneret P, Poulet E, et al.

Objectives: Attention Deficit with/without Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with frequent comorbid psychiatric disorders. Several studies have underlined the increased risk of developing a psychotic disorder subsequent to a childhood ADHD. The aim of our review is not only to clarify this association and the related physiopathology but also to understand the consequences for therapeutic management.

Methods: We processed a narrative review of available literature based on a research of the PubMed database. Articles related to ADHD and psychotic disorder on a genetical, clinical or biological level were selected by one of the authors.

Results: ADHD and psychotic disorders share neonatal, environmental, and genetic risk factors. On a neurobiological level, both disorders are concerned by a dysfunction of the dopaminergic system with an abnormal regulation of dopaminergic neurons phasic and tonic activity. Our review aims to explain the -½ dynamic -+ model of dopaminergic dysfunctions and propose some guidance for pharmacological treatment of ADHD, with or without psychotic disorder. This model offers a better understanding of why methylphenidate is not associated to an increased risk of psychotic disorder and could act as a protective factor. Association between ADHD and psychotic disorders could be explained by some comorbidities such as substance use disorders which are frequently associated with both conditions and could act as mediator in the genesis of psychotic disorders following ADHD during childhood. Our review also focuses on an epidemiological bias that could be found in some studies such as possible diagnostic errors, as some non-specific clinical signs could be found in both late diagnosed ADHD and in at risk mental state of psychosis.

Conclusion: ADHD and psychotic disorders share common risk factors, neurobiological pathways and clinical symptoms. Perspectives for future studies are proposed considering a dimensional aspect of psychiatric disorders using, for example, Research Domain Criteria and exploring the link between the two conditions

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Encephale. 2021.

IMPROVEMENT OF THE IMPULSIVE CONTROL IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AFTER A COGNITIVE BEHAVIORAL THERAPY.

Grandjean A, Suarez I, et al.

Aim: MPH is the more often prescribed stimulant for Attention Deficit Hyperactivity Disorder (ADHD), but it has been estimated that 30% of patients do not adequately respond or cannot tolerate it. Therefore, some other therapies are needed, such as cognitive behavioral therapy. Cognitive behavioral therapy is an intervention proposed over several sessions and aimed at modifying behavior by teaching different techniques that participants can re-use to control their symptoms. In our Institute, we used a program centered on attentional and metacognitive functions. It consists of a series of workshops performed in group at the rate of one workshop of 90 minutes per week for 12 weeks. Positive effects on the behavior of adolescents with ADHD have been reported by parents and educators, but the effects of the program on specific cognitive processes have never been precisely investigated.

Method: In the present study, we evaluated the impact of the program on impulsive control in adolescents with ADHD who are known to present impaired impulsive control. Impulsive control is required each time there is a conflict between an inappropriate prepotent action and a goal-directed action. At an experimental level, impulsive control can be studied with conflict tasks, such as the Simon reaction time task. Interpreted within the theoretical framework of the so-called -½ Dual-process activation suppression -+ (DPAS) model,

this task is a powerful conceptual and experimental tool to separately investigate the activation and inhibition of impulsive actions, which is almost never done in studies about impulsive control. Twenty adolescents followed the program and were tested before and at the end of the program by using dynamic analyses of performance associated with DPAS model.
Results: The results have shown an improvement of the impulsive control after three months of cognitive behavioral therapy, and this improvement was due to both a decrease of the propensity to trigger impulsive actions and an improvement of inhibitory processes efficiency.
Conclusion: This program could be a relevant alternative to the stimulant medication, more particularly when parents are reluctant with medication or when the adolescent suffers from important side effects

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Environ Res. 2021 May;196:110320.

PRENATAL AIR POLLUTION EXPOSURE AND NEURODEVELOPMENT: A REVIEW AND BLUEPRINT FOR A HARMONIZED APPROACH WITHIN ECHO.

Volk HE, Perera F, Braun JM, et al.

BACKGROUND: Air pollution exposure is ubiquitous with demonstrated effects on morbidity and mortality. A growing literature suggests that prenatal air pollution exposure impacts neurodevelopment. We posit that the Environmental influences on Child Health Outcomes (ECHO) program will provide unique opportunities to fill critical knowledge gaps given the wide spatial and temporal variability of ECHO participants.
OBJECTIVES: We briefly describe current methods for air pollution exposure assessment, summarize existing studies of air pollution and neurodevelopment, and synthesize this information as a basis for recommendations, or a blueprint, for evaluating air pollution effects on neurodevelopmental outcomes in ECHO.
METHODS: We review peer-reviewed literature on prenatal air pollution exposure and neurodevelopmental outcomes, including autism spectrum disorder, attention deficit hyperactivity disorder, intelligence, general cognition, mood, and imaging measures. ECHO meta-data were compiled and evaluated to assess frequency of neurodevelopmental assessments and prenatal and infancy residential address locations. Cohort recruitment locations and enrollment years were summarized to examine potential spatial and temporal variation present in ECHO.
DISCUSSION: While the literature provides compelling evidence that prenatal air pollution affects neurodevelopment, limitations in spatial and temporal exposure variation exist for current published studies. As >90% of the ECHO cohorts have collected a prenatal or infancy address, application of advanced geographic information systems-based models for common air pollutant exposures may be ideal to address limitations of published research.
CONCLUSIONS: In ECHO we have the opportunity to pioneer unifying exposure assessment and evaluate effects across multiple periods of development and neurodevelopmental outcomes, setting the standard for evaluation of prenatal air pollution exposures with the goal of improving children's health

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Epilepsy and Behavior Reports. 2021;16.

METHYLPHENIDATE TREATMENT FOR COGNITIVE SYMPTOMS ASSOCIATED WITH ADHD IN A PEDIATRIC EPILEPSY PATIENT FOLLOWING RESECTION OF A LEFT FRONTAL CORTICAL DYSPLASIA.

Bearden DJ, Shakil S, O'Banion D, et al.

We present data on a 10-year-old patient with drug-resistant epilepsy who was treated with methylphenidate for symptoms of attention deficit hyperactivity disorder (ADHD) that developed after she underwent surgical resection of a left frontal cortical dysplasia. The patient's parents reported methylphenidate was helpful in improving their child's reading performance. Based on parents report, we examined benefits of methylphenidate on our patient's cognitive problems in a controlled setting. The patient underwent a neuropsychological evaluation completed in three sessions over a five-day period. Methylphenidate was administered prior to the second testing session only and was associated with improvements in the patient's attention, executive function, processing speed, and short-term memory performances. In comparison, word-reading performance, a task less susceptible to neurological impairment, was stable over the three sessions. The patient remained seizure-free after surgery and use of methylphenidate did not reduce seizure threshold.

These findings support the use of methylphenidate in treating targeted cognitive problems associated with ADHD emerging after epilepsy surgery in children

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Epilepsy Behav. 2020 Oct;111:107242.

PILOT DATA AND CASE EXAMPLE OF THE INITIAL VISIT IN A MULTIDISCIPLINARY TRANSITION-AGE PROGRAM (TAP).

Hughes-Scalise A, Reger KL, Gergen MA.

The process of transition from pediatric to adult epilepsy care has received increased attention and emphasis in recent literature, particularly related to the assertion that effective transition is likely to lead to improved medical and psychosocial outcomes. However, the majority of current transition literature focuses on the structure of a transition program, with very little research providing relevant clinical data during the transition period and beyond. The current paper attempts to address this gap in the literature by providing pilot data on participants who engaged in the initial visit of a multidisciplinary transition-focused program housed in a level 4 epilepsy center in the Midwest. Pilot data are presented on 28 participants (36% female) who completed the initial transition appointment. All but one participant presented with a positive history for a neurobehavioral comorbidity, the most common of which included anxiety (61%), attention-deficit/hyperactivity disorder (ADHD; 39%) and depression (36%). Seventy-seven percent of participants further identified a current neurobehavioral comorbidity that was impacting their psychosocial functioning. Recommendations provided most frequently involved increased independence with epilepsy management (64%), increased independence with self-care/independent living (82%), psychological intervention (43%), and increased socialization (43%). A case example is also provided to further highlight program process and outcomes of the initial visit. Pilot results emphasize the value of multidisciplinary care involving psychosocial providers to facilitate a smooth transition between pediatric and adult healthcare

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Eur Child Adolesc Psychiatry. 2021 May;30:733-45.

A NOVEL APPROACH TO INTRA-INDIVIDUAL PERFORMANCE VARIABILITY IN ADHD.

Bluschke A, Zink N, MÃ¼ckschel M, et al.

Patients with attention deficit/(hyperactivity) disorder (AD(H)D) show increased intra-individual variability (IIV) in behavioral performance. This likely reflects dopaminergic deficiencies. However, the precise performance profile across time and the pattern of fluctuations within it have not yet been considered, partly due to insufficient methods. Yet, such an analysis may yield important theory-based implications for clinical practice. Thus, in a case-control cross-sectional study, we introduce a new method to investigate performance fluctuations in patients with ADD (n=76) and ADHD (n=67) compared to healthy controls (n=45) in a time estimation task. In addition, we also evaluate the effects of methylphenidate (MPH) treatment on this performance pattern in 29 patients with AD(H)D. Trial-by-trial differences in performance between healthy controls and patients with AD(H)D do not persist continuously over longer time periods. Periods during which no differences in performance between healthy controls and patients occur alternate with periods in which such differences are present. AD(H)D subtype and surprisingly also medication status does not affect this pattern. The presented findings likely reflect (phasic) deficiencies of the dopaminergic system in patients with AD(H)D which are not sufficiently ameliorated by first-line pharmacological treatment. The presented findings carry important clinical and scientific implications

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Eur Child Adolesc Psychiatry. 2021 May;30:809-21.

FUNCTIONAL IMPAIRMENT OUTCOMES IN CLINICAL TRIALS OF DIFFERENT ADHD MEDICATIONS: POST HOC RESPONDER ANALYSES AND BASELINE SUBGROUP ANALYSES.

Coghill DR, Werner-Kiechle T, Farahbakhshian S, et al.

Several recent phase 3 clinical trials of attention-deficit/hyperactivity disorder (ADHD) medications have used the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). Here, we assess WFIRS-P response in individual patients in two pivotal trials of lisdexamfetamine dimesylate (LDX) and guanfacine extended release (GXR). We also analysed pooled WFIRS-P data from seven phase 3 studies of ADHD medications to shed light on factors associated with baseline functional impairment. The proportion of

patients with a change in WFIRS-P score that exceeded the minimal important difference (MID) criteria for response was greater for LDX than placebo in the Family, Learning and School, and Risky Activities domains, and was greater for GXR than placebo in the Social Activities, Learning and School, and Family domains. Responders had significantly worse baseline scores in all WFIRS-P domains (all pâ€‰<â€‰0.001) than non-responders. In the pooled analyses, baseline WFIRS-P scores in all domains were significantly worse in participants with oppositional defiant disorder (ODD) than in those without ODD. Having combined type or hyperactive-impulsive type ADHD, being enrolled into a study in Europe, being male and being younger also had modest negative effects on baseline WFIRS-P scores. The present analysis of WFIRS-P response shows that previously reported group-level improvements in WFIRS-P functional impairment score translated into clinically relevant improvements in many individual participants. Functional impairment is a diverse and subjective construct that is influenced by multiple factors. Optimal management of individuals with ADHD should involve monitoring improvements in functioning and quality of life, as well as symptomatic improvement

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Eur Addict Res. 2021;27:87-96.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CLIENTS DIAGNOSED WITH A SUBSTANCE USE DISORDER IN THE THERAPEUTIC COMMUNITIES: PREVALENCE AND PSYCHIATRIC COMORBIDITY.

Miovska M, Lukavský K, et al.

Background: Most severe substance use disorders (SUDs) are connected with attention deficit hyperactivity disorder (ADHD) and other mental health problems. Therapeutic communities (TCs) provide a suitable option for the treatment of severe SUDs. The relationship between ADHD, the severity of the SUD, and other comorbidities in residential TCs is unknown.

Objective: To estimate the prevalence of ADHD among clients with an SUD in residential rehab, and to compare the mental health of clients with and without ADHD. Methods: A cohort study was conducted in 5 residential TCs (N = 180, 76.7% male, 53.9% 25-34 years, 79.2% diagnosed with methamphetamine use disorder). We assessed ADHD symptoms, substance use, mental health problems, and psychiatric symptoms.

Results: ADHD was found in 51% of the clients who showed significantly higher scores for their psychiatric status composite score (ASI-PSY) ($F = 9.08$, $p < 0.001$; $t = 5.05$, $p < 0.001$), the positive psychiatric symptoms total (SCL-PST) ($F = 3.36$, $p < 0.05$; $t = 3.15$, $p < 0.01$), and the global severity index (SCL-GSI) ($F = 3.27$, $p < 0.05$; $t = 3.18$, $p < 0.01$). The ASI-PSY and SCL correlated significantly with the symptoms of attention deficit disorder (Pearson's r's = 0.30-0.42, p's < 0.001) and the symptoms of hyperactivity disorder (r's = 0.24-0.30, p's < 0.01). Even when severity of substance use was accounted for, ADHD was confirmed as a significant predictor of ASI-PSY ($B = 0.14$, $p < 0.001$ for combined disorder; $B = 0.20$, $p < 0.001$ for attention disorder) and partially of SCL-PST ($B = 8.12$, $p < 0.05$ for attention disorder).

Conclusions: The ADHD prevalence in TCs was nearly 10-fold compared to the globally recorded values. ADHD diagnostic procedures and interventions should become an integral part of the standard diagnostic and treatment process

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Frontiers in Computational Neuroscience. 2021;15.

CAN DEEP LEARNING HIT A MOVING TARGET? A SCOPING REVIEW OF ITS ROLE TO STUDY NEUROLOGICAL DISORDERS IN CHILDREN.

Sargolzaei S.

Neurological disorders dramatically impact patients of any age population, their families, and societies. Pediatrics are among vulnerable age populations who differently experience the devastating consequences of neurological conditions, such as attention-deficit hyperactivity disorders (ADHD), autism spectrum disorders (ASD), cerebral palsy, concussion, and epilepsy. System-level understanding of these neurological disorders, particularly from the brain networks' dynamic perspective, has led to the significant trend of recent scientific investigations. While a dramatic maturation in the network science application domain is evident, leading to a better understanding of neurological disorders, such rapid utilization for studying pediatric neurological disorders falls behind that of the adult population. Aside from the specific technological needs

and constraints in studying neurological disorders in children, the concept of development introduces uncertainty and further complexity topping the existing neurologically driven processes caused by disorders. To unravel these complexities, indebted to the availability of high-dimensional data and computing capabilities, approaches based on machine learning have rapidly emerged a new trend to understand pathways better, accurately diagnose, and better manage the disorders. Deep learning has recently gained an ever-increasing role in the era of health and medical investigations. Thanks to its relatively more minor dependency on feature exploration and engineering, deep learning may overcome the challenges mentioned earlier in studying neurological disorders in children. The current scoping review aims to explore challenges concerning pediatric brain development studies under the constraints of neurological disorders and offer an insight into the potential role of deep learning methodology on such a task with varying and uncertain nature. Along with pinpointing recent advancements, possible research directions are highlighted where deep learning approaches can assist in computationally targeting neurological disorder-related processes and translating them into windows of opportunities for interventions in diagnosis, treatment, and management of neurological disorders in children

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Frontiers in Neuroscience. 2021;15.

GENETIC OVERLAP BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN SHANK2 GENE.

Ma SL, Chen LH, Lee CC, et al.

Background: Recent findings indicated a high comorbidity between attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), as well as shared genetic influences on them. The latter might contribute at least partly to the former clinical scenario. This study aimed at investigating whether SHANK genes were potential pleiotropic genes to the two said disorders, underlying their genetic overlap.

Methods: This study recruited 298 boys with ADHD (including 256 family trios of 1 ADHD boy and his 2 biological parents), 134 boys with ASD, 109 boys with both ADHD and ASD, and 232 typically developing boys as community controls. They were aged between 6 and 11 years old.

Results: There was no significant difference in allele frequency of a number of single nucleotide polymorphisms (SNPs) in SHANK2/SHANK3 between the three clinical groups (ADHD, ASD, and ADHD + ASD) and between the two control groups (community controls and pseudo-controls), respectively. The three clinical groups and the two control groups were thus, respectively, combined. A comparison between the two aggregated samples identified significant evidence of disease association for three SHANK2 SNPs with both ADHD and ASD, even after multiple testing correction: rs11236616 (OR = 0.762, permuted p = 0.0376), rs7106631 (OR = 0.720, permuted p = 0.0034), and rs9888288 (OR = 0.770, permuted p = 0.0407). Comparisons among individual groups pointed to a similar trend of findings.

Conclusion: SHANK2 could be considered a potential pleiotropic gene underlying the genetic overlap between ADHD and ASD. This might contribute partly to their high comorbidity in the afflicted children

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Front Psychiatry. 2021;12.

AN EXPLORATORY STUDY OF EMOTIONAL DYSREGULATION DIMENSIONS IN YOUTH WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND/OR BIPOLAR SPECTRUM DISORDERS.

Masi G, Sesso G, Pfanner C, et al.

Emotional dysregulation (ED) is currently the most frequently used term to describe children with an impaired regulation of emotional states. Recent research studies speculate whether ED may be a neurodevelopmental disorder itself, a shared risk factor, or a common key feature of several psychiatric disorders, including, among others, attention deficit hyperactivity disorder (ADHD), and bipolar spectrum disorders (BSD). The association between ADHD and ED is one of the main reasons of misconceptions in the definition of boundaries between ADHD and BSD, leading to the frequent misdiagnosis of ADHD as BSD. Since ED is a multidimensional concept, a novel instrument the Reactivity, Intensity, Polarity and Stability (RIPoSt) scale was recently developed to assess the different dimensions of ED, which could help in detecting specific ED profiles in clinical youths. Our study included 154 patients, aged 13.8 -¦ 2.3 years, diagnosed with either ADHD, BSD, or comorbid condition, and a school-based sample of 40 healthy control (HC) adolescents,

aged 12.5 -¦ 1.2 years. The RIPoSt scale and the Child Behavior Checklist were administered to both groups. Our results indicate that affective instability and negative emotionality subscales, as well as negative emotional dysregulation, are higher in BSD, both pure and comorbid with ADHD, while emotional impulsivity is higher in the comorbid condition and similar in the ADHD and BSD alone group; all clinical groups scored higher than HC. Conversely, positive emotionality is similar among clinical groups and within them and HC. Our findings also support the validity of the RIPoSt questionnaire, since the instrument proved to have good-to-excellent internal consistency, and strongly significant positive correlations were found with the CBCL-Dysregulation Profile, which is a commonly used, indirect measure of ED. Hence, the five subscales of the RIPoSt can be reliably used as an effective tool to study the emotional dysregulation in different clinical conditions, to help disentangle the complex relationship between ADHD and juvenile BSD and to provide clinicians with crucial evidence for better diagnostic characterization and therapeutic indications

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Front Psychiatry. 2021;12.

INTENTIONAL DISCONTINUATION OF PSYCHOSTIMULANTS USED TO TREAT ADHD IN YOUTH: A REVIEW AND ANALYSIS.

Lohr WD, Wanta JW, Baker M, et al.

Objectives: This paper reviews the literature on intentional discontinuation of psychostimulants in ADHD to summarize what is known about clinical course of controlled discontinuation and guide practitioners who are considering stopping these medications for youth with ADHD.

Methods: A systematic search was executed in Cochrane CENTRAL, EMBASE, Psychinfo, and MEDLINE databases to identify all articles that addressed the topic of deprescribing of psychotropic medications in children and adolescents. Keywords and search strings were developed using PICO framework, involving Population of interest (<18 y.o.), Intervention (discontinuation, deprescribing, and synonyms), Comparator (continuation of specific medications), and Outcomes. Ten reviewers conducted the initial screen via a single reviewer system. Articles that met a set of three inclusionary criteria were selected for full text review and identification as specific to discontinuation of stimulants in ADHD.

Results: The literature review identified 35 articles specifically addressing intentional deprescribing, discontinuation, tapering, or withdrawal of stimulants for children and adolescents with ADHD. In addition to providing broad support for the efficacy of stimulants to treat ADHD and reduce negative outcomes, there is a distinct population of children and adolescents with ADHD who do not relapse or deteriorate when taken off medications for ADHD. The majority of articles addressed either the re-emergence of ADHD symptoms or side effects, both desired and adverse, following discontinuation of stimulants. While confirming the ability of stimulants to treat ADHD in youth, our results support periodic consideration of trials of stopping medications to determine continued need.

Conclusions: This systematic review summarizes the literature on deprescribing stimulants for ADHD in children and adolescents. Further research is needed to determine the optimal duration of treatment, identify patients that may benefit from medication discontinuation, and inform evidence-based guidelines for discontinuation when appropriate. More research is needed to understand and define the subgroup of youth who may succeed with stimulant discontinuation

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Front Psychiatry. 2021;12.

EXAMINING THE ROLE OF ATTENTION DEFICITS IN THE SOCIAL PROBLEMS AND WITHDRAWN BEHAVIOR OF CHILDREN WITH SLUGGISH COGNITIVE TEMPO SYMPTOMS.

Yung TWK, Lai CYY, Chan JYC, et al.

Previous studies have found that sluggish cognitive tempo (SCT) symptoms are often associated with social problems and withdrawn behavior. However, the possible neuropsychological mechanism underlying this relationship remains unclear. Some studies have also found that SCT symptoms are related to deficits in sustained attention and selective attention. However, no study has examined whether attention deficits are related to social problems and withdrawn behavior in children with SCT. This study was the first to examine the neuropsychological correlates of social problems and withdrawn behavior among children with SCT symptoms. The results showed that sustained attention measure (omission) predicted the severity of social

problems and withdrawn behavior in children with SCT even after controlling for symptoms of attention-deficit hyperactivity disorder. Selective attention measure (response latency mean) was also found to predict the severity of social problems. These results suggest that the social problems commonly exhibited by children with SCT are related to deficits in sustained attention and attentional control. Thus, our results provide an initial support to the link between attention deficits and social problems among children with SCT

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Genet Med. 2021 May;23:872-80.

DEEP PHENOTYPING IN 3Q29 DELETION SYNDROME: RECOMMENDATIONS FOR CLINICAL CARE.

Sanchez RR, Gambello MJ, Murphy MM, et al.

PURPOSE: To understand the consequences of the 3q29 deletion on medical, neurodevelopmental, psychiatric, brain structural, and neurological sequalae by systematic evaluation of affected individuals. To develop evidence-based recommendations using these data for effective clinical care.

METHODS: Thirty-two individuals with the 3q29 deletion were evaluated using a defined phenotyping protocol and standardized data collection instruments.

RESULTS: Medical manifestations were varied and reported across nearly every organ system. The most severe manifestations were congenital heart defects (25%) and the most common were gastrointestinal symptoms (81%). Physical examination revealed a high proportion of musculoskeletal findings (81%). Neurodevelopmental phenotypes represent a significant burden and include intellectual disability (34%), autism spectrum disorder (38%), executive function deficits (46%), and graphomotor weakness (78%). Psychiatric illness manifests across the lifespan with psychosis prodrome (15%), psychosis (20%), anxiety disorders (40%), and attention deficit-hyperactivity disorder (ADHD) (63%). Neuroimaging revealed structural anomalies of the posterior fossa, but on neurological exam study subjects displayed only mild or moderate motor vulnerabilities.

CONCLUSION: By direct evaluation of 3q29 deletion study subjects, we document common features of the syndrome, including a high burden of neurodevelopmental and neuropsychiatric phenotypes. Evidence-based recommendations for evaluation, referral, and management are provided to help guide clinicians in the care of 3q29 deletion patients

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Health Soc Care Community. 2020 Oct.

EXPERIENCES OF TRANSITION FROM CHILDREN'S TO ADULT'S HEALTHCARE SERVICES FOR YOUNG PEOPLE WITH A NEURODEVELOPMENTAL CONDITION.

Shanahan P, Ollis L, Balla K, et al.

Previous research has highlighted a lack of continuity of care when young people with a neurodevelopmental condition make the transition from children's to adult specialist healthcare services. A lack of planning, consistency, and availability of adult services has been found to lead to; increased anxiety, poor health outcomes, reduced support and some young people not receiving healthcare. The majority of transition research has focused on what health professionals consider important in the transition process, rather than focusing on the experiences of the young people and those closest to them. Our objective was to gather evidence from young people (and their families) who had experienced transition from children's to adult specialist healthcare services through semi-structured interviews. Volunteers were recruited from two London boroughs. All young people were aged between 18 and 25Â years with a neurodevelopmental condition (Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder and/or an Intellectual Disability). Overall, we interviewed six young people with support from a family member. Five further family members were interviewed on behalf of the young person. In total, ten semi-structured interviews were transcribed verbatim and analysed using Interpretative Phenomenological Analysis. Four themes emerged from the analysis: (a) Parents as advocates, (b) Availability of adult's specialist health and social care services, (c) Lack of information sharing and (d) Transition as a binary, abrupt change. Our findings suggest the transition experience could be improved by changing service specifications to incorporate assessment and handover across the age range of 16-20Â years. Additionally, statutory services should understand and provide the coordination role now offered by parents in transition. We suggest future research could evaluate

the feasibility of a patient-owned online information sharing tool with information about relevant services for young people and their families

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Indian J Pediatr. 2021 Jun;88:589-92.

DEVELOPMENT AND EVALUATION OF A WORKING MEMORY INTERVENTION KIT IN CHILDREN WITH EPILEPSY IN LOW-RESOURCE SETTINGS.

Phakey N, Sharma S, Garg D, et al.

OBJECTIVES: In this pilot study, the authors developed and evaluated a working memory intervention (WMI) using a combination of mobile phone-based application and an activity booklet, among children with idiopathic generalized epilepsy.

METHODS: Pre- and post-intervention cognitive evaluation at 8 wk included: subtests comprising working memory index from Wechsler Intelligence Scale-IV, color cancellation task for sustained attention, and parent's rating from the Conners' ADHD/DSM-IV Scales of the Conners' Rating Scales-Revised.

RESULTS: Fourteen children completed the intervention; one was lost to follow-up. Significant improvement in most working memory parameters occurred at 8 wk: digit span [scaled scores: median 7 (IQR 4-9) to 12 (IQR 9-14.25); p=0.001]; letter-number sequencing [scaled scores: median 9 (IQR 5-10) to 11.5 (IQR 6.75-13); p=0.03]; WMI [median 14 (IQR 9-18) to 22 (IQR 16.75-27); p=0.001] and sustained attention [time for cancellation test improved from 95 (72-117) to 85 (63-98) s; p=0.001].

CONCLUSION: This indigenous WMI was feasible and efficacious in improving working memory deficits in CWE in low-resource settings

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Int J Environ Res Public Health. 2021;18.

MOVEMENT PATTERNS IN STUDENTS DIAGNOSED WITH ADHD, OBJECTIVE MEASUREMENT IN A NATURAL LEARNING ENVIRONMENT.

Sempere-Tortosa M, et al.

Attention deficit hyperactivity disorder is the most common neuropsychological disorder in childhood and adolescence, affecting the basic psychological processes involved in learning, social adaptation and affective adjustment. From previous research, the disorder is linked to problems in different areas of development, with deficiencies in psychological processes leading to the development of the most common characteristics of the disorder such as inattention, excess of activity and lack of inhibitory control. As for the diagnosis, in spite of being a very frequent disorder, there are multiple controversies about which tools are the most suitable for evaluation. One of the most widespread tools in the professional field is behavior inventories such as the Strengths and Difficulties Questionnaires for Parents and Teachers or the ADHD Rating Scale-V. The main disadvantage of these assessment tools is that they do not provide an objective observation. For this reason, there are different studies focused on recording objective measures of the subjectsΓÇÖ movement, since hyperkinesia is one of the most characteristic symptoms of this disorder. In this sense, we have developed an application that, using a Kinect device, is capable of measuring the movement of the different parts of the body of up to six subjects in the classroom, being a natural context for the student. The main objective of this work is twofold, on the one hand, to investigate whether there are correlations between excessive movement and high scores in the inventories for the diagnosis of ADHD, Rating Scale-V and Strengths and Difficulties Questionnaire (SDQ) and, on the other hand, to determine which sections of the body present the most significant mobility in subjects diagnosed with ADHD. Results show that the control group, composed of neurotypical subjects, presents less kinaesthetic activity than the clinical group diagnosed with ADHD. This indicates that the experimental group presents one of the main characteristics of the disorder. In addition, results also show that practically all the measured body parts present significant differences, being higher in the clinical group, highlighting the head as the joint with the highest effect size

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International Ophthalmology. 2021.

THE ASSOCIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND RETINAL NERVE FIBER/GANGLION CELL LAYER THICKNESS MEASURED BY OPTICAL COHERENCE TOMOGRAPHY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Li SL, Kam KW, Chee ASH, et al.

Purpose: Retinal nerve fiber/ganglion cell layer (RNFL/GCL) thickness measured using optical coherence tomography has been proposed as an ocular biomarker for children with attention-deficit/hyperactivity disorder (ADHD), but findings varied in different studies. This study aims to determine the association between RNFL/GCL thickness and ADHD in children by systematic review and meta-analysis.

Methods: We performed a literature search in Embase, PubMed, Medline, Web of Science, and PsycINFO for relevant articles published up to February 29, 2020. All studies with original data comparing RNFL/GCL thickness in ADHD and healthy children were included. The Newcastle Ottawa Scale was used to assess bias risk and quality of evidence. Pooled estimates of the differences in thickness of RNFL or GCL between ADHD and healthy subjects were generated using meta-analysis with a random-effect model due to significant inter-study heterogeneity. Sensitivity analysis was also performed.

Results: We identified four eligible studies involving a total of 164 ADHD and 150 control subjects. Meta-analysis revealed that ADHD in children was associated with a reduction in global RNFL thickness (SMD, 0.23; 95% CI 0.46, 0.01; p = 0.04). The global GCL thickness was examined in two studies with 89 ADHD and 75 control subjects, but the pooled difference in global GCL thickness between ADHD children and controls was not statistically significant (SMD, 0.34; 95% CI 1.25, 0.58; p = 0.47).

Conclusion: Existing evidence suggests a possible association between ADHD and RNFL thinning in children. In view of the limited number of reports, further studies in large cohorts should be warranted

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Ir J Psychol Med. 2021.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) SYMPTOMS, COMORBID PSYCHOPATHOLOGY, BEHAVIOUR PROBLEMS AND GASTROINTESTINAL SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER.

Leader G, Moore R, Chen JL, et al.

Objectives: The study aims to investigate attention deficit hyperactivity disorder (ADHD) symptoms, gastrointestinal (GI) symptoms, comorbid psychopathology and behaviour problems in children and adolescents with autism spectrum disorder (ASD).

Methods: Parents of 147 children and adolescents with ASD aged 6-18 years completed the Conners 3 Parent-Short Form, Gastrointestinal Symptom Inventory, Behavior Problems Inventory-Short Form and Autism Spectrum Disorder-Comorbid for Children.

Results: Fifty-six per cent of children and adolescents had a comorbid diagnosis of ADHD, yet over 70% presented with clinically significant ADHD symptoms. Forty per cent of participants received a diagnosis of ADHD before ASD and 25.6% received a diagnosis of ASD first. Relationships were found between ADHD symptoms and comorbid psychopathology, GI symptoms, and behaviour problems.

Conclusions: The outcomes suggest that ADHD is being underestimated as a comorbid disorder of ASD. This may have implications on treatment and interventions for children and adolescents who have a diagnosis of both ASD and ADHD

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J Affect Disord. 2021 May;287:101-06.

FURTHER EVIDENCE THAT SUBSYNDROMAL MANIFESTATIONS OF DEPRESSION IN CHILDHOOD PREDICT THE SUBSEQUENT DEVELOPMENT OF MAJOR DEPRESSION: A REPLICATION STUDY IN A 10 YEAR LONGITUDINALLY ASSESSED SAMPLE.

Uchida M, Hirshfeld-Becker D, DiSalvo M, et al.

BACKGROUND: We have previously shown that subsyndromal scores on the Child Behavior Checklist (CBCL)-Anxiety/Depression (Anx/Dep) scale at baseline predicted the subsequent development of Major Depressive Disorder (MDD) in youth with ADHD. The present study aimed to replicate these findings in a separate, long-term, longitudinal sample of children at high- and low- risk for depression.

METHODS: 219 children of parents with and without depression and/or anxiety, ages 2-25, were stratified into 3 groups: 1) children with familial risk for depression (by presence of parental MDD) plus subsyndromal scores on the CBCL-Anx/Dep scale, 2) children with familial risk for depression without subsyndromal scores, and 3) children with neither familial risk for depression nor subsyndromal scores. Subjects were reassessed at both 5 and 10 year follow-ups.
RESULTS: Children with both subsyndromal scores on the CBCL-Anx/Dep plus a familial risk for depression were at greater risk for developing MDD at the 10 year follow-up when compared with all other groups. Those with familial risk but no subsyndromal scores had an intermediate risk that was greater than the controls, who had the lowest risk.
LIMITATIONS: The recruitment of the study included families with parental panic disorder, so the sample likely included more families with anxiety disorders than the general population.
CONCLUSIONS: Our results showed that subsyndromal scores of the CBCL-Anx/Dep scale increased the risk for the subsequent development of MDD, particularly in children at high risk for depression. These results confirm the CBCL-Anx/Dep scale's utility in identifying children at high risk for developing MDD

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J Am Acad Child Adolesc Psychiatry. 2021 May;60:540-42.
KSADS-COMP PERSPECTIVES ON CHILD PSYCHIATRIC DIAGNOSTIC ASSESSMENT AND TREATMENT PLANNING.
Kaufman J, Kobak K, Birmaher B, et al.
Gibbons et al.(1) demonstrated the utility of computerized adaptive tests (CATs) based on multidimensional item response theory for the assessment of depression, anxiety, mania/hypomania, attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, and suicidality in children and adolescents. The Kiddie-Computerized Adaptive Test (K-CAT) demonstrated good convergent validity, test-retest reliability, and diagnostic concordance with diagnoses derived using the paper-and-pencil Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) child psychiatric interview

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J Am Acad Child Adolesc Psychiatry. 2021 May;60:577-78.
EDITORIAL: THE ROLE OF COMPUTATIONAL MODELS TO UNCOVER THE COGNITIVE MECHANISMS UNDERPINNING DISRUPTIVE MOOD DYSREGULATION DISORDER.
Salum GA.
Computational models mimic important concepts inherent to brain function and the relationships among these concepts in a mathematical form.(1) These models offer a suitable approach to quantitatively explore properties of complex systems across levels of investigation. Therefore, these models may be well suited to linking molecular, cellular, circuits, cognition, and behavior in psychiatry.(2) Although some progress has been made in applying such models for understanding other mental disorders,(2,3) their role in uncovering the cognitive mechanisms underpinning disruptive mood dysregulation disorder (DMDD) has not previously been explored in the medical literature. In fact, very little is known about the neurocognitive correlates of DMDD in children

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J Atten Disord. 2021 Jun;25:1107-19.
DO CHANGES IN BLOOD NUTRIENT LEVELS MEDIATE TREATMENT RESPONSE IN CHILDREN AND ADULTS WITH ADHD CONSUMING A VITAMIN-MINERAL SUPPLEMENT?
Rucklidge JJ, Eggleston MJF, Boggis A, et al.
Objective: We investigated whether changes in serum nutrient levels mediate clinical response to a micronutrient intervention for ADHD.
Method: Data were compiled from two ADHD trials (8-10 weeks), one in adults (n = 53) and one in children (n = 38). Seven outcomes included change in ADHD symptoms, mood, overall functioning (all clinician-rated) as well as response status. Change in serum/plasma nutrient levels (vitamins B(12) and D, folate, ferritin, iron, zinc, and copper) were considered putative mediators.
Results: A decrease in ferritin and an increase in copper were weakly associated with greater likelihood of being identified as an ADHD responder; none of the other nutrient biomarkers served as mediators.

Conclusion: Further research looking at nutrients more broadly from other tissues are required to confirm these initial observations of the limited value of nutrient levels in deciphering mechanism of action. Monitoring these biomarkers on their own is unlikely helpful in understanding clinical response to a broad-spectrum micronutrient approach

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J Atten Disord. 2021 Jun;25:1096-106.

EFFICACY OF OMEGA-3/OMEGA-6 FATTY ACIDS IN PRESCHOOL CHILDREN AT RISK OF ADHD: A RANDOMIZED PLACEBO-CONTROLLED TRIAL.

DÃpfner M, Dose C, Breuer D, et al.

Objective: To evaluate the efficacy of an Omega-3/Omega-6 fatty acid supplement in preschool children at risk for ADHD.

Method: Forty preschool children with elevated levels of ADHD symptoms were randomly assigned to either a verum or a placebo group. Children in the verum group received a 4-month treatment with Omega-3/Omega-6 fatty acids. Outcome measures comprised parent- and teacher-rated ADHD symptoms, which were the primary outcome variables, internalizing and externalizing problems, and intellectual abilities.

Results: Intention-to-treat analyses of covariance, controlling for age and baseline data, revealed effects on parent- and teacher-rated ADHD symptoms (primary outcomes; parent ratings: $F = 4.51$, $df = 1$, $p = .04$, $d = 0.63$; teacher ratings: $F = 4.67$, $df = 1$, $p = .04$, $d = 0.70$), parent-rated internalizing symptoms ($F = 8.47$, $df = 1$, $p < .01$, $d = 0.63$), and parent- and teacher-rated externalizing symptoms (parent ratings: $F = 4.58$, $df = 1$, $p = .04$, $d = 0.54$; teacher ratings: $F = 5.99$, $df = 1$, $p = .02$, $d = 0.79$). Analyses involving only cases with available data yielded significant moderate effects on teacher-rated inattention symptoms ($F = 4.60$, $df = 1$, $p = .04$, $d = 0.79$) and parent-rated internalizing problems ($F = 6.04$, $df = 1$, $p = .02$, $d = 0.57$).

Conclusion: The intention-to-treat analyses provide some evidence for positive effects of Omega-3/Omega-6 fatty acids. However, the results require replication in larger samples to allow for firm conclusions for practice

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J Atten Disord. 2021 Jun;25:1177-86.

COGNITION, ADHD SYMPTOMS, AND FUNCTIONAL IMPAIRMENT IN CHILDREN AND ADOLESCENTS WITH NEUROFIBROMATOSIS TYPE 1.

Payne JM, Haebich KM, MacKenzie R, et al.

Objective: We examined the contribution of attention and executive cognitive processes to ADHD symptomatology in NF1, as well as the relationships between cognition and ADHD symptoms with functional outcomes.

Methods: The study sample consisted of 141 children and adolescents with NF1. Children were administered neuropsychological tests that assessed attention and executive function, from which latent cognitive variables were derived. ADHD symptomatology, adaptive skills, and quality of life (QoL) were assessed using parent-rated questionnaires. Path analyses were conducted to test relationships among cognitive functioning, ADHD symptomatology, and functional outcomes.

Results: Significant deficits were observed on all outcome variables. Cognitive variables did not predict ADHD symptomatology. Neither did they predict functional outcomes. However, elevated ADHD symptomatology significantly predicted functional outcomes.

Conclusion: Irrespective of cognitive deficits, elevated ADHD symptoms in children with NF1 negatively impact daily functioning and emphasize the importance of interventions aimed at minimizing ADHD symptoms in NF1

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J Atten Disord. 2021 Jun;25:1146-59.

GAMIFIED ATTENTION TRAINING IN THE PRIMARY SCHOOL CLASSROOM: A CLUSTER-RANDOMIZED CONTROLLED TRIAL.

Kirk HE, Spencer-Smith M, Wiley JF, et al.

Objective: This randomized controlled trial evaluated the efficacy of attention training delivered in class on cognitive attention processes, inattention, hyperactivity, working memory, and numeracy in primary school children.

Method: Eight classes (n = 98 children; 5-9 years) were cluster randomized to gamified attention training, a placebo program, or a no-contact control condition. Assessments were conducted at baseline, immediately after the 5-week intervention (posttraining), and 6 months later (follow-up).

Results: Posttraining, attention training was associated with reduced inattention and hyperactivity within the classroom compared with controls, and reduced hyperactivity at home compared with the no-contact control. At follow-up, reduced hyperactivity within the classroom compared with the no-contact control persisted. No effects of training on cognitive attention processes, working memory, and numeracy were observed posttraining.

Conclusion: Classroom-based attention training has select benefits in reducing inattention and hyperactivity, but may not promote gains in cognitive or academic skills in primary school children

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J Atten Disord. 2021 Jun;25:1135-45.

DOES CO-OCCURRING ANXIETY MODULATE ADHD-RELATED COGNITIVE AND NEUROPHYSIOLOGICAL IMPAIRMENTS?

Adamo N, Michelini G, Cheung CHM, et al.

Objective: This study investigates whether anxiety modulates cognitive-performance, electrophysiological and electrodermal processes that we previously found impaired in individuals with ADHD.

Method: Self-reported anxiety symptoms, cognitive-electrophysiological measures of response inhibition, working memory, attention, conflict monitoring, error processing, and peripheral arousal during three cognitive tasks were obtained from 87 adolescents and young adults with ADHD and 169 controls. We tested the association of anxiety symptoms with each measure and whether controlling for anxiety symptoms attenuates the ADHD-control difference for each measure.

Results: Individuals with ADHD showed significantly elevated anxiety symptoms compared with controls. Only commission errors on a Continuous Performance Test (measuring response inhibition) were significantly associated with anxiety symptoms and only among controls, with the ADHD-control difference in this measure remaining significant.

Conclusion: Using a wide range of cognitive, electrophysiological, and electrodermal measures, our investigation suggests, overall, limited malleability of these impairments in individuals with ADHD irrespective of their levels of anxiety

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J Atten Disord. 2021 Jun;25:1058-67.

PREVALENCE OF ADHD AND ITS COMORBIDITIES IN A POPULATION-BASED SAMPLE.

Mohammadi MR, Zarafshan H, Khaleghi A, et al.

Objective: We aimed to investigate the prevalence of ADHD and its comorbidities and some associated demographic factors in a large sample population-based study.

Method: As part of a population-based survey among 30,532 children and adolescents between 6 and 18 years, we used K-SADS-PL to screen and detect ADHD and its comorbidities.

Results: The prevalence of ADHD was 4%, with more prevalence among boys (5.2% vs. 2.7%), younger participants, urban residents, and offspring of mothers who had a history of psychiatric hospitalization. Anxiety disorders (37.9%) and behavioral disorders (31%) are the most prevalent group of comorbidities, and oppositional defiant disorder (ODD) is the most prevalent comorbid disorder (26.1%). Mood disorders and anxiety disorders are more common among girls, but conduct disorder has a higher rate among boys.

Conclusion: ADHD is a common neurodevelopmental disorder which is accompanied by several comorbid conditions. The high rate of comorbidities makes it complicated and difficult to manage

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J Atten Disord. 2021 Jun;25:1187-95.

CHILDREN WITH ADHD ENGAGE IN LESS PHYSICAL ACTIVITY.

Mercurio LY, Amanullah S, Gill N, et al.

Background: Children with ADHD should engage in physical activity, given its known role as a treatment adjunct.

Objective: The main objective of this study is to assess the relationship between ADHD diagnosis and physical activity among children in the United States.

Methods: This retrospective population-based cross-sectional study used data from the 2016 caregiver reported, National Survey of Children's Health (NSCH).

Results: In the adjusted binary model, children with an ADHD diagnosis had 21% lower odds of engaging in daily physical activity than their nondiagnosed counterparts. In the adjusted multinomial model, children with ADHD were increasingly unlikely to report additional days of physical activity as compared to those without a diagnosis.

Conclusion: Given the known benefits of physical activity for those with ADHD, this study underscores the need for enhanced access to an important treatment adjunct for this population

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J Atten Disord. 2021 Jun;25:1129-34.

THE ASSOCIATION BETWEEN AUTISM SYMPTOMS AND CHILD FUNCTIONING IN A SAMPLE WITH ADHD RECRUITED FROM THE COMMUNITY.

Stephens K, O'Loughlin R, Green JL, et al.

Objective: Although autism spectrum disorder (ASD) symptoms are associated with poorer functioning in children with attention-deficit/hyperactivity disorder (ADHD), it is unclear which ASD symptom domains are most impairing. This study investigated whether specific ASD symptom domains were associated with child functioning in children with ADHD.

Method: Parents of 164 children with ADHD completed a diagnostic interview to assess ADHD and comorbidities. Parents reported on ASD symptoms (Social Communication Questionnaire) and child quality of life (Pediatric Quality of Life Inventory 4.0). Parents and teachers completed the Strengths and Difficulties Questionnaire (emotional, conduct, and peer problems).

Results: Repetitive and stereotyped behaviors were independently associated with emotional (p = .02) and conduct (p = .03) problems, and poorer quality of life (p = .004). Reciprocal social interaction deficits were independently associated with peer problems (p = .03).

Conclusion: Reciprocal social interaction deficits and repetitive and stereotyped behaviors are important areas that should be focused on in ADHD assessment and treatment

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J Child Psychol Psychiatry. 2021 Jun;62:798-800.

EDITORIAL PERSPECTIVE: COVID-19 PANDEMIC-RELATED PSYCHOPATHOLOGY IN CHILDREN AND ADOLESCENTS WITH MENTAL ILLNESS.

Jefsen OH, Rohde C, NÃ¸rremark B, et al.

The coronavirus disease (COVID-19) pandemic is likely to have negative health consequences way beyond those caused by the virus per se - including significant psychological distress. Children and adolescents who already live with a mental illness may be particularly vulnerable to the distress associated with the pandemic - due to, for example, fear of the virus as well as the significant societal changes launched to minimize spread of the virus (social distancing and quarantine). In this editorial perspective, we (a) provide data on COVID-19 pandemic-related psychopathology in children and adolescents from a large psychiatric treatment setting in Denmark, (b) give advice on how the likely harmful effects of the COVID-19 pandemic on the mental health of children and adolescents may be minimized, and (c) propose six lines of research into pandemic-related

psychopathology with emphasis on children and adolescents. Finally, we underline the necessity of politicians, health authorities, and funding bodies supporting these research initiatives here and now

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J Dev Behav Pediatr. 2021 May;42:314-21.

USE OF TELEHEALTH IN FELLOWSHIP-AFFILIATED DEVELOPMENTAL BEHAVIORAL PEDIATRIC PRACTICES DURING THE COVID-19 PANDEMIC.

Wallis KE, MulÃ C, Mittal S, et al.

OBJECTIVE: This study aims to describe the use of telehealth in developmental behavioral pediatric (DBP) fellowship-affiliated practices during the coronavirus disease 2019 (COVID-19) global pandemic.

METHODS: An electronic survey was disseminated to all DBP fellowship-associated practice locations to determine the use of telehealth in DBP care provision, before and since the beginning of the COVID-19 pandemic. We analyzed responses using descriptive statistics.

RESULTS: A total of 35 of 42 eligible practice sites responded (83% response rate). Most sites (51.4%) reported using telehealth less than once per month before the COVID-19 pandemic. Since the onset of COVID-19, 100% of programs reported conducting video-based telehealth visits multiple days per week. Most sites reported conducting evaluations and follow-up visits for attention-deficit/hyperactivity disorder, autism spectrum disorder, behavioral concerns, developmental delay, genetic disorders, and learning disability. Most sites were able to continue medication management by telehealth (>88%), offer interpreter services for families with limited English proficiency participating in telehealth visits (>90%), and incorporate trainees and interdisciplinary team members in telehealth visits (>90%). Greater variability was observed in sites' ability to collect telehealth practice evaluation measures.

CONCLUSION: Most sites are providing evaluations and ongoing care for DBP conditions through telehealth. The rapid adoption of telehealth can have ramifications for the way that DBP care is delivered in the future; therefore, it is imperative to understand current practice patterns and variations to determine the best use of telehealth

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J Am Med Assoc. 2021;325:2067-75.

α2-ADRENERGIC AGONISTS OR STIMULANTS FOR PRESCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Harstad E, Shults J, Barbaresi W, et al.

Importance: Attention-deficit/hyperactivity disorder (ADHD) is diagnosed in approximately 2.4% of preschool-age children. Stimulants are recommended as first-line medication treatment. However, up to 25% of preschool-age children with ADHD are treated with α2-adrenergic agonist medications, despite minimal evidence about their efficacy or adverse effects in this age range.

Objective: To determine the frequency of reported improvement in ADHD symptoms and adverse effects associated with α2-adrenergic agonists and stimulant medication for initial ADHD medication treatment in preschool-age children.

Design, Setting, and Participants: Retrospective electronic health record review. Data were obtained from health records of children seen at 7 outpatient developmental-behavioral pediatric practices in the Developmental Behavioral Pediatrics Research Network in the US. Data were abstracted for 497 consecutive children who were younger than 72 months when treatment with an α2-adrenergic agonist or stimulant medication was initiated by a developmental-behavioral pediatrician for ADHD and were treated between January 1, 2013, and July 1, 2017. Follow-up was complete on February 27, 2019. Exposures: α2-Adrenergic agonist vs stimulant medication as initial ADHD medication treatment. Main Outcomes and Measures: Reported improvement in ADHD symptoms and adverse effects.

Results: Data were abstracted from electronic health records of 497 preschool-age children with ADHD receiving α2-adrenergic agonists or stimulants. Median child age was 62 months at ADHD medication initiation, and 409 children (82%) were males. For initial ADHD medication treatment, α2 α2-adrenergic agonists were prescribed to 175 children (35%; median length of +¦2-adrenergic agonist use, 136 days) and stimulants were prescribed to 322 children (65%; median length of stimulant use, 133 days). Improvement was reported in 66% (95% CI, 57.5%-73.9%) of children who initiated α2-adrenergic agonists and 78% (95%

CI, 72.4%-83.4%) of children who initiated stimulants. Only daytime sleepiness was more common for those receiving α2-adrenergic agonists vs stimulants (38% vs 3%); several adverse effects were reported more commonly for those receiving stimulants vs α2-adrenergic agonists, including moodiness/irritability (50% vs 29%), appetite suppression (38% vs 7%), and difficulty sleeping (21% vs 11%).
Conclusions and Relevance: In this retrospective review of health records of preschool-age children with ADHD treated in developmental-behavioral pediatric practices, improvement was noted in the majority of children who received α2-adrenergic agonists or stimulants, with differing adverse effect profiles between medication classes. Further research, including from randomized clinical trials, is needed to assess comparative effectiveness of α2-adrenergic agonists vs stimulants

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JAMA. 2021 May;325:2049-50.
COMPARISON OF MEDICATION TREATMENTS FOR PRESCHOOL CHILDREN WITH ADHD: A FIRST STEP TOWARD ADDRESSING A CRITICAL GAP.
Froehlich TE.

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J Autism Dev Disord. 2021.
HOW DOES TEMPERAMENT IN TODDLERS AT ELEVATED LIKELIHOOD FOR AUTISM RELATE TO SYMPTOMS OF AUTISM AND ADHD AT THREE YEARS OF AGE?
Konke LA, Forslund T, Nilsson-Jobs E, et al.
The current study investigated longitudinal associations between parent-rated temperament, observed exuberance and accelerometer activity level at 18-months and symptoms of ASD and ADHD at 36-months in a sample of 54 children at elevated likelihood for ASD. For the specific parent-rated temperament scales, most observed significant associations appeared to be specific for either ASD or ADHD symptoms. Indeed, by controlling for overlapping symptoms a different pattern of associations emerged. These results illustrate how temperamental measures may signal risk for later ASD versus ADHD symptomatology in infants at elevated likelihood for ASD. In addition, they indicate the potential of adopting a broader view on neurodevelopmental disorders by investigating not only ASD traits, but also co-occurring disorders such as ADHD in samples of elevated likelihood for ASD

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J Autism Dev Disord. 2021.
ALCOHOL AND TOBACCO USE WHILE BREASTFEEDING AND RISK OF AUTISM SPECTRUM DISORDER OR ATTENTION DEFICIT/HYPERACTIVITY DISORDER.
Gibson L, Porter M.
Research has linked prenatal alcohol and tobacco use with Attention Deficit Hyperactivity Disorder (ADHD), and variably with Autism Spectrum Disorder (ASD). Lactational use has been scantly considered. This study examined whether it may alter ADHD or ASD risk. Participants were 5107 infants recruited in 2004 and assessed longitudinally for the Growing Up in Australia Study. Logistic regression did not find any associations between maternal alcohol and tobacco use while breastfeeding and ADHD or ASD diagnosis at ages 6-7 or 10-11-áyears. Alcohol and tobacco use during lactation may not increase ADHD or ASD risk. Abstaining from alcohol and tobacco, however, may still be the safest option. Analyses were limited by lack of alcohol timing and retrospective variables that future research should address

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J Autism Dev Disord. 2021.
THE EFFECT OF PHYSICAL ACTIVITY INTERVENTIONS ON EXECUTIVE FUNCTION AMONG PEOPLE WITH NEURODEVELOPMENTAL DISORDERS: A META-ANALYSIS.
Sung MC, Ku B, Leung W, et al.
The current meta-analysis comprehensively examined the effects of physical activity interventions on executive function among people with neurodevelopmental disorders. The meta-analysis included 34 studies

with 1058 participants aged 5-33 years. Results indicated an overall significant medium effect of physical activity interventions on improving executive function in people with neurodevelopmental disorders under the random-effect model (Hedges g = 0.56, p <.001). Significant moderators of the effects of physical activity intervention on executive function included age, intervention length and session time, executive function subdomains, and intervention dose (total minutes in the intervention). This meta-analysis provides support for the effectiveness of physical activity interventions on executive function among people with neurodevelopmental disorders. Future studies and limitations are discussed

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J Autism Dev Disord. 2021.

AUTISM DIAGNOSTIC INTERVIEW-REVISED WITHIN DSM-5 FRAMEWORK: TEST OF RELIABILITY AND VALIDITY IN CHINESE CHILDREN.

Lai KYC, Yuen ECW, Hung SF, et al.

This study examines the psychometric properties of the Autism Diagnostic Interview-Revised (ADI-R) in the context of DSM-5 in a sample of Chinese children. Using re-mapped ADI-R items and algorithms matched to DSM-5 criteria, and administering to children with autism spectrum disorder (ASD) with and without intellectual disability, attention-deficit hyperactivity disorder, and typically developing, it evidenced high sensitivity and specificity. However, similar to DSM-IV algorithm, the DSM-5 algorithms were better at classifying ASD among children with intellectual disability than among those without intellectual disability. With the DSM-5ΓÇÖs recognition of the spectrum nature of ASD, the performance of the ADI-R can be improved by having finer gradations in the ADI-R scoring and adding more items on the restricted and repetitve behavior domain

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J Clin Sleep Med. 2021;17:639-43.

RESTLESS SLEEP DISORDER IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kapoor V, Ferri R, Stein MA, et al.

Study Objectives: Restless sleep is a very common parental complaint in children with attention-deficit/hyperactivity disorder (ADHD), but restless sleep has been seen in association with other comorbidities such as restless legs syndrome and obstructive sleep apnea. Restless sleep disorder (RSD) needs to be identified from other disorders when evaluating children with ADHD. In this study we aim to identify the prevalence of RSD in children with ADHD referred to our sleep center.

Methods: This is a retrospective study of children with ADHD who underwent polysomnography. The following diagnostic and descriptive data were obtained for each patient: Age, sex, presence/absence of RSD, other sleep disorders, psychiatric comorbidities, and medications. RSD was diagnosed per diagnostic criteria.

Results: There were 66 children with ADHD. All of them underwent polysomnography, 17 were females, and 49 were males. Mean age was 11.6 years (-¦ 3.6 standard deviation). The complaint of restless sleep was reported by the parents of 54 (81.1%) of the children; however, only 6 of them (9.1%) were diagnosed with RSD. Seventy-one percent had obstructive sleep apnea and 19.7% had restless legs syndrome. A significant number of patients had psychiatric comorbidities and were on various medications.

Conclusions: Although restless sleep is a common complaint reported in 81.1% of children with ADHD, only 9.1% had RSD. Most causes of restless sleep are secondary and associated with other sleep disorders, psychiatric comorbidities, or medication use

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J Consult Clin Psychol. 2021;89:21-33.

A RANDOMIZED CONTROLLED TRIAL EXAMINING CBT FOR COLLEGE STUDENTS WITH ADHD .

Anastopoulos AD, Langberg JM, Eddy LD, et al.

Objective: College students with attention deficit/hyperactivity disorder (ADHD) are at increased risk for numerous educational and psychosocial difficulties. This study reports findings from a large, multisite randomized controlled trial examining the efficacy of a treatment for this population, known as ACCESS Accessing Campus Connections and Empowering Student Success.

Method: ACCESS is a cognitive behavioral therapy program delivered via group treatment and individual mentoring across two semesters. A total of 250 students (18ΓÇô30 years of age, 66% female, 6.8% Latino, 66.3% Caucasian) with rigorously defined ADHD and comorbidity status were recruited from two public universities and randomly assigned to receive ACCESS immediately or on a 1-year delayed basis. Treatment response was assessed on three occasions, addressing primary (i.e., ADHD, executive functioning, depression, anxiety) and secondary (i.e., clinical change mechanisms, service utilization) outcomes.
Results: Latent growth curve modeling (LGCM) revealed significantly greater improvements among immediate ACCESS participants in terms of ADHD symptoms, executive functioning, clinical change mechanisms, and use of disability accommodations, representing medium to large effects (Cohen's d,.39-1.21). Across these same outcomes, clinical significance analyses using reliable change indices (RCI; Jacobson & Truax, 1992) revealed significantly higher percentages of ACCESS participants showing improvement. Although treatment-induced improvements in depression and anxiety were not evident from LGCM, RCI analyses indicated that immediate ACCESS participants were less likely to report a worsening in depression/anxiety symptoms.
Conclusions: Findings from this RCT provide strong evidence in support of the efficacy and feasibility of ACCESS as a treatment for young adults with ADHD attending college. (PsycInfo Database Record (c) 2021 APA, all rights reserved) What is the public health significance of this article? College students with attention deficit/hyperactivity disorder (ADHD) face numerous challenges in their daily lives that make it difficult to achieve personal and career goals. Findings from our recently completed clinical trial show that ACCESS-Accessing Campus Connections and Empowering Student Success'is a promising new evidence-based treatment that gives college students with ADHD the knowledge and skills necessary to be more successful. (PsycInfo Database Record (c) 2021 APA, all rights reserved)

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J Exp Clin Med. 2021;38:176-81.

THE EFFECT OF LOWERING SCHOOL ENTRY AGE ON ATTENTION DEFICIT HYPERACTIVITY DISORDER DIAGNOSIS.

Gumus YY, Yurumez E.

The school entry age was changed from 72 to 66 months in 2012 with a new education system adjustment in Turkey. The aim of the study was to investigate the effects of lowering school entry age on Attention Deficit Hyperactivity Disorder (ADHD) diagnosis and symptom severity. The records of children at first and second grade diagnosed with ADHD according to the DSM-IV diagnostic criteria in the Child Psychiatry outpatient clinic between January and July 2010 (when the old system was in use) and between January-July 2013 (when the new system was in use) were retrospectively screened to create the old-system and new system groups. Among the two groups, T-DSM-IV-S fulfilled by parents and teachers were used to assess symptom severity. The frequency of ADHD and ADHD predominantly inattentive subtype diagnosis we found to be significantly higher among the girls in the new system compared to old system (25.8%, 8.9%, p=0.027 - 56.3%, 0%, p=0.012). Additionally, motherΓÇÖs subscale scores of T-DSM-IV-S were lower among the children in the new system compared to the ones in the old system. By lowering school entry age due to the new education system, frequency of ADHD diagnosis increased while symptom severity rates decreased among the first-grade girls. Thus, it may be suggested that despite decreased symptom severity, the girls who started school with the new system were diagnosed with ADHD more frequently due to a marked disruption in academic, social, and behavioral functionality associated with insufficient neurodevelopmental maturity

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J Intellect Disabil Res. 2021.

EFFICACY AND SAFETY OF METHYLPHENIDATE ON ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH DOWN SYNDROME.

Roche M, Mircher C, Toulas J, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common co-morbidity that affects up to 44% of children with Down syndrome (DS). There is a need for reliable, good quality research on the use of methylphenidate within this population. The objective of this study is to report our experience regarding the management of ADHD in these children using methylphenidate.

Methods: This study is a retrospective observation of 21 children with DS, followed at J+®r+¦me Lejeune Institute between 2000 and 2018. The diagnosis of ADHD was made using the Diagnostic and Statistical Manual of Mental Disorders criteria. Efficacy was measured as response or non-response on two main symptoms: attention/concentration and hyperactivity/impulsivity. Safety was evaluated by the presence or absence of side effects.
Results: Sixteen out of the 21 children (76%) showed improvement with methylphenidate. The average age of treatment onset in responding children was 8-áyears and 10-ámonths versus 6 years and 3 months in non-responders (P=0.05). Average dose/weight was significantly different in responders and non-responders (0.82 vs. 0.54 mg/kg/day, respectively; P=0.03). Twelve children out of 21 (57%) experienced side effects; only three experienced side effects severe enough to require treatment interruption. Most common side effects were loss of appetite and difficulties in falling asleep.
Conclusion: Methylphenidate was effective and safe in treating ADHD in 76% of cases in children with DS, with few serious side effects to report. Early diagnosis of ADHD is important to improve the quality of life, learning, inclusion and socialisation of children with DS

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Journal of Multidisciplinary Healthcare. 2021;14:997-1005.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND ASSOCIATED FACTORS AMONG FIRST-YEAR ELEMENTARY SCHOOL STUDENTS.

Hoang HH, Ngoc Tran AT, Nguyen VH, et al.

Purpose: Attention deficit hyperactivity disorder (ADHD) is a mental health disorder commonly in children. This study aimed to examine the prevalence of ADHD and risk factors among first-year pupils in Vietnam's urban city.
Patients and Methods: A cross-sectional study was conducted in four randomly selected primary schools. Information on 525 pupils in grade 1 (ages 6 to 7 years) was collected from 525 parents/caregivers and 28 teachers. We used the Vanderbilt Assessment Scales with two separate versions for parents and teachers to screen children with ADHD symptoms.
Results: Among the total of 525 pupils, 24 (4.6%) were found to have ADHD symptom types (boy: 6.5%; girl: 2.1%). The combined ADHD type accounted for the highest proportion of 3.4%, followed by predominantly inattentive and predominantly hyperactivity type. ADHD prevalence rated by teachers was higher than those rated by parents. High agreement between parents and teachers was reported (+¦ > 0.6). The risk of ADHD increased in male participants (aOR=4.90, 95% CI 1.51ΓÇô15.85), those having a first-degree relative with ADHD (aOR=85.2, 95% CI 1.66-4371.8), in-utero exposure to tobacco smoke (aOR=4.78, 95% CI 1.31-17.44), and prenatal alcohol drinking (aOR=8.87, 95% CI 2.29-34.42).
Conclusion: These findings suggest the importance of ADHD screening for pupils attending elementary schools, particularly those with a family history of ADHD. Public health programs should reduce prenatal exposure to the potential risk factors of ADHD (smoking and alcohol consumption)

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J Neural Transm. 2021.

LIFETIME EVOLUTION OF ADHD TREATMENT.

Mucci F, Carpita B, Pagni G, et al.

Attention-deficit hyperactivity disorder (ADHD), has been traditionally considered a neurodevelopmental disorder affecting children and adolescents characterized by inattention, hyperactivity, disruptive behavior, and impulsivity. Although still debated, it is evident that ADHD is also present in adulthood, but this diagnosis is rarely carried out, mainly for-áthe frequent comorbidity with other psychiatric and/or substance abuse disorders. Given the need to shed more light on the pharmacological treatment of ADHD, we performed a naturalistic review to review and comment on the available literature of ADHD treatment across the lifespan. Indeed, stimulants are endowed of a prompt efficacy and safety, whilst non-stimulants,-áalthough requiring some weeks to be fully effective, are useful when a substance abuse history is detected. In any case, the pharmacological management of ADHD appears to be still largely influenced by the individual experience of the clinicians. Further longitudinal studies with a careful and detailed characterization of participants across

different phases of the lifespan are also required to provide relevant confirmations (or denials) regarding pharmacological treatments amongst the different age groups

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J Neural Transm. 2021.

IMPACT OF THE COVID-19 LOCKDOWN ON SCREEN MEDIA USE IN PATIENTS REFERRED FOR ADHD TO CHILD AND ADOLESCENT PSYCHIATRY: AN INTRODUCTION TO PROBLEMATIC USE OF THE INTERNET IN ADHD AND RESULTS OF A SURVEY.

Werling AM, Walitza S, Drechsler R.

The COVID-19 outbreak and lockdown have been associated with multiple consequences for mental health, including an excessive and potentially harmful increase in screen media use. The specific consequences for children, adolescents and young adults with ADHD are still unknown. In the first part of this study, a short review of problematic use of the internet (PUI) in ADHD is presented, showing that patients with ADHD are at risk for different aspects of PUI, such as excessive gaming or problematic social media use. In the second part, we report original data of an online survey on screen media use before, during and after the lockdown completed by parents of children and adolescents clinically referred for ADHD. Parents rated children's/adolescents media-related behavior and media time on a new screening questionnaire for PUI. Each item was rated three times, referring to the observed behavior before, during and 1-2 months after the lockdown. N = 126 parents of patients referred for ADHD aged 10ΓÇô18-áyears participated in the study. Total media time increased by 46% during the lockdown and did not completely return to pre-Corona levels afterwards. Patients with difficulties concentrating, high irritability or deterioration of ADHD problems under lockdown spent more time with screen media than those with milder or no such problems. While the effects of the lockdown on screen media use and its negative impact on everyday life appear to be largely reversible, a small proportion of patients with ADHD apparently continue to show increased media use

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J Paediatr Child Health. 2021.

EMERGENCY MENTAL HEALTH PRESENTATIONS IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Bourke EM, Say DF, Carison A, et al.

Aim: To characterise the key features and management of young people presenting to the emergency department (ED) with a mental health (MH) complaint and a known diagnosis of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).

Methods: Retrospective review of all ED MH presentations in children aged 7ΓÇô17 years, presenting over a 12-month period from the 1st of January 2018 to the 31st of December 2018, to the Royal Children's Hospital in Melbourne, Australia. Univariate analyses were carried out to examine the relationship between an underlying diagnosis of ASD and/or ADHD and a number of key presentation variables. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for ED management outcomes.

Results: There were 374 presentations in this cohort, representing 28% of the total MH presentations in 2018. The most common reason for presentation was acute severe behavioural disturbance. Young people with ASD and ADHD were at increased risk of having an acute crisis team response activated (ASD RR 2.3, CI 1.6-3.3, ADHD RR 2.2, CI 1.2-4.1). Compared to those without either diagnosis, young people with ASD were more likely to be physically restrained (RR 2.8, CI 1.7-4.6), managed in seclusion (RR 3.3, CI 1.7-6.4) and to receive medication to assist with behavioural de-escalation (RR 2.8, CI 1.6ΓÇô4.9).

Conclusions: Children with ASD and/or ADHD represent one-quarter of all children presenting to the ED with MH complaints. They experience high rates of acute severe behavioural disturbance. Future research is needed to co-design, implement and evaluate better approaches for their management

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J Paediatr Child Health. 2021.

SPECTRUM SUPPORT: CO-WORKING BETWEEN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER/AUTISM SPECTRUM DISORDER, THEIR FAMILIES AND PAEDIATRICIANS.

Banerjee T, Riley S, Saunders S.

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J Pediatr Urol. 2021.

NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS IN PEDIATRIC BLADDER AND BOWEL DYSFUNCTION.

Wang R, Van den Heuvel M, Rickard M, et al.

Background: Bladder and bowel dysfunction (BBD) is a common pediatric problem that describes a constellation of lower urinary tract symptoms associated with constipation and/or encopresis. Its association with neurodevelopmental and psychiatric (NDP) problems is not well understood.

Objectives: Our primary aim was to identify pre-existing NDP disorders in children with BBD. Secondarily, we aimed to screen for new behavioral problems and evaluate the association between bladder or bowel symptoms and behaviors symptoms.

Methods: A cross sectional study was conducted in urology clinics. New patients referred for BBD between 4 and 17 years old were recruited and completed: a demographics survey, Dysfunctional Voiding Score System questionnaire, assessment of bowel movements with the Bristol Stool Scale, and Strength and Difficulties questionnaire (SDQ). Those with known spinal dysraphism were excluded. SDQ scores were evaluated for abnormal screens in different subscales and total difficulties scores. Pearson correlation analyses were conducted for association.

Results: We included 61 participants (age 9.5 -¦ 4.1 years), including 33 females and 28 males. One or more pre-existing NDP disorder(s) was reported in 14 (23%) children; most commonly being learning disability (43%) and attention deficit hyperactivity disorder (29%). This cohort had more severe BBD symptoms as reflected in DVSS scores. SDQ scores demonstrated that 12 patients without pre-existing NDP diagnoses scored in the clinical range, with hyperactivity as the most common difficulty (6/12; 50%).

Conclusions: A significant proportion of children with BBD have a comorbid NDP disorder and present with more severe symptomatology. The SDQ can be used as a behavioral screening tool this population for the identification of children who may benefit from formal developmental pediatrics assessment. [Table presented]

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J Pediatr. 2021.

PERSPECTIVES OF US ADOLESCENTS ON DIVERTED STIMULANT USE.

Hadler N, Strome A, Waselewski M, et al.

Objective: To evaluate perspectives of youth regarding diverted stimulant use among a contemporary sample of adolescents and young adults.

Study design: This study used MyVoice, a longitudinal national text message survey of American youth. In February 2019, 1228 MyVoice youth were asked 4 open-ended questions to elicit their perspectives on diverted stimulant use. Responses were assessed using thematic analysis, and quantitative results were summarized using descriptive statistics.

Results: Of 1228 youth, 906 responded to at least one survey question (relative risk, 74%). Respondents ages ranged from 14 to 24 years with a mean age of 18.8 -¦ 2.9 years, 57% were female, and 66% identified as White. Peer pressure and coping were commonly perceived reasons for diversion, and respondents believed that many youth misuse stimulants. Many were aware of health risks of misuse, but few mentioned potential legal consequences. Youth thought stimulants could be obtained from peers, people with a prescription, dealers, and family, and some mentioned access through unnecessary prescriptions.

Conclusions: The perspectives of a national sample of youth suggest that stimulant diversion continues to be a significant problem among American youth, with many noting that diverted stimulants are easy to obtain and are used to self-treat mental health issues. Standardized interventions at schools and in healthcare settings, as well as universal screening for diversion and mental health conditions, may combat this public health concern

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J Psychiatr Res. 2021;138:569-75.

BRAIN STATE-DEPENDENT DYNAMIC FUNCTIONAL CONNECTIVITY PATTERNS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sun Y, Lan Z, Xue SW, et al.

Attention-deficit/hyperactivity disorder (ADHD) patients have presented aberrant static brain networks, however identifying ADHD patients based on dynamic information in brain networks is not fully clear. Data were obtained from 32 boys with ADHD and 52 sex- and age-matched typically developing controls; a sliding-window method was used to assess dynamic functional connectivity (dFC), and two reoccurring dFC states (the hot and cool states) were then identified using a k-means clustering method. The results showed that ADHD patients had significant changes in occurrence, transitions times and dFC strength of the cingulo-opercular network (CON) and sensorimotor network (SMN) in the cool state. The severity of ADHD symptoms showed significant correlations with the regional amplitude of dFC fluctuations in the ventral medial prefrontal cortex (vmPFC), anterior medial prefrontal cortex (amPFC) and precuneus. These findings could provide insights on the state-dependent dynamic changes in large-scale brain connectivity and network configurations in ADHD

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J Psychiatr Res. 2021;138:477-84.

THE CHILD BEHAVIOR CHECKLIST CAN AID IN CHARACTERIZING SUSPECTED COMORBID PSYCHOPATHOLOGY IN CLINICALLY REFERRED YOUTH WITH ADHD.

Biederman J, DiSalvo M, Vaudreuil C, et al.

Objective: To examine the utility of the Child Behavior Checklist (CBCL) to aid in the identification of comorbid psychopathological conditions affecting referred youth with suspected ADHD prior to the evaluation. The CBCL is an easy-to-use assessment tool that may provide invaluable information regarding the severity and characteristics of the presenting complaints.

Methods: The sample included 332 youths consecutively referred to an ADHD program for the assessment of suspected ADHD. Parents completed the CBCL, parent-rated ADHD Self-Report Scale (ASRS), Social Responsiveness Scale (SRS), and Behavior Rating Inventory of Executive Function (BRIEF). Because of the established association between the CBCL Attention Problems scale and a structured diagnostic interview of ADHD, all youths analyzed had abnormal Attention Problems T-scores (60).

Results: Seventy-six percent of youths with elevated Attention Problems T-scores had 3 additional abnormal CBCL scales, suggesting they were likely affected with multiple comorbid psychopathological conditions. Moreover, 44% had 1 CBCL clinical scale with a T-score more severe than their Attention Problems T-score, suggesting the putative comorbid condition was more severe than the ADHD symptoms. Additional CBCL scale elevations were associated with more severe functional impairments as assessed by the ASRS, SRS, BRIEF, and CBCL competence scales.

Conclusion: The CBCL obtained before the clinical assessment identified high rates of comorbid psychopathology in youths referred for the assessment of ADHD. It provided detailed information about the types and severity of suspected psychopathological conditions impacting a particular youth, which is critical to guide the assessing clinician on likely differing needs of the affected child

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J Psychopharmacol. 2021.

ROLE OF THE NOREPINEPHRINE TRANSPORTER POLYMORPHISMS IN ATOMOXETINE TREATMENT: FROM RESPONSE TO SIDE EFFECTS IN CHILDREN WITH ADHD.

Gul MK, Sener EF, Onal MG, et al.

Objective: Atomoxetine (ATX), one of the most commonly used drugs after stimulants in attention deficit hyperactivity disorder (ADHD) treatment, is an inhibitor of the norepinephrine transporter (NET/SLC6A2), which is also associated with the etiology of ADHD. In this study, we aimed to investigate the effect of NET gene polymorphisms on response to ATX treatment and to find the answers to the questions about whether there is a relationship between the severity of the disorder and the observed side effects in children with ADHD.

Method: About 100 children with ADHD and 80 healthy controls (HCs) were included in this study. The dose of ATX was started at 0.5 mg/kg/day and titrated at 1.2 mg/kg/day. Response to treatment of 78 patients was evaluated 2 months after the beginning of the treatment. After whole blood samples were obtained, DNAs were isolated, and samples were stored at 80. Two single-nucleotide polymorphisms (SNPs) (rs12708954 and rs3785143) were analyzed by real-time quantitative PCR (qRT-PCR).
Results: The patients with both rs12708954 and rs3785143 heterozygous genotype had better treatment response and more side effects than patients with wild type. There was not found any association between any of the investigated NET polymorphisms and ADHD severity.
Conclusion: It was, however, found that the NET rs12708954 and rs3785143 genotypes affect the treatment response to ATX in our study; thus, further studies with a large population are needed to understand the effects of NET polymorphisms on treatment, side effects, and also the severity of ADHD

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J Am Acad Child Adolesc Psychiatry. 2021.

POLYGENIC RISK AND THE COURSE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FROM CHILDHOOD TO YOUNG ADULTHOOD: FINDINGS FROM A NATIONALLY REPRESENTATIVE COHORT.

Agnew-Blais JC, Belsky DW, Caspi A, et al.

Objective: To understand whether genetic risk for attention-deficit/hyperactivity disorder (ADHD) is associated with the course of the disorder across childhood and into young adulthood.
Method: Participants were from the Environmental Risk (E-Risk) Longitudinal Twin Study, a population-based birth cohort of 2,232 twins. ADHD was assessed at ages 5, 7, 10, and 12 with mother- and teacher-reports and at age 18 with self-report. Polygenic risk scores (PRSs) were created using a genome-wide association study of ADHD case status. Associations with PRS were examined at multiple points in childhood and longitudinally from early childhood to adolescence. We investigated ADHD PRS and course to young adulthood, as reflected by ADHD remission, persistence, and late onset.
Results: Participants with higher ADHD PRSs had increased risk for meeting ADHD diagnostic criteria (odds ratios ranging from 1.17 at age 10 to 1.54 at age 12) and for elevated symptoms at ages 5, 7, 10, and 12. Higher PRS was longitudinally associated with more hyperactivity/impulsivity (incidence rate ratio = 1.18) and inattention (incidence rate ratio = 1.14) from age 5 to age 12. In young adulthood, participants with persistent ADHD exhibited the highest PRS (mean PRS = 0.37), followed by participants with remission (mean PRS = 0.21); both groups had higher PRS than controls (mean PRS = Γêæ0.03), but did not significantly differ from one another. Participants with late-onset ADHD did not show elevated PRS for ADHD, depression, alcohol dependence, or marijuana use disorder.
Conclusion: Genetic risk scores derived from case-control genome-wide association studies may have relevance not only for incidence of mental health disorders, but also for understanding the longitudinal course of mental health disorders

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J Am Acad Child Adolesc Psychiatry. 2021.

A LONGITUDINAL STUDY OF PSYCHIATRIC DISORDERS IN OFFSPRING OF PARENTS WITH BIPOLAR DISORDER FROM PRESCHOOL TO ADOLESCENCE.

Birmaher B, Merranko J, Hafeman D, et al.

Objective: To compare the prevalence of psychopathology, particularly bipolar disorder (BD), between preschool offspring of parents with BD and community controls.
Method: A total of 116 offspring of BD-I/II parents and 98 controls (53 parents with non-BD psychopathology and 45 healthy parents) were recruited at ages 2 to 5 years and followed on average 9.6 years (on average: 2-5: 1.6 times; after age 5: 4 times) (average ages at intake/last follow-up: 3.8/13.4, retention: 98%). Participants were evaluated with standardized instruments blinded to parental diagnoses.
Results: After adjusting for confounders, offspring of BD parents only showed more attention-deficit/hyperactivity disorder (ADHD) during ages 2 to 5 years than the other 2 groups. After age 5, offspring of BD parents did not differ from offspring of parents with non-BD psychopathology, but they had more anxiety, ADHD, and behavior problems than offspring of healthy parents. Only offspring of BD parents developed BD-I/II: 3.4% (n = 4) and BD not-otherwise-specified (BD-NOS): 11.2% (n = 13), with mean onset

ages 11.4 and 7.4, respectively. About 70% of offspring with BD had non-BD disorders before BD. Only ADHD, diagnosed before age 6 years, and early-onset parental BD were significantly associated with BD risk.
Conclusion: Most offspring of BD parents did not develop BD, but they were at specific high risk for developing BD, particularly those with preschool ADHD and early-onset parental BD. BD symptoms were scarce during the preschool years and increased throughout the school age, mainly in the form of BD-NOS, a disorder that conveys poor prognosis and high risk to develop BD-I/II. Developing early interventions to delay or, ideally, to prevent its onset are warranted

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Lancet Psychiatry. 2021 May;8:373-86.
GENE-ENVIRONMENT CORRELATIONS AND CAUSAL EFFECTS OF CHILDHOOD MALTREATMENT ON PHYSICAL AND MENTAL HEALTH: A GENETICALLY INFORMED APPROACH.
Warrier V, Kwong ASF, Luo M, et al.
BACKGROUND: Childhood maltreatment is associated with poor mental and physical health. However, the mechanisms of gene-environment correlations and the potential causal effects of childhood maltreatment on health are unknown. Using genetics, we aimed to delineate the sources of gene-environment correlation for childhood maltreatment and the causal relationship between childhood maltreatment and health.
METHODS: We did a genome-wide association study meta-analysis of childhood maltreatment using data from the UK Biobank (n=143-473), Psychiatric Genomics Consortium (n=26-290), Avon Longitudinal Study of Parents and Children (n=8346), Adolescent Brain Cognitive Development Study (n=5400), and Generation R (n=1905). We included individuals who had phenotypic and genetic data available. We investigated single nucleotide polymorphism heritability and genetic correlations among different subtypes, operationalisations, and reports of childhood maltreatment. Family-based and population-based polygenic score analyses were done to elucidate gene-environment correlation mechanisms. We used genetic correlation and Mendelian randomisation analyses to identify shared genetics and test causal relationships between childhood maltreatment and mental and physical health conditions.
FINDINGS: Our meta-analysis of genome-wide association studies (N=185-414) identified 14 independent loci associated with childhood maltreatment (13 novel). We identified high genetic overlap (genetic correlations 0·24-1·00) among different maltreatment operationalisations, subtypes, and reporting methods. Within-family analyses provided some support for active and reactive gene-environment correlation but did not show the absence of passive gene-environment correlation. Robust Mendelian randomisation suggested a potential causal role of childhood maltreatment in depression (unidirectional), as well as both schizophrenia and ADHD (bidirectional), but not in physical health conditions (coronary artery disease, type 2 diabetes) or inflammation (C-reactive protein concentration).
INTERPRETATION: Childhood maltreatment has a heritable component, with substantial genetic correlations among different operationalisations, subtypes, and retrospective and prospective reports of childhood maltreatment. Family-based analyses point to a role of active and reactive gene-environment correlation, with equivocal support for passive correlation. Mendelian randomisation supports a (primarily bidirectional) causal role of childhood maltreatment on mental health, but not on physical health conditions. Our study identifies research avenues to inform the prevention of childhood maltreatment and its long-term effects.
FUNDING: Wellcome Trust, UK Medical Research Council, Horizon 2020, National Institute of Mental Health, and National Institute for Health Research Biomedical Research Centre

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Laryngoscope. 2021 Jun;131:1416-19.
OBESITY AS A POSSIBLE RISK FACTOR FOR PEDIATRIC SENSORINEURAL HEARING LOSS.
Bluher A, Kawai K, Wang A, et al.
OBJECTIVES/HYPOTHESIS: Childhood hearing loss impacts linguistic, academic, social, and psychologic development, and may have lasting implications for future workforce performance. Current evidence for obesity as a pediatric sensorineural hearing loss (SNHL) risk factor is intriguing but equivocal. We

hypothesized that obesity is associated with a higher risk of SNHL. We additionally examined whether underweight is associated with a higher risk of SNHL.
STUDY DESIGN: Retrospective database review.
METHODS: A single-institution audiologic database from 2015 to 2020 was queried for audiograms with type-A tympanograms from children aged 5 to 18 years old. Comorbidities known to be associated with hearing loss were excluded. We then examined both for sub-clinical (15dB) high- or low-frequency hearing loss, and for clinical (21dB) hearing loss, with the aim of examining the association between obesity and SNHL. Multivariable logistic regression was performed to adjust for age, gender, diabetes mellitus, attention deficit hyperactivity disorder, and autism.
RESULTS: A total of 3,142 children were included. Obesity was not associated with risk of SNHL (adjusted OR 0.82; 95% CI: 0.60, 1.12). Underweight children had a higher risk of SNHL than normal weight children (adjusted OR 1.78; 95% CI: 1.08, 2.95). Autism was significantly associated with increased risk of sub-clinical SNHL only (adjusted OR 2.00; 95% CI 1.34, 2.98).
CONCLUSIONS: No association was found between obesity and pediatric SNHL. Underweight children may represent a higher-risk population for SNHL. There appears to be an increasing risk of SNHL as children approach adolescence. Further study of systemic risk factors for SNHL is indicated.
LEVEL OF EVIDENCE: 3 Laryngoscope, 131:1416-1419, 2021

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Medicine and Pharmacy Reports. 2020;93:175-80.

RISK FACTORS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CASE-CONTROL STUDY IN 5 TO 12 YEARS OLD CHILDREN.

Soheilipour F, Shiri S, Ahmadkhaniha HR, et al.

Background and aims. Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder known by a pattern of diminished sustained attention and increased impulsivity or hyperactivity. This study aimed to evaluate the risk factors associated with ADHD.
Methods. This case-control study included 297 ADHD children aged 5-12 years admitted to Tehran Institute of Psychiatry, Iran (2012-2013). They were compared with 297 non-ADHD (as controls matched to cases 1:1) who were of the same age (-¦1 years) selected from outpatients in general pediatric medical centers in Tehran. ADHD Rating Scale IV (ADHD-RS-IV)-Home Version was used to confirm ADHD. Data were analyzed using conditional binary logistic regression.
Results. Mean-¦SD age were 8.18-¦3.11 and 8.11-¦2.9 years in the case and control groups, respectively (P=0.61). Mean-¦SD birth weight (BW) was higher in ADHD patients compared with the controls (3245.09-¦0.66 vs 3026.56-¦0.45 gr, P=0.045). The results showed that odds of ADHD in children with high BW (>3500g) was 3.36 (1.96-5.78) times the odds of ADHD in normal BW children (2500-3500g) controlling for other risk factors. ADHD risk in low BW children (<2500 g) was not statistically different compared with normal BW children [OR:1.74 (0.7-3.7)]. Experience of neonatal disease, fewer offspring, lower level of mothersΓÇÖ education, and preterm delivery were also risk factors for higher odds of ADHD.
Conclusion. Based on our sample, preterm birth, neonatal disease, high BW, lower level of mother's education, and fewer offspring were ADHD risk factors

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Mol Psychiatry. 2021 May;26:1696-705.

POLYGENIC RISK FOR AUTISM, ATTENTION-DEFICIT HYPERACTIVITY DISORDER, SCHIZOPHRENIA, MAJOR DEPRESSIVE DISORDER, AND NEUROTICISM IS ASSOCIATED WITH THE EXPERIENCE OF CHILDHOOD ABUSE.

Ratanatharathorn A, Koenen KC, Chibnik LB, et al.

People who experience childhood abuse are at increased risk of mental illness. Twin studies suggest that inherited genetic risk for mental illness may account for some of these associations. Yet, the hypothesis that individuals who have experienced childhood abuse may carry genetic loading for mental illness has never been tested with genetic data. Using polygenic risk scores for six psychiatric disorders-attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BPD), major depressive disorder (MDD), neuroticism, and schizophrenia-we tested whether genetic risk for mental illness was associated with increased risk of experiencing three types of childhood abuse: physical/emotional abuse,

physical assault, and sexual abuse, in a cohort of white non-Hispanic women (n=11,315). ADHD and MDD genetic risk scores were associated with a higher risk of experiencing each type of childhood abuse, while neuroticism, schizophrenia, BPD, and ASD genetic scores were associated with a higher risk of experiencing physical/emotional abuse and physical assault, but not sexual abuse. Sensitivity analyses examining potential bias from the differential recall of childhood trauma, parental socioeconomic status, and population stratification were consistent with the main findings. A one-standard-deviation increase in genetic risk for mental illness was associated with a modestly elevated risk of experiencing childhood abuse (OR range: 1.05-1.19). Therefore, inherited genetic risk may partly account for the association of childhood abuse with mental illness. In addition, future treatments for mental illness will benefit from taking into consideration the co-occurrence of childhood trauma and genetic loading

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Molecular Biology Reports. 2021;48:3213-22.

ADHESION G PROTEIN-COUPLED RECEPTOR L3 GENE VARIANTS: STATISTICALLY SIGNIFICANT ASSOCIATION OBSERVED IN THE MALE INDO-CAUCASOID ATTENTION DEFICIT HYPERACTIVITY DISORDER PROBANDS.

Chatterjee M, Saha S, Shom S, et al.

Primary symptoms of Attention Deficit Hyperactivity Disorder (ADHD) are age inappropriate inattention, hyperactivity and impulsivity. Caucasoid individuals showed increased susceptibility to ADHD and disruptive behaviour in presence of Adhesion G-protein-coupled receptor L3 (ADGRL3) gene variants. We investigated ADGRL3 rs1868790, rs6551665, rs2345039 in Indo-Caucasoid families with ADHD probands (N = 249) and controls (N = 350). Behavioural traits, executive function, and IQ of probands were measured through Conner's Parent Rating Scale-Revised, Parental Account of ChildrenΓÇÖs Symptoms, Barkley Deficit in Executive Functioning-Child & Adolescent Scale, and Wechsler Intelligence Scale for Children-III respectively. After obtaining informed written consent, peripheral blood was collected for genomic DNA isolation and target sites were analyzed by PCR based methods or TaqMan assay. Case-control analysis showed higher frequency of rs2345039 C allele, CC genotype and A-A-C haplotype in the ADHD probands, principally due to higher occurrence of the C allele and A-A-C haplotype in the male probands ($P < 0.05$). Mother of the probands also showed higher occurrence of the C allele and CC genotype ($P < 0.01$). Executive function was better in presence of rs2345039 GG ($P = 0.04$) while IQ score was higher in presence of rs6551665 AA ($P = 0.06$). Linkage disequilibrium between rs6551665 and rs2345039 was stronger in the ADHD cases, chiefly in the male probands. Multifactor dimensionality reduction analysis showed strong interaction between rs6551665 and rs2345039 in the male probands while in the female probands rs1868790 and rs6551665 revealed non-linear interaction. Based on these observations, we infer that ADGRL3 may have a role in the aetiology of ADHD in this population warranting further in depth investigation

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Mol Psychiatry. 2021.

PLACEBO AND NOCEBO RESPONSES IN RANDOMISED, CONTROLLED TRIALS OF MEDICATIONS FOR ADHD: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Faraone SV, Newcorn JH, Cipriani A, et al.

The nature and magnitude of placebo and nocebo responses to ADHD medications and the extent to which response to active medications and placebo are inter-correlated is unclear. To assess the magnitude of placebo and nocebo responses to ADHD and their association with active treatment response. We searched literature until June 26, 2019, for published/unpublished double-blind, randomised placebo-controlled trials (RCTs) of ADHD medication. Authors were contacted for additional data. We assessed placebo effects on efficacy and nocebo effects on tolerability using random effects meta-analysis. We assessed the association of study design and patient features with placebo/nocebo response. We analysed 128 RCTs (10,578 children/adolescents and 9175 adults) and found significant and heterogenous placebo effects for all efficacy outcomes, with no publication bias. The placebo effect was greatest for clinician compared with other raters. We found nocebo effects on tolerability outcomes. Efficacy outcomes from most raters showed significant positive correlations between the baseline to endpoint placebo effects and the baseline to endpoint drug effects. Placebo and nocebo effects did not differ among drugs. Baseline severity and type of rating scale influenced the findings. Shared non-specific factors influence response to both placebo and active

medication. Although ADHD medications are superior to placebo, and placebo treatment in clinical practice is not feasible, clinicians should attempt to incorporate factors associated with placebo effects into clinical care. Future studies should explore how such effects influence response to medication treatment. Upon publication, data will be available in Mendeley Data: PROSPERO (CRD42019130292)

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Neuropsychology. 2021 May;35:399-410.

STRONGER IMPULSE CAPTURE AND IMPAIRED INHIBITION OF PREPOTENT ACTION IN CHILDREN WITH ADHD PERFORMING A SIMON TASK: AN ELECTROMYOGRAPHIC STUDY.

Grandjean A, Suarez I, Diaz E, et al.

Objective: A deficit in interference control is commonly reported in children with attention deficit hyperactivity disorder (ADHD). This has mainly been interpreted as a difficulty in inhibiting inappropriate responses. However, it could be due to at least two distinct and independent processes, which are often confounded: The activation or suppression of impulsive responses. The aim of the present study was to separate the contribution of these two processes.

Method: We compared performance of 26 children with ADHD to that of 26 nonADHD children using a novel approach based on electromyographic activity (EMG) analysis. EMG allows two distinct indices to be computed: Incorrect activation rate, which is an index of the intensity of impulse capture and correction rate, which provides a direct measure of the ability to suppress automatic responses.

Results: Children with ADHD were slower, committed more errors, and had a larger interference effect than nonADHD children. Moreover, we observed a greater incorrect activation rate and a lower correction rate in the ADHD group.

Conclusions: Our data suggest that the difficulties in interference control found in children with ADHD are explained by both impaired inhibitory processes and a greater propensity to activate automatic responses.

Question: We investigated how ADHD affects impulsivity control.

Findings: Interference control was impaired in children with ADHD.

Importance: Impulsivity and hyperactivity could be due to both a greater propensity to activate impulsive responses and a greater difficulty in inhibiting them.

Next Steps: Future research should investigate the effect of treatments on these two components of impulsivity control

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Neurosci Biobehav Rev. 2021;127:514-19.

HOW CHILDREN WITH NEURODEVELOPMENTAL DISORDERS CAN BENEFIT FROM THE NEUROCOGNITIVE EFFECTS OF EXERCISE.

Ludyga S, et al.

Exercise is an integral part of children's lives, and research in educational settings has found that regular engagement promises improvements in executive function (i.e. top-down control of goal-directed behavior). Based on recent advances in understanding the moderators and the neurocognitive mechanisms of these effects, we highlight a potential application of exercise in the treatment of executive dysfunction. Even though different neurodevelopmental disorders are characterized by a heterogeneity in core symptoms, children affected by these disorders often face common executive function deficits. So far, exercise has not been recognized as an alternative or additional treatment for this specific cognitive impairment. The limited experimental evidence in children with neurodevelopmental disorders provides a first indication that regular exercise engagement benefits executive function. However, we identified key research questions that need to be answered before a prescription of exercise to children with executive dysfunction can be encouraged in clinical practice

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Nord J Psychiatry. 2021 May;75:301-05.

THE ROAD TO DIAGNOSIS AND TREATMENT IN GIRLS AND BOYS WITH A.

KlefsjÃ U, Kantzer AK, Gillberg C, et al.

INTRODUCTION: The number of referrals for diagnostic assessments of Attention Deficit/Hyperactivity Disorder (ADHD) has increased in the last decade. There is a lack of studies examining the diagnostic process and the treatment provided, particularly from a gender perspective.

METHODS: From a consecutive cohort of Child and Adolescent Psychiatric (CAP) outpatients, the medical records of 50 boys and 50 girls (under 18 years of age) with a diagnosis of ADHD were selected by an Excel random numbers generator. Data about referral reason, diagnostic process and treatment were analysed.

RESULTS: Emotional symptoms were more common as a reason for referral to CAP among girls, whereas neurodevelopmental disorders were more common among boys. Compared to the boys, the girls were older at first visit to CAP and at the ADHD diagnosis. The girls had had more visits to the clinic prior to the ADHD diagnostic decision and had more often been prescribed non-ADHD medication both before and after the ADHD diagnosis. The rate of ADHD medication was similar in boys and girls. Girls had more often been admitted to a CAP inpatient care unit prior to the ADHD diagnosis due to acute psychiatric symptoms, and had received more individual psychotherapeutic counselling.

CONCLUSION: The results highlight the need for broader psychiatric investigations including neuropsychiatric symptoms in girls referred for 'emotional problems'

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Paediatr Croat. 2021;65:27-35.

SYMPTOMS OF IMPULSIVENESS/HYPERACTIVITY AND INATTENTION IN SCHOOLCHILDREN WITH BEHAVIOURAL DIFFICULTIES.

Vlah N, et al.

The main aim of this research was to examine homeroom teacher assessment of attention deficit/hyperactivity disorder (ADHD) symptoms and some demographic and socio-pedagogical characteristics of schoolchildren with behavioural difficulties, as well as the relations between the mentioned variables. Homeroom teachers assessed 1463 schoolchildren of all grades from 125 primary schools throughout Croatia, for whom they felt and/or thought to have behavioural difficulties, on the Vanderbilt scale in two dimensions: impulsiveness/hyperactivity and inattention. Homeroom teachers assessed occasional to frequent impulsiveness-hyperactivity and frequent inattention in children. In boys and younger participants, impulsiveness-hyperactivity and inattention were assessed more often than in girls, except for inattention that was as frequently assessed in all boys regardless of age. Better academic achievement and material status were recorded in higher assessments of impulsiveness and hyperactivity. Poorer academic achievement was characterized by higher occurrence of inattention. Decisions on the suitable education program were associated with ADHD symptoms only in boys, and were negative for impulsiveness and hyperactivity but positive for inattention. The expressed need for additional help in learning and correcting behaviour was greater when assessments of all ADHD symptoms were higher. Prompt recognition of developmental difficulties and early diagnosis had a significant impact on forming appropriate support in the school and family system

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Pediatr Rep. 2021;13:234-40.

POLY-UNSATURATED FATTY ACIDS IN ADHD AND IN OTHER NEUROPSYCHIATRIC CONDITIONS: A MULTIPLE CASE PRESENTATION.

Chiappedi M.

Neurodevelopmental disorders are seen quite commonly by general pediatricians. They should be managed with a multi-professional approach. The potential beneficial effect of polyunsaturated fatty acids (PUFAs) has been reported in recent literature, but guidelines describing their use in everyday practice are still lacking. We describe four cases as examples of the possible integration of a supplementation with PUFAs in the management of four relatively common clinical situations (i.e., children too young to receive pharmacological treatment for ADHD, children with nonspecific neurodevelopmental disorders, children whose parents refuse

consent for pharmacological treatment of ADHD, and children for whom methylphenidate is not sufficient to achieve expected results)

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Pediatr Int. 2020.

SLEEP PROBLEMS IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND TYPICAL DEVELOPMENT.

Inthikoot N, Chonchaiya W.

Background: Although higher sleep problems have been mostly reported in children with autism spectrum disorder (ASD) compared with typically developing (TD) children, particularly in Western countries, such evidence is relatively scarce in developing countries. We therefore investigated sleep difficulties in Thai children aged 3-16-áyears with ASD compared with age- and gender-matched TD children by using the Children's Sleep Habits Questionnaire (CSHQ)-Thai version.

Methods: Sixty-five children with ASD (mean age 97.7, SD 44.5-ámonths; boys 70.8%) and 65 TD individuals (mean age 98.5, SD 43.5 months) were enrolled at a university-based hospital in Bangkok. Background characteristics, sleep duration variables, and the CSHQ were completed by the participants' parents. The CSHQ subscales and total score between children with ASD and TD controls were then compared.

Results: Children with ASD were more likely to have longer sleep latency than TD individuals for both weekdays and the weekend. Those with ASD had higher CSHQ subscales including bedtime resistance, sleep onset delay, sleep anxiety, and night waking in addition to the CSHQ total scores than TD controls. In the ASD group, those who took psychostimulants for treatment of ADHD had lower scores on the sleep duration subscale compared with unmedicated individuals.

Conclusions: Sleep difficulties were more prevalent in children with ASD compared with TD individuals. Parents should be advised to be aware of sleep problems in individuals with ASD. As such, sleep disturbances will be identified early, resulting in appropriate management and improved quality of life, not only for those with ASD but also their families

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PLoS ONE. 2021;16.

NO SUPPORT FOR WHITE MATTER CONNECTIVITY DIFFERENCES IN THE COMBINED AND INATTENTIVE ADHD PRESENTATIONS.

Saad JF, Griffiths KR, Kohn MR, et al.

Evidence from functional neuroimaging studies support neural differences between the Attention Deficit Hyperactivity Disorder (ADHD) presentation types. It remains unclear if these neural deficits also manifest at the structural level. We have previously shown that the ADHD combined, and ADHD inattentive types demonstrate differences in graph properties of structural covariance suggesting an underlying difference in neuroanatomical organization. The goal of this study was to examine and validate white matter brain organization between the two subtypes using both scalar and connectivity measures of brain white matter. We used both tract-based spatial statistical (TBSS) and tractography analyses with network-based Statistics (NBS) and graph-theoretical analyses in a cohort of 35 ADHD participants (aged 8ΓÇô17 years) defined using DSM-IV criteria as combined (ADHD-C) type (n = 19) or as predominantly inattentive (ADHD-I) type (n = 16), and 28 matched neurotypical controls. We performed TBSS analyses on scalar measures of fractional anisotropy (FA), mean (MD), radial (RD), and axial (AD) diffusivity to assess differences in WM between ADHD types and controls. NBS and graph theoretical analysis of whole brain interregional tractography examined connectomic differences and brain network organization, respectively. None of the scalar measures significantly differed between ADHD types or relative to controls. Similarly, there were no tractography connectivity differences between the two subtypes and relative to controls using NBS. Global and regional graph measures were also similar between the groups. A single significant finding was observed for nodal degree between the ADHD-C and controls, in the right insula (corrected p = .029). Our result of no white matter differences between the subtypes is consistent with most previous findings. These findings together might suggest that the white matter structural architecture is largely similar between the DSM-based ADHD presentations is similar to the extent of being undetectable with the current cohort size

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2021;110.

WHITE MATTER MICROSTRUCTURAL INTEGRITY CORRELATES OF EMOTION DYSREGULATION IN CHILDREN WITH ADHD: A DIFFUSION IMAGING TRACTOGRAPHY STUDY.

Tsai CJ, Lin HY, Tseng IWY, et al.

Background: Emotion dysregulation (ED) is prevalent in youths with attention-deficit hyperactivity disorder (ADHD) and causes more social impairment and poor adaptive function. Alterations in the integrity of white matter (WM) tracts might have important implications for affective processing related to ED. However, little is known about the WM correlates underpinning ED in ADHD.

Methods: Using diffusion spectrum image tractography, we obtained generalized fractional anisotropy (GFA) values of 76 WM tracts in 77 children with ADHD and 105 typically developing controls (TDC). ED severity was defined by the dysregulation profile from the child behavior checklist. Canonical correlation analysis (CCA) was performed to identify modes that relate WM microstructural property to ED severity and cognitive measures.

Results: The application of CCA identified one significant mode (r = 0.638, FWE-corrected p = 0.046) of interdependencies between WM property patterns and diagnosis, ADHD total symptom levels, dysregulation by diagnosis interaction, and full-scale intellectual quotient (FIQ). GFA values of 19 WM tracts that were linked to affective-processing, sensory-processing and integration, and cognitive control circuitry were positively correlated with ED severity in TDC but negatively correlated with ED severity in ADHD. ADHD symptom severity and diagnosis were negatively associated with the GFA patterns of this set of tract bundles. In contrast, FIQ was positively correlated with this set of tract bundles.

Conclusions: This study used the CCA to show that children with ADHD and TDC had distinct multivariate associations between ED severity (diagnosis by ED interaction) and microstructural property in a set of WM tracts. These tracts interconnect the cortical regions that are principally involved in emotion processing, integration, and cognitive control in multiple brain systems. The WM microstructure integrity impairment might be an essential correlate of emotion dysregulation in ADHD

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Psychiatr Serv. 2021 Mar;72:362-65.

A SECOND-OPINION PROGRAM FOR THE CARE OF YOUTHS PRESCRIBED FIVE OR MORE PSYCHOTROPICS IN WASHINGTON STATE.

Barclay RP, Dillon-Naftolin E, Russell D, et al.

This retrospective study describes a second-opinion review program for the care of children in Washington State who received Medicaid coverage and who were prescribed five or more psychotropic medications, primarily by mental health specialists. In total, 136 second-opinion reviews from 2013 and 169 from 2018 were included in this study. Attention-deficit hyperactivity disorder (ADHD), behavioral difficulties, anxiety, and trauma were prevalent among these children, and participants were commonly prescribed ADHD medications, selective serotonin reuptake inhibitors, and second-generation antipsychotics. The incidence of reviews remained stable over the two periods, but psychosocial treatment increased significantly over this time. This study sheds light on the initiation, maintenance, and identification of polypharmacy psychotropic regimens and highlights psychosocial treatment as an intervention that increases best practice care for at-risk patients

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Psychiatr Invest. 2021;18:166-71.

THE TEMPORAL HYPER-MORBIDITY OF ASTHMA AND ATTENTION DEFICIT DISORDER: IMPLICATIONS FOR INTERPRETATION BASED ON COMPARISON OF PROSPECTIVE AND CROSS-SECTIONAL POPULATION SAMPLES.

Chai PH, Chang S, Cawthorpe D.

Objective The purpose of this study was to test the hypothesis that a significant temporal relationship exists between asthma and attention deficit hyperactivity disorder (ADHD).

Methods The population dataset consisted of 95,846,511 physician diagnoses for 768,460 (46% male) individuals spanning 1993-2010. Four groups were labeled as having neither Asthma nor ADHD, Asthma only, ADHD only, or both Asthma and ADHD and formed the basis of calculating the odds ratios for each sex describing the association of Asthma and ADHD by age, and, in addition, a prospective sample age (<5

years) between 1993 and 1996 was utilized to evaluate the temporal association between Asthma and ADHD.
Results There was a significant relationship between ADHD and Asthma within the age strata of the sample, one from the cohort and two from the whole sample. When both ADHD and Asthma were diagnosed in the same patients, the age was younger in both cross-sectional and prospective cohort samples. ADHD arose significantly more often after Asthma in the cross-sectional samples stratified on age and in the prospective cohort sample.
Conclusion The results are consistent with previous literature where ADHD has been linked to allergic diseases, such as asthma

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Psychiatry Res. 2021;301.
INVESTIGATING THE VALIDITY OF THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE TO ASSESS ADHD IN YOUNG ADULTHOOD.
Riglin L, Agha SS, Eyre O, et al.
Attention Deficit Hyperactivity Disorder (ADHD) symptoms typically onset early and persist into adulthood for many. Robust investigation of symptom continuity and discontinuity requires repeated assessments using the same measure, but research is lacking into whether measures used to assess ADHD symptoms in childhood are also valid in adulthood. The Strengths and Difficulties Questionnaire (SDQ) is widely used to assess ADHD symptoms in children, but little is known about its utility in adulthood. The aim of this study was to assess the validity of the SDQ hyperactivity/ADHD subscale to distinguish between cases and non-cases of DSM-5 ADHD at age 25 years in a UK population cohort (N = 4121). ADHD diagnosis was derived using the Barkley Adult ADHD Rating Scale-IV. Analyses suggested that the self-rated SDQ ADHD subscale had high validity in distinguishing ADHD cases/non-cases in young adulthood (area under the curve=0.90, 95% CI=0.87ΓÇô0.93) and indicated a lower cut-point for identifying those who may have an ADHD diagnosis in this age group compared to that currently recommended for younger ages. Findings were similar for parent-reports. Our findings suggest that the SDQ is suitable for ADHD research across different developmental periods, which will aid the robust investigation of ADHD from childhood to young adulthood

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Psychol Med. 2021 Apr;51:835-45.
EFFECTS OF THE DOPAMINE TRANSPORTER GENE ON STRIATAL FUNCTIONAL CONNECTIVITY IN YOUTHS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Shang CY, Lin HY, Gau SS-F.
Background: The dopamine transporter gene (DAT1), striatal network dysfunction, and visual memory deficits have been consistently reported to be associated with attention-deficit/hyperactivity disorder (ADHD). This study aimed to examine the effects of the DAT1 rs27048 (C)/rs429699 (T) haplotype on striatal functional connectivity and visual memory performance in youths with ADHD.
Method: After excluding those who had excessive head motion, a total of 96 drug-naïve youths with ADHD and 114 typically developing (TD) youths were assessed with the resting-state functional magnetic resonance imaging and the delayed matching to sample (DMS) task for visual memory. We examined the effects of ADHD, DAT1 CT haplotype, and the ADHD × CT haplotype interaction on the functional connectivity of five striatal seeds. We also correlated visual memory performance with the functional connectivity of striatal subregions, which showed significant diagnosis × genotype interactions.
Results: Compared with TD youths, ADHD youths showed significant hypoconnectivity of the left dorsal caudate (DC) with bilateral sensorimotor clusters. Significant diagnosis × genotype interactions were found in the connectivity between the left DC and the right sensorimotor cluster, and between the right DC and the left dorsolateral prefrontal/bilateral anterior cingulate clusters. Furthermore, the connectivity of the left DC showing significant diagnosis × genotype interactions was associated with DMS performance in youths with ADHD who carried the DAT1 CT haplotype.
Conclusions: A novel gene-brain-behavior association between the left DC functional connectivity and visual memory performance in ADHD youths with the DAT1 rs27048 (C)/rs429699 (T) haplotype suggests a

differential effect of DAT1 genotype altering specific brain function causing neuropsychological dysfunction in ADHD

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Psychol Sci. 2021 Apr;32:496-518.

Challenging the link between early childhood television exposure and later attention problems: A multiverse approach.

McBee MT, Brand RJ, Dixon WEJr.

In 2004, Christakis and colleagues published findings that he and others used to argue for a link between early childhood television exposure and later attention problems, a claim that continues to be frequently promoted by the popular media. Using the same National Longitudinal Survey of Youth 1979 data set (N = 2,108), we conducted two multiverse analyses to examine whether the finding reported by Christakis and colleagues was robust to different analytic choices. We evaluated 848 models, including logistic regression models, linear regression models, and two forms of propensity-score analysis. If the claim were true, we would expect most of the justifiable analyses to produce significant results in the predicted direction. However, only 166 models (19.6%) yielded a statistically significant relationship, and most of these employed questionable analytic choices. We concluded that these data do not provide compelling evidence of a harmful effect of TV exposure on attention

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Research on Child and Adolescent Psychopathology. 2021 May;49:643-56.

CHILDREN'S ADHD SYMPTOMS AND FRIENDSHIP PATTERNS ACROSS A SCHOOL YEAR.

Lee Y, Mikami AY, Owens JS.

Symptoms of attention-deficit/hyperactivity disorder (ADHD) in elementary school-age children are associated with poor relationships with classroom peers, as indicated by poor social preference, low peer support, and peer victimization. Less is known about how friendship patterns relate to ADHD symptoms, or how friendships may buffer risk for negative peer experiences. Participants were 558 children in 34 classrooms (grades K-5). At the beginning (fall) and end (spring) of an academic year, children completed (a) sociometric interviews to index friendship patterns and social preference, and (b) self-report questionnaires about their support and victimization experiences from classmates. In fall, higher teacher-reported ADHD symptoms were associated with children having more classmates with no friendship ties (non-friends) and who the child nominated but did not receive a nomination in return (unreciprocated friends), and with having fewer classmates with mutual friendship ties (reciprocated friends) and who nominated the child but the child did not nominate in return (unchosen friends). Higher fall ADHD symptoms predicted more non-friend classmates, poorer social preference, and more victimization in the spring, after accounting for the same variables in fall. However, having many reciprocated friends (and to a lesser extent, many unchosen friends) in fall buffered against the trajectory between fall ADHD symptoms and poor peer functioning in spring. By contrast, having many unreciprocated friends in fall exacerbated the trajectory between fall ADHD symptoms and poor peer functioning in spring. Thus, elevated ADHD symptoms are associated with poorer friendship patterns, but reciprocated friendship may protect against negative classroom peer experiences over time

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Scand J Occup Ther. 2021 Feb;28:78-90.

PROOF OF CONCEPT: THE TRANSITION PROGRAM FOR YOUNG ADULTS WITH AUTISM SPECTRUM DISORDER AND/OR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Jonsson U, Coco C, Fridell A, et al.

BACKGROUND: The support needs of people with neurodevelopmental disorders are not sufficiently met during the initial years of adulthood. AIM: To evaluate feasibility and preliminary effects of a novel programme designed to empower young adults with autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD) to make progress within significant life domains (i.e. work, education, finance, housing/household management, health, leisure/participation in society, and relationships/social network).

MATERIAL AND METHOD: TRANSITION is a 24-week programme that combines group-based workshops with personalised support based on goal attainment scaling. The study enrolled 26 young adults (50% females; age 17-24 years) in the normative intellectual range, diagnosed with ASD (n=8), ADHD (n=4), or both (n=14). The intervention was delivered by the regular staff of publicly funded psychiatric services in Stockholm, Sweden.
RESULTS: The programme was possible to implement with minor deviations from the manual. Participants and staff generally viewed the intervention positively, but also provided feedback to guide further improvement. There was a high degree of attendance throughout, with 21 participants (81%) completing the programme. All completers exceeded their predefined goal expectations within at least one domain.
CONCLUSIONS: The TRANSITION-programme is a promising concept that deserves further evaluation

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Sensors (Basel). 2021 May;21.
A LEAN UX PROCESS MODEL FOR VIRTUAL REALITY ENVIRONMENTS CONSIDERING ADHD IN PUPILS AT ELEMENTARY SCHOOL IN COVID-19 CONTINGENCY.
Cardona-Reyes H, MuÃ±oz-Arteaga J, Villalba-Condori K, et al.
Today, the world is experiencing the COVID-19 health contingency, which prevents people from being exposed to one another and restricts physical contact. Under this context, the use of technology has become an essential tool to face the challenges of daily life, and virtual reality can be an alternative in the development of solutions that effectively support the acquisition of learning skills and knowledge transmission through the execution of tasks designed by multi-disciplinary groups. In addition, it can encourage the user to continue with the acquisition of learning skills in a friendly and fun way in a health and education context. This work proposes the use of virtual reality environments as an alternative to support the learning process in children with special educational needs such as Attention Deficit Hyperactivity Disorder (ADHD) and other associated disorders that occur in basic education. These proposed reality environments are designed under the Lean UX process model and their contents are designed according to expert therapeutic guidelines. As a result of this proposal, a case study is presented in which the user experience is evaluated through the use of an interactive environment to support the special educational needs of elementary school children attending an educational institution in Mexico

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Sensors (Basel). 2021 May;21.
DETECTING ATTENTION LEVELS IN ADHD CHILDREN WITH A VIDEO GAME AND THE MEASUREMENT OF BRAIN ACTIVITY WITH A SINGLE-CHANNEL BCI HEADSET.
Serrano-Barroso A, Siugzdaite R, Guerrero-Cubero J, et al.
Attentional biomarkers in attention deficit hyperactivity disorder are difficult to detect using only behavioural testing. We explored whether attention measured by a low-cost EEG system might be helpful to detect a possible disorder at its earliest stages. The GokEvolution application was designed to train attention and to provide a measure to identify attentional problems in children early on. Attention changes registered with NeuroSky MindWave in combination with the CARAS-R psychological test were used to characterise the attentional profiles of 52 non-ADHD and 23 ADHD children aged 7 to 12 years old. The analyses revealed that the GokEvolution was valuable in measuring attention through its use of EEG-BCI technology. The ADHD group showed lower levels of attention and more variability in brain attentional responses when compared to the control group. The application was able to map the low attention profiles of the ADHD group when compared to the control group and could distinguish between participants who completed the task and those who did not. Therefore, this system could potentially be used in clinical settings as a screening tool for early detection of attentional traits in order to prevent their development

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Sleep. 2020;43.

EFFECT OF TREATMENT ON COGNITIVE AND ATTENTION PROBLEMS IN CHILDREN WITH NARCOLEPSY TYPE 1.

Janssens KAM, Quaedackers L, Lammers GJ, et al.

Study Objectives: To ascertain the presence of cognitive and attention problems in treatment na+»ve children with narcolepsy type 1 (NT1) and to explore whether children recently diagnosed with NT1 improve with respect to cognition and attention problems 1 year after regular treatment for NT1.

Methods: A total of 15 treatment na+»ve children (7-15 years) with recently diagnosed NT1 were recruited from three sleep medicine centers in the Netherlands. The control group consisted of 15 healthy children, being frequency matched on age and gender. Both groups were investigated at baseline to examine intelligence profile (Wechsler Intelligence Scale for Children [WISC] III), attention problems, and processing speed (Bourdon Vos and sustained attention to respond task [SART]). These tests were repeated in children with NT1 1 year after regular (behavioral and medication) treatment for NT1.

Results: Children with NT1 scored significantly lower on the verbal scale and processing speed subscale of the WISC III, showed more fluctuations in reaction time of the Bourdon Vos and made more mistakes during the SART than the healthy control group at baseline. Children with NT1 significantly improved on total IQ score, and on the WISC indices processing speed, and perceptual organization 1 year after treatment. At follow-up, test scores of treated children were largely comparable to those of the control group at baseline.

Conclusions: Children with NT1 show improvement in several cognitive domains 1 year after start of treatment. Our findings stress the need for early detection and treatment of narcolepsy in childhood

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Sleep Med. 2021;83:1-3.

eTNS used for ADHD can disrupt sleep architecture.

Shah YD, Kelly-Pieper K, Kothare S.

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Sleep Med. 2021.

A BRIEF CLINICIAN TRAINING PROGRAM TO MANAGE SLEEP PROBLEMS IN ADHD: WHAT WORKS AND WHAT DO CLINICIANS AND PARENTS THINK?

Sciberras E, Mulraney M, Hayes N, et al.

Objective/Background: Brief behavioural sleep interventions have been shown to be effective in treating sleep problems in children with ADHD. Little research, however, has focused on the translational aspects of these programs from the consumer perspective. This study aimed to explore clinician and parent views of a brief training program in managing sleep problems in children with ADHD.

Participants: Fifty-nine community-based clinicians (32 paediatricians, 27 psychologists) were trained to deliver a brief behavioural sleep intervention as part of the Sleeping Sound with ADHD translational trial; 183 families were allocated to receive the sleep intervention and 115 provided follow-up data.

Methods: Clinicians reported on competency, confidence and perceived barriers pre- and post-training. Parents reported on usefulness of the program and frequency of sleep strategy use at 3 months post-randomisation. Parent-report of severity of the child sleep problem was also measured at 3 and 6 months post-randomisation.

Results: Clinicians feelings of competency and confidence in managing sleep difficulties increased from pre- to post-training, while perceptions of barriers decreased. Parent-reported usefulness of the program and frequency of sleep use varied by program domain and sleep strategy. Increased parent-reported use of sleep strategies was associated with improved sleep at 3 and 6 months post-randomisation.

Conclusions: A brief sleep training program leads to improvements in clinician confidence and competence in managing sleep problems in children with ADHD and positive parent perspectives. The findings highlight the potential for the Sleeping Sound with ADHD program to be optimized to better help parents in their implementation of sleep strategies

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Sleep Med. 2021;82:172-78.

THE EFFECT OF SLEEP DISTURBANCE ON SOCIAL COGNITION IN DRUG-NA+»VE CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Xahin B, et al.

Background: A wide variety of psychiatric conditions are associated with social cognitive deficits. The relationship between social cognition and many factors, especially executive functions (EF), has been examined, but there is no study examining sleep and social cognition in children with attention deficit activity disorder (ADHD). It is important to find new approaches and intervention areas to improve their social cognitive skills. The main hypothesis of our study was that sleep disturbance would predict lower social cognition scores. We hypothesized that sleep disturbances and EF impairment could predict lower social cognitive performance.

Methods: Eighty-five children aged 7ΓÇô12 years with drug-naïve ADHD were included in the study. Reading the Mind in the Eyes Test (RMET) and Faux Pas Recognition Test (FPRT) were used for social cognition performance; Stroop test was used for executive function performance. Sleep disturbance was evaluated with Children's Sleep Habits Questionnaire (CSHQ), ADHD severity with Conners Parent Rating Scale (CPRS). Hierarchical multiple regression analyses were performed to determine predictive factors of the FPRT and RMET.

Results: Age, gender, and comorbidity were included at step 1, CPRS-RS score was included at step 2, Stroop test part V score was included at step 3, CSHQ total score and sleep duration were included at step 4. Lower sleep disturbance score on CSHQ was associated with higher social cognition FPRT score ($p = 0.014$). There was no significant relationship between CSHQ and social cognition RMET score. Lower EF score on Stroop test part V was associated with higher social cognition FPRT score ($p = 0.002$) and higher social cognition RMET score ($p < 0.001$).

Conclusion: These results showed that sleep disturbance and EF are both associated with social cognitive impairment, sleep particularly with the cognitive component. Identifying sleep problems in children with ADHD may provide helpful information in understanding and treating social cognitive impairments. This study is the first to draw attention to the relationship between sleep and social cognition

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Soc Sci Med. 2021;278.

THE DOUBLE HELIX AT SCHOOL: BEHAVIORAL GENETICS, DISABILITY, AND PRECISION EDUCATION.

Sabatello M, Insel BJ, Corbeil T, et al.

The prospect of using behavioral genetic data in schools is gaining momentum in the U.S., with some scholars advocating for the tailoring of educational interventions to students' genetic makeup (precision education). Public perspectives on testing for and using behavioral genetic data in schools can affect policies but are unknown. We explored public views in the U.S. (n = 419) on key issues in precision education. The introduction of a child's behavioral genetic information regarding Attention-Deficit/Hyperactivity-Disorder was associated with beliefs that such data should be considered in educational planning for the child and increased medicalization, but also a belief in treatment efficacy. Most participants expressed interest in learning about children's behavioral genetic predispositions but would disapprove of testing without parental consent. Differences by participants' race, ethnicity and educational attainment were observed. Our findings indicate the public's complex understanding of genetic information and the challenges for wide implementation of precision education in the U.S

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Syst Rev. 2021 Feb;10:46.

PRIMARY CARE DURING THE TRANSITION TO ADULT CARE FOR ADOLESCENTS INVOLVED WITH PEDIATRIC SPECIALTY SERVICES: A SCOPING REVIEW PROTOCOL.

Schraeder K, Allemang B, Scott C, et al.

BACKGROUND: Of the 15-20% of youth in North America affected by a chronic health condition (e.g., type 1 diabetes, cystic fibrosis) and/or mental health or neurodevelopmental disorder (e.g., depression, eating disorder, Attention Deficit-Hyperactivity Disorder), many often require lifelong specialist healthcare services. Ongoing primary care during childhood and into young adulthood is recommended by best practice

guidelines. To date, it is largely unknown if, how, and when primary care physicians (PCPs; such as family physicians) collaborate with specialists as AYAs leave pediatric-oriented services. The proposed scoping review will synthesize the available literature on the roles of PCPs for AYAs with chronic conditions leaving pediatric specialty care and identify potential benefits and challenges of maintaining PCP involvement during transition.
METHODS: Arksey and O'Malley's original scoping review framework will be utilized with guidance from Levac and colleagues and the Joanna Briggs Institute. A search of databases including MEDLINE (OVID), EMBASE, PsycINFO, and CINAHL will be conducted following the development of a strategic search strategy. Eligible studies will (i) be published in English from January 2004 onwards, (ii) focus on AYAs (ages 12-25) with a chronic condition(s) who have received specialist services during childhood, and (iii) include relevant findings about the roles of PCPs during transition to adult services. A data extraction tool will be developed and piloted on a subset of studies. Both quantitative and qualitative data will be synthesized.
DISCUSSION: Key themes about the roles of PCPs for AYAs involved with specialist services will be identified through this review. Findings will inform the development and evaluation of a primary-care based intervention to improve transition care for AYAs with chronic conditions

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COGNITIVE REFLECTIONS IN CHILDREN WITH ADHD AND PROPOSALS TO PROMOTE LOGICAL THINKING.

Melgar, Quispe-Cutipa WA, et al.

The present study shows the need to reflect on the sequences of cognitive processes of logical thinking in children with ADHD, andit also provides strategies to promote them. The research was carried out on a sample of 11 children with ADHD within the ages of 5 and 6, identified by the checklist of the DSM_IV in addition to the interview sessions with their teachers and classmates. Due to the characteristics described, the study is based on the qualitative approach of ethnographic design and documentary review. It was concluded that these children often make frequent errors in the resolution of logical operations due to lack of attention and concentration during the algorithmization of arithmetic operations. They cannot combine the implicit data of situations in problems with literal statements, and they also show a high level of dyscalculia. On the other hand, the learning of these children is manifested with the manipulation of concrete materials, documents with clear and colorful texts, activities with serial games, which allow activating their attention by means of graphics, silhouettes, guides and sequences with defined procedures for the achievement in following instructions

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EFFICACY AND ACCEPTABILITY OF PHARMACOLOGICAL, PSYCHOSOCIAL, AND BRAIN STIMULATION INTERVENTIONS IN CHILDREN AND ADOLESCENTS WITH MENTAL DISORDERS: AN UMBRELLA REVIEW.

Correll CU, Cortese S, Croatto G, et al.

Top-tier evidence on the safety/tolerability of 80 medications in children/adolescents with mental disorders has recently been reviewed in this-ájour-¡nal.-áTo guide clinical practice, such data must be combined with evidence on efficacy and acceptability. Besides medications, psychosocial-áinter-¡ventions and brain stimulation techniques are treatment options for children/adolescents with mental disorders. For this umbrella review, we-ásystematically searched network meta-analyses (NMAs) and meta-analyses (MAs) of randomized controlled trials (RCTs) evaluating 48 medications, 20 psychosocial interventions, and four brain stimulation techniques in children/adolescents with 52 different mental disorders or groups of mental disorders, reporting on 20 different efficacy/acceptability outcomes. Co-primary outcomes were disease-specific symptom reduction and all-cause discontinuation (acceptability). We included 14 NMAs and 90 MAs, reporting on 15 mental disorders or groups of mental disorders. Overall, 21 medications outperformed placebo regarding the co-primary outcomes, and three psychosocial interventions did so (while seven outperformed waiting list/no treatment). Based on the meta-analytic evidence, the most convincing efficacy profile emerged for amphetamines, methylphenidate and, to a smaller extent, behavioral therapy in attention-deficit/hyperactivity disorder; aripiprazole, risperidone and several psychosocial interventions in autism; risperidone and behavioral interventions in disruptive behavior disorders; several antipsychotics in

schizophrenia spectrum disorders; fluoxetine, the combination of fluoxetine and cognitive behavioral therapy (CBT), and interpersonal therapy in depression; aripiprazole in mania; fluoxetine and group CBT in anxiety disorders; fluoxetine/selective serotonin reuptake inhibitors, CBT, and behavioral therapy with exposure and response prevention in obsessive-compulsive disorder; CBT in post-traumatic stress disorder; imipramine and alarm behavioral intervention in enuresis; behavioral therapy in encopresis; and family therapy in anorexia nervosa. Results from this umbrella review of interventions for mental disorders in children/adolescents provide evidence-based information for clinical decision making

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Article

Neuropsychological Profile, Emotional/Behavioral Problems, and Parental Stress in Children with Neurodevelopmental Disorders

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Abstract: Background: The aim of our study was to trace a specific neuropsychological profile, to investigate emotional-behavioral problems and parental stress in children with Autism Spectrum Disorder Level 1/High functioning (ASD-HF), Specific Learning Disorders (SLD) and Attention Deficit/Hyperactivity Disorder (ADHD) disorders and to highlight similarities and differences among the three groups. Methods: We retrospectively collected the data from a total of 62 subjects with ASD-HF (n = 19) ADHD (n = 21), SLD (n = 22) and 20 typical development. All the participants underwent neuropsychological standardized test for the evaluation of cognitive profile (Wechsler Intelligence Scale for Children Fourth Edition—WISC-IV), behavioral and emotional problems (Child Behavior CheckList CBCL), and parental stress (Parental Stress Index Short Form—PSI-SF). The scores of the ASD-HF, ADHD, and SLD groups were compared using non-parametric statistic methods (Kruskall–Wallis H test and U Mann–Whitney for post-hoc analysis). Results: The ASD-HF group were significantly higher in all areas of the WISC-IV than the other two clinical groups. The SLD group performed significantly lower than ASD-HF in Working Memory Index. The SLD group showed lower scores on the somatic problems subscale than the other two groups. In the Difficult Child subscale of the PSI-SF, parents of ADHD children scored lower than the mothers of SLD subjects and higher than the fathers of SLD subjects. In all three groups there are specific deficiencies compared to the control group in the cognitive profile, behavioral and emotional problems, and parental stress. Conclusions: Our comparative analysis highlighted similarities and differences in three groups of children with different neurodevelopmental disorders, helping to better define cognitive, behavioral, and emotional characteristics of these children and parental stress of their parents.

Keywords: Autism Spectrum Disorder; Specific Learning Disorder; Attention Deficit/Hyperactivity Disorder; cognitive profile; emotional/behavioral problems; parental stress

1. Introduction

Neurodevelopmental disorders are clinical conditions that share early abnormalities in neurobiological development, and determine an impairment of personal, social, school or work functioning. Neurodevelopmental disorders may share not only an etiopathogenetic

matrix [1] but also some clinical and neuropsychological characteristics [2]. Among the neurodevelopmental disorders, according to Diagnostic and Statistical Manual of Mental Disorders—Five edition (DSM-5) [1], there are Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD) and Specific Learning Disorders (SLD). Autism Spectrum Disorders characterized by impaired communication and socio-relational skills and restricted, repetitive, and stereotyped behaviors and interests [1]. The symptoms must be present in the early period of development and are not better explained by the intellectual disability. DSM-5 eliminated subtype characterization of ASD and introduced the term "spectrum" to emphasize the heterogeneity of the clinical features of this condition [1]. The severity of the disorder can range from very mild to severe and is divided into three levels, from 1 to 3. According to DSM-5 [1], individuals with ASD level 1, previously also called "high functioning" (ASD-HF), have intelligence and language within the limits of the norm. Several studies examined the neuropsychological profile of children with ASD-HF, showing deficit in the pragmatic aspects of language (e.g., monotonous prosody, inadequate volume, difficulty in respecting conversational shifts, limited mimicry and gestures, difficulty in understanding the double meanings and the latent meaning of the conversation). Furthermore, children with ASD-HF usually present behavior aimed at socialization, although not always functional and adequate [3]. Another neurodevelopmental disorder is Attention Deficit/Hyperactivity Disorder (ADHD), characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity and [1] the worldwide prevalence in childhood population studies is about 5% [4]. To diagnose ADHD, symptoms must be present in two different contexts, develop before age 12, and have a negative impact on psychosocial functioning [1]. DSM-5 includes in neurodevelopmental disorders the Specific Learning Disorders (SLD), in which individuals have an impairment of reading, writing, and calculating skills, despite a normal intelligence. Deficient academic skills are far below the expected level for the individual's age and involve interference with academic performance and/or daily living activities. Difficulties are not best explained by intellectual disability, impaired vision or hearing, lack of knowledge of the language of school instruction or inadequate education [1].

One of the most frequently used tests to assess intelligence in school-aged individuals is the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV).

Some studies showed that subjects with ASD-HF score higher on some index WISC-IV while had lower in other index [3,5]. Globally, the perceptual reasoning index (PRI) is highest in ASD-HF and the working memory index (WMI) is the lowest in children with typical development [3]. According to recent studies [6,7] subjects with ADHD, have the average full-scale intelligent quotient score lower than the typically developing children and tend to perform worse on the working memory index (WMI) and on the processing speed index (PSI) than the verbal comprehension index (VCI) and the perceptual reasoning index (PRI). Many studies have demonstrated the usefulness of the WISC-IV scale [8] to evaluate the cognitive profile of subjects diagnosed with SLD [8,9]. Some authors reported that cognitive functioning of SLD subjects is different than subject with typical development [9–11]. The results of the Poletti study [9] showed that in these subjects the General Ability Index (GAI) usually has a higher score than the Cognitive Proficiency Index (CPI).

In literature there are few studies that compared cognitive profile of children with ASD-HF, SLD and ADHD, for example, there is a study by Craig et al. (2016) [12] in which these three categories of subjects are compared, although the cognitive level was assessed using the WISC-III. A research by Kim and Song [2] compared the ASD-HF and the ADHD subjects with Total Intelligence Quotient (TIQ) > 70, founding that Verbal Comprehension ability was significantly lower in the ASD-HF group. The ASD-HF group displayed slower processing speed, while the ADHD group exhibited poor working memory and graphomotor skills. Few studies compared cognitive profile in children with SLD and ADHD; for example, in a study by Faedda and collegues [13], the ADHD group showed lower TIQ than the SLD group, although the scores of both groups were within the mean range. Furthermore, Children with ADHD often show externalizing problems and 30–50%

of individuals ADHD fulfill the criteria for Conduct Disorder (CD) or Oppositional Defiant Disorder (ODD) [14]. Biederman et al. [11] suggested that children with ADHD have poor self-regulation, low frustration tolerance, impatience, easy emotional reactions, and anger. These symptoms are directly associated with higher scores on specific Child Behavior CheckList scales (CBCL). The ADHDs may also show internalization problems, such as anxiety or depression [15].

In literature [16] studies provide evidence to support the high prevalence of behavioral and emotional problems which could result in multiple psychiatric diagnoses among children with high functioning ASD-HF. Studies which used CBCL [17,18] found significantly higher scores on the scales Withdrawn/Depressed Syndrome, Social Problems, Thinking Problems and Attention Problems in children with ASD-HF than children in a mixed clinical control group. Often there is the overlap between internalizing and externalizing problems that can be mediated with emotional dysregulation and associated neurobiological bases. Subjects with learning problems can develop externalizing and internalizing problems than subject with typical development [19]. Furthermore, there are some studies that used CBCL questionnaire, in which children with reading difficulties showed attention problems [12,20] and problems related to the social sphere [20]. Another study [19] showed more internalizing behaviors and inattention among young people with poor reading skills compared with their peers with typical reading skills during the adolescence. In the literature there are very few studies that compare the externalized and internalizing problems of ASD-HF, ADHD and SLD children using the CBCL questionnaire and comparing them with each other. In a study by Craig et al. [12] was found that children with ADHD reported higher scores in both total and externalizing problems on the CBCL questionnaire than other groups of children with neurodevelopmental disorders, including ASD-HF and SLD. Compared with typically developing subjects, children with these disorders showed higher levels of externalizing, internalizing and behavioral problems mostly in social withdrawal and anxiety/depression [12].

In addition to the intellectual and behavioral profile in children with neurodevelopmental disorders, the stress level of the caregiver was also explored. Parental stress is defined as the aversive psychological reaction to the request to be a parent, typically when the request to be a parent is not associated with the perception of a parent's available resource [21]. Studies have shown that child, parent, family, and ecological characteristics reciprocally influence each other and determine parental stress [22,23]. These factors are reflected in the Abidin Parental Stress Index (PSI), designed to measure various parental stressors [24]. High levels of parenting stress can negatively impact the general well-being of the family and parents. Previous studies in the literature [12,25] showed that parents of children with ADHD, ASD-HF and SLD report higher parental stress scores than TD children. Potential patient characteristics that may contribute to increased parental stress are emotional problems and cognitive dysfunction.

Since there are very few studies in the literature that have systematically analyzed subjects ADHD, ASD-HF and SLD, the purpose of our study was to trace the neuropsychological profiles of these subjects, evaluate their cognitive, emotional-behavioral functioning and parental stress and compare them with each other and with a control group.

2. Materials and Methods

2.1. Participants

Our clinical sample consisted of 62 children and adolescents diagnosed with ASD-HF (n = 19; males = 13; mean age 8.84 $\pm$ 2.36) ADHD (n = 21; males = 18; mean age 9.09 $\pm$ 1.99) or SLD mixed-type (n = 22; males = 14 mean age = 9.77 $\pm$ 1.63). All the participants were consecutively recruited to the Child and Adolescents Neuropsychiatry Unit—University-Hospital of Salerno (Italy) after receiving the clinical diagnosis. The diagnoses were made independently by two neuropsychiatrist experts according to DSM-5 criteria. Specifically, ADOS-2 and ADI-R tests were used for the diagnosis of ASD; Conners' Parent Rating Scale—Revised and Conners' Teacher Rating Scale—Revised were used for the diagnosis of ADHD; MT 3 clinical tests, Battery for the Evaluation of Dyslexia and Evolutionary

Dysorthography-2 (DDE 2), Standardized assessment of calculation and problem-solving skills (ACMT), Battery for the Assessment of Writing and Spelling Proficiency—2 (BVSCO) were used for the diagnosis of SLD.

The control group (TD) consisted of 20 typical children (males = 11) with an average age of 10.88 ± 1.67. The control group was recruited among healthy subjects participating in a screening project on learning difficulties, in which ADHD, ASD and SLD were excluded.

The exclusion criteria for the study were the Total Intelligence Quotient score (TIQ), <70 and the presence of comorbidities and familiarity for neurological (cerebral palsy, epilepsy), psychiatric (anxiety, depression, and psychosis) and other relevant medical conditions. Furthermore, subjects with ADHD, ASD and SLD subjects did not have any comorbidities between them.

All participants carried out a neuropsychological assessment using standardized tests for the assessment of cognitive profile, emotional behavior, and parental stress, as in our clinical practice.

All the subjects recruited agreed to participate in our study. The parents of all the participants provided their written informed consent after receiving a full description about the purpose and the protocol of the study. The study design was approved by the Campania Sud Ethics Committee and it was conducted according to the rules of good clinical practice, in line with the Declaration of Helsinki.

2.2. Measures

The neuropsychological assessment included the administration of a direct test to the children for the evaluation of cognitive profile and of two self-administration questionnaires to the parents for the evaluation of the emotional-behavioral problems and the parental stress. Cognitive development was assessed by the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003) [26]. The WISC-IV provides, in addition to Total Intelligence Quotient score (TIQ), four different indices: Verbal Comprehension Index; Perceptual Reasoning Index; Working Memory Index; lastly Processing Speed Index. A score between 70 and 84 indicates a limit intellectual functioning, while from 85 it is in an average range. The four indices and the Full-Scale IQ are expressed as age-weighted scores, with a mean =100 and a standard deviation =15. The CBCL/6-18 is an evidence-based instrument [27] for evaluating emotional, social, and behavioral problems and functioning in children between the ages of 6 and 18 years. The questionnaire contains 113 items and there are three types of responses recorded on a Likert scale: 0 Not True, 1 Somewhat or Sometimes True, 2 Very True or Often True. The results are divided into many subscales in the form of T scores. According to CBCL normative data, a t-score $\leq$64 indicates non-clinical symptoms, a t-score between 65 and 69 indicates a borderline range, and a t-score $\geq$70 indicates clinical symptoms. For the "internalization", "externalization" and "total" problems subscales, a t-score $\leq$59 indicates non-clinical symptoms, a t-score between 60 and 64 indicates that the child is in a border range and a t-score $\geq$65 indicates high levels of maladaptive behavior. The PSI Short Form (PSI/SF) derives by Parenting Complete test of the stress index (PSI) [24] and consists of 36 items for parents of children up to 12 years. Each item requires the parent/guardian whether he agrees, on a five-point Likert scale from strongly agree to strongly disagree, with the statement they read.

In this self-report tool, there are various subscales: Parental Distress (PD), Parent-Child Dysfunctional Interaction Scale (P-CDI), Difficult Child Scale (DC) which respectively evaluate: the level of distress a caregiver is experiencing in his or her parental role, also taking into account personal factors directly related to this role; then how satisfied they are in the relationship with their own child, and lastly how difficult the child is perceived as being [28]. In the PSI/SF, a higher score suggests a higher stress level and a score above 85 indicates (at the 90th percentile) clinically significant parental stress [24]. The total stress score (TS) is obtained by adding the scores of the three subscales PD, PCD-I and DC. The test also includes a defensive response scale (DF) to check the validity of the protocol as it indicates whether the parent tends, for example, to give a better self-image or to minimize problems and perceived stress in the relationship with the child.

2.3. Statistical Analysis

First, the raw scores obtained from each subscale of CBCL, and PSI/SF have been transformed into T scores so that an individual's response can be compared to that of the population norms. In the case of WISC instead, the raw scores were converted into weighted scores. All the scores obtained from the neuropsychological tests were expressed as mean and standard deviation. For the statistical analysis, a comparison was first made between the means of the three groups (ASD-HF, ADHD, SLD) using the non-parametric statistic methods (Kruskall–Wallis H test from which significant differences emerged. To evaluate significant differences between groups, post hoc analysis was conducted using U Mann–Whitney test. P values less than or equal to 0.05 were considered statistically significant.

All data were analyzed using the Statistical Package for Social Science, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, IBM Corp: Armonk, NY, USA).

3. Results

All the results are summarized in Table 1. In this study, WISC-IV assessment showed in ASD-HF group an average TIQ = 110.16 ± 10.17; they obtained the highest performance in the PRI (118.31 ± 9.55) and the lowest in the PSI (92.05 ± 6.64). There is an average performance in the WMI (101.16 ± 12.84) and a high score in the VCI. The ADHD group obtained an average TIQ = 93.67 ± 9.43; the strength was PRI (96.1 ± 12.6), while the weakness was the PSI (91.90 ± 9.06). VCI (94.43 ± 13.71) and WMI (93.19 ± 10.36) did not different each other. The SLD group obtained an average TIQ score of 96.90 ± 7.14, average performance in the VCI (100.38 ± 10.19), PRI (102.57 ± 8.77) and PSI (95.09 ± 12.39), while a lower performance was recorded, somewhat discrepant with respect to the others, in the working memory index (88.14 ± 9.53). The comparison analysis between clinical groups and TD group, showed significant differences in all WISC-IV indices: Total TIQ ($p < 0.001$), VCI ($p < 0.001$), PRI ($p < 0.001$), WMI ($p < 0.001$), PSI ($p < 0.001$). Post-Hoc analysis revealed that: ADHD group and SLD group had significantly lower scores in TIQ compared to the control group. The VCI index is significantly lower in the ADHD group and significantly higher in the ASD-HF group than in the control group, while there is no significant difference between SLD and control group. The PRI index of the ASD-HF group was significantly higher than TD. No significant differences were detected between SLD group and ADHD group compared to control group in PRI. The WMI is significantly lower in the ADHD group ($p = 0.001$) and in the SLD group ($p < 0.001$) than in the control group. All the clinical groups performed significantly lower than the TD in the PSI. The comparison between the three clinical groups showed that the TIQ score of ASD-HF was significantly higher than SLD ($p < 0.001$) and ADHD groups ($p < 0.001$), that not significantly differed each other ($p = 0.150$). The VCI is significantly higher in ASD-HF group than both SLD ($p = 0.001$) and ADHD groups ($p < 0.001$), while there were not significantly differences between the SLD and ADHD groups ($p = 0.069$). Furthermore, the performance in the PRI is higher in the ASD-HF group than in children with SLD ($p < 0.001$) and with ADHD ($p < 0.001$), while there were no significant differences between the SLD and ADHD groups ($p = 0.133$). The ASD-HF subjects recorded a significantly higher performance in the compared to SLD subjects ($p = 0.002$) while the other comparisons did not give significant results. The comparison between clinical groups and TD group showed significant differences in all the CBCL indices. The post-hoc analysis showed the ASD-HF, ADHD, SLD groups had significantly higher scores compared to the TD group in all the CBCL scales. Regarding the comparison between the three clinical groups, significant differences emerged in three areas: socialization, mood disorders area and somatic disorders area. From the analysis of the PSI/SF scores it emerged that there are significant differences between clinical groups and TD group in all subscales except in the DR subscale of the mothers ($p = 0.78$) (Table 1). There are significant differences only in the DC subscale of mothers between the SLD and ADHD group ($p = 0.008$): the mothers of SLD show a higher score. This section may be divided by subheadings. It should provide a

concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

4. Discussion

The goal of our study was to evaluate the cognitive profiles, emotional/behavioral problems and parental stress in children and adolescents with ASD-HF, ADHD and SLD by comparing the three clinical groups with each other and with a control group.

To the best of our knowledge, there are no previous studies that parallel or compare the neuropsychological profiles of ASD-HF, ADHD and SLD, while also analyzing emotional/behavioral problems and parental stress levels in all three groups.

The results of our study contributed to delineate some neuropsychological characteristics of the three groups of neurodevelopmental disorders.

The ASD-HF group was characterized by a cognitive profile in the normal range with better performances in visual perceptual reasoning skills and in the verbal area. Children and adolescents with ASD-HF appeared to have greater difficulty in rapidly scanning visual stimuli, and in focusing attention. About the emotional-behavioral profile, these subjects experienced both internalizing and externalizing problems; in particular, they could experience problems in social relationships, mood disorders like anxiety and depression, and attention/hyperactivity problems. Both mothers and fathers of these children and adolescents reported high levels of stress in their role as a parent. In addition, there is a high perception of having a difficult child; it is possible that the parents have difficulty obtaining the cooperation of the child or to manage his behavior.

Our study also showed that the neuropsychological profile of children and adolescents with ADHD was characterized by a cognitive level within the norm; although the intellectual functioning was overall homogeneous in the various abilities, the visual-perceptive and verbal abilities were strengths and the processing speed and working memory were weaknesses, thus showing greater difficulty in executive functions in individuals with this neurodevelopmental disorder. As for the emotional aspects, in our study, ADHD children manifested both externalizing and internalizing problems, such as mood disorders, attention problems as well as anxiety and depression problems. Furthermore, parents of ADHD children had high levels of stress and mothers seemed to have more problems interacting with their children.

Finally, the SLD children in our study also showed a peculiar neuropsychological profile. Regarding the intellectual profile, children, and adolescents with SLD showed better performances in verbal and visual-perceptual skills, while the weakest point was working memory. The emotional profile of children with SLD was characterized by internalizing and externalizing problems, such as anxiety, depression, and attention problems. Parents of children with this diagnosis showed high stress levels.

From the comparative analysis of the cognitive abilities, we found that the global intelligence, represented by the Total Intelligence Quotient (TIQ), was in normal range in all three clinical groups. Furthermore, the ADHD and SLD group scored significantly lower compared to ASD-HF group and control group, without significant differences between them [3]. Analyzing more in detail the single sub-indices of the intelligence, we found that Verbal comprehension skills (VCI) were significantly higher in ASD-HF group than all other groups. In Rabiee's study [3], ASD-HFs subjects showed good Verbal skills (VCI) and Processing Speed abilities (PSI), as well as the control group; in our study, on the other hand, the ASD-HF group scored higher than the TD group in the verbal skills (VCI), but lower in the Processing Speed abilities (PSI), consistent with the results of the study by Oliveras Rentas [10]. As for Visual Perceptual Reasoning (PRI) skills, the ASD-HF group performed significantly better than the other three groups. We can therefore consider this ability the strength of ASD-HF subjects, as confirmed in the literature [3]. Conversely, the ASD-HF group obtains a lower performance in the Processing Speed skill (PSI) than the control group, resulting as the point of weakest in this group. The Working Memory Index (WMI) was significantly lower in SLD and ADHD groups [7,9,13] while Processing Speed Index

(PSI) was lower in all three clinical groups compared to controls. Furthermore, we found that all three clinical groups have a significantly different profile and a Cognitive Processing Index (WMI + PSI) lower than the General Ability Index (VCI + PRI) compared to typically developing children. These data agree with the literature [6,9,28] and highlight that children with neurodevelopmental disorders have specific deficiencies related to working memory and processing speed while typical children have a more uniform cognitive profile. These data confirmed a deficit of executive functions, such as focused attention, working memory and graphic-motor skills in all three neurodevelopmental disorders analyzed, compared with typical children [29,30]. In line with our results, the study of Zhang et al. (2020) [31] highlighted that ADHD and ASD-HF subjects performed worse in WMI than typical developing subjects. Another study [13] showed that subjects with SLD go better than subjects with ADHD in executive functions.

Regarding the emotional behavioral profile, all three groups showed externalizing (aggressive behavior, violation of rules) and internalizing (mood and anxiety disorders) problems compared to the control group. The comparison between the clinical groups, showed that the subjects with SLD had less problems in socialization, mood, and somatic disorders than the ASD-HFs and the ADHDs. The data about somatic problems is not in agreement with the data in the literature [12]; our result could be due to an early diagnosis and to an early treatment of subjects with SLD which may had allowed them to not develop somatic symptoms.

Concerning PSI/SF, the Total Stress of parents of all the three clinical groups was higher than those of the parents of typically developing children. The Parental Distress (PD) score was higher in ASD-HF and ADHD group compared to controls, revealing a higher perception of stress related to parental role in these two groups. The perception of having a Difficult Child (DC) was higher in all three groups than in the control, particularly mothers in all three clinical groups had a higher perception of having a difficult child than fathers. On the Difficult Child (DC) scale, mothers of children with SLD scored significantly higher than ADHD. One possible explanation might be that school performance is important for mothers and they lose more confidence in the child's ability to achieve good academic competence [12]. Compared to the control group, the perception of having a complicated relationship with children (P-CDI) was significantly higher in all parents despite the heterogeneity of the disorders. Our results about parental stress agree with those of m. Parents of children who received diagnosis of neurodevelopmental disorder, experience higher levels of stress than parents of typically developing children. These results lead to consider necessary a possible support intervention also for the parents of children with SLD, who generally are not taken into consideration in this aspect, and to improve the quality of family life, especially in children who also have emotional behavioral problems.

The results of our study may be useful to better understand the characteristics and specificities of the neurodevelopmental disorders considered, and to support a precise differential diagnosis. These findings can also clarify the strengths and weaknesses of the children and adolescents receiving these diagnoses. Knowing more precisely the main characteristics and differences of neurodevelopmental disorders can be of great help to clinicians working in the sector to identify and propose early and targeted treatments. For example, children with falls in specific cognitive dimensions could benefit from early treatment on those areas. Treating children with specific disorders early could prevent emotional-behavioral symptoms (such as anxiety or depression or low self-esteem) that could affect their quality of life. Finally, underlining the presence of stress in the parents of children with neurodevelopmental disorders, allows us to understand that it is important to take care of the whole family unit to allow a harmonious development of the child. There are very few studies comparing children and adolescents with ASD, ADHD and LSD, for this reason our study could bring more information on the possible presence of specific differences between these groups.

Table 1. Statistical comparison between the average scores of the different groups.

	SLD (m ± SD)	ADHD (m ± SD)	ASD-HF (m ± SD)	Control (m ± SD)	Kruskal–Wallis H Test		U Mann–Witney Post-Hoc Test					
							SLD vs. Control	ADHD vs. Control	ASD-HF vs. Control	SLD vs. ADHD	SLD vs. ASD-HF	ASD-HF vs. ADHD
WISC-IV												
TIQ	96.90 ± 7.14	93.67 ± 9.43	110.16 ± 10.17	104.60 ± 8.30	30.97	0.000 *	$p = 0.003$ *	$p = 0.000$ *	$p = 0.052$	$p = 0.150$	$p = 0.000$ *	$p = 0.000$ *
VCI	100.38 ± 10.19	94.43 ± 13.71	111.00 ± 10.27	103.15 ± 8.46	19.66	0.000 *	$p = 0.233$	$p = 0.009$ *	$p = 0.021$ *	$p = 0.069$	$p = 0.001$ *	$p = 0.000$ *
PRI	102.57 ± 8.77	96.1 ± 12.6	118.31 ± 9.55	104.35 ± 14.42	25.42	0.000 *	$p = 0.771$	$p = 0.126$	$p = 0.003$ *	$p = 0.133$	$p = 0.000$ *	$p = 0.000$ *
WMI	88.14 ± 9.53	93.19 ± 10.36	101.16 ± 12.84	103.30 ± 8.42	22.80	0.000 *	$p = 0.000$ *	$p = 0.001$ *	$p = 0.396$	$p = 0.090$	$p = 0.002$ *	$p = 0.082$
PSI	95.09 ± 12.39	91.90 ± 9.06	92.05 ± 6.64	103.00 ± 5.84	19.59	0.000 *	$p = 0.024$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.367$	$p = 0.365$	$p = 0.765$
CBCL												
Total problems	60.09 ± 10.54	63.76 ± 11.57	64.31 ± 9.52	51.50 ± 5.45	20.33	0.000 *	$p = 0.002$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.224$	$p = 0.218$	$p = 0.914$
Anxiety/Depression	62 ± 11.92	65.57 ± 9.57	65.16 ± 9.09	54.40 ± 5.67	20.72	0.000 *	$p = 0.023$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.067$	$p = 0.156$	$p = 0.694$
Withdrawn/Depressed	60.95 ± 11.79	62.14 ± 9.22	62.84 ± 10.35	51.80 ± 4.82	23.19	0.000 *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.367$	$p = 0.364$	$p = 0.838$
Somatic complaints	58.81 ± 9.08	61.76 ± 8.43	64.05 ± 10.29	54.25 ± 5.40	13.45	0.004 *	$p = 0.157$	$p = 0.002$ *	$p = 0.001$ *	$p = 0.148$	$p = 0.071$	$p = 0.586$
Social problems	60.90 ± 10.59	62.57 ± 11.69	67.05 ± 10.59	54.80 ± 4.09	15.04	0.002 *	$p = 0.073$	$p = 0.019$ *	$p = 0.000$ *	$p = 0.549$	$p = 0.032$ *	$p = 0.134$
Thought problems	54.85 ± 5.75	59.66 ± 10.12	59.58 ± 9.97	53.55 ± 4.95	11.15	0.011 *	$p = 0.274$	$p = 0.008$ *	$p = 0.004$ *	$p = 0.099$	$p = 0.060$	$p = 0.838$
Attention problems	62.95 ± 11.43	66.09 ± 14.48	66.21 ± 12.42	52.80 ± 5.54	18.02	0.000 *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.464$	$p = 0.282$	$p = 0.754$
Rule breaking behavior	56.52 ± 7.20	59.38 ± 9.12	58.74 ± 6.50	50.35 ± 3.82	6.65	0.000 *	$p = 0.003$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.321$	$p = 0.192$	$p = 0.881$
Aggressive Behavior	58.95 ± 10.68	62.81 ± 12.49	58.58 ± 9.75	50.603.95	17.18	0.001 *	$p = 0.002$ *	$p = 0.000$ *	$p = 0.003$ *	$p = 0.283$	$p = 0.000$	$p = 0.293$
Affective problems	61.0 ± 8.47	67.14 ± 11.49	66.79 ± 9.41	53.75 ± 4.77	25.54	0.000 *	$p = 0.003$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.110$	$p = 0.039$ *	$p = 0.860$
Anxiety problems	62.38 ± 7.46	65.14 ± 8.95	64.05 ± 7.94	54.40 ± 4.31	20.91	0.000 *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.341$	$p = 0.762$	$p = 0.634$
Somatic problems	55.09 ± 7.73	60.95 ± 6.52	60.95 ± 7.78	55.50 ± 5.53	15.79	0.001 *	$p = 0.426$	$p = 0.005$ *	$p = 0.010$ *	$p = 0.003$ *	$p = 0.006$ *	$p = 0.978$
Attention deficit/Hyperactivity Problems	60.14 ± 7.10	62.24 ± 9.34	61.58 ± 8.07	54.30 ± 3.83	10.95	0.003 *	$p = 0.001$ *	$p = 0.005$ *	$p = 0.004$ *	$p = 0.551$	$p = 0.875$	$p = 0.957$
Oppositional defiant problems	56.38 ± 5.32	59.62 ± 9.14	57.05 ± 7.29	50.80 ± 3.76	8.32	0.000 *	$p = 0.000$ *	$p = 0.001$ *	$p = 0.002$ *	$p = 0.538$	$p = 0.833$	$p = 0.428$
Conduct problems	56.95 ± 8.54	59.76 ± 9.62	58.16 ± 7.28	49.60 ± 3.76	5.46	0.000 *	$p = 0.001$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.506$	$p = 0.384$	$p = 0.774$
Internalizing	61.0 ± 10.38	67.14 ± 11.49	65.47 ± 11.54	53.35 ± 4.78	19.42	0.000 *	$p = 0.002$ *	$p = 0.000$ *	$p = 0.000$ *	$p = 0.154$	$p = 0.276$	$p = 0.946$
Externalizing	55.90 ± 9.59	60.62 ± 11.88	56.58 ± 10.01	49.00 ± 3.37	11.19	0.004 *	$p = 0.025$ *	$p = 0.001$ *	$p = 0.003$ *	$p = 0.154$	$p = 0.724$	$p = 0.296$
PSI/SF												
TS mothers	89.05 ± 7.52	85.24 ± 10.89	85.53 ± 10.12	44.75 ± 20.29	39.14	0.000 *	0.000 *	0.000 *	0.000 *	$p = 0.154$	$p = 0.283$	$p = 0.648$
PD mothers	49.28 ± 31.79	62.86 ± 25.77	59.47 ± 20.94	43.00 ± 20.86	11.15	0.011 *	0.073	0.004 *	0.006 *	$p = 0.119$	$p = 0.416$	$p = 0.384$
P-CDI mothers	64.05 ± 23.11	67.38 ± 27.46	68.16 ± 18.27	36.50 ± 25.65	14.86	0.002 *	0.002 *	0.001 *	0.006 *	$p = 0.971$	$p = 0.378$	$p = 0.550$
DC mothers	94.28 ± 7.63	91.43 ± 9.24	90.79 ± 11.09	50.00 ± 19.87	27.27	0.000 *	0.000 *	0.001 *	0.000 *	$p = 0.008$ *	$p = 0.116$	$p = 0.394$
DR mothers	54.05 ± 26.15	52.86 ± 29.18	66.84 ± 21.42	64.50 ± 20.29	6.82	0.078	0.391	0.052	0.038	$p = 0.145$	$p = 0.101$	$p = 0.653$
TS fathers	84.76 ± 9.42	88.33 ± 9.40	85.53 ± 15.26	45.25 ± 16.36	43.76	0.000 *	0.000 *	0.000 *	0.000 *	$p = 0.411$	$p = 0.268$	$p = 0.730$
PD fathers	55.09 ± 22.17	67.38 ± 27.46	62.89 ± 21.69	39.00 ± 20.43	10.40	0.015 *	0.273	0.005 *	0.002 *	$p = 0.164$	$p = 0.454$	$p = 0.282$
P-CDI fathers	66.90 ± 29.73	60.24 ± 24.92	62.37 ± 23.71	31.00 ± 21.98	21.14	0.000 *	0.000 *	0.002 *	0.000 *	$p = 0.567$	$p = 0.906$	$p = 0.586$
DC fathers	60.24 ± 24.92	76.67 ± 25.17	80.79 ± 25.94	55.75 ± 21.96	38.62	0.000 *	0.000 *	0.000 *	0.000 *	$p = 0.309$	$p = 0.439$	$p = 0.922$
DR fathers	60.24 ± 24.92	67.86 ± 26.81	71.84 ± 26.15	67.00 ± 20.86	12.55	0.006 *	0.017 *	0.249	0.000 *	$p = 0.826$	$p = 0.072$	$p = 0.225$

m = mean; SD = Standard Deviation; SLD = Specific Learning Disorders; ADHD = Attention Deficit/Hyperactivity Disorder; ASD-HF = Autism Spectrum Disorder level 1/High functioning; TIQ = Total Intelligence Quotient; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; TS = Total Stress; PD = Parental Distress; P-CDI = Parent-Child Dysfunctional Interaction; DR = Defensive Responding; DC = Difficult Child. asterisks (*) mark significant differences.

Some limitations inherent this study should be reported. The first limitation is related to the stress assessment procedure used. Although PSI and CBCL have good psychometric properties and are fundamental when assessing internalized states, they are subjective self-related measures that could lead to feasible prejudices. Our work is a cross-sectional study, in the future it will be useful to carry out prospective studies to evaluate the development trajectory. Furthermore, adaptive functioning could also be considered, and the executive functions of the three groups of patients could be assessed with specific tools. Moreover, another limitation of this study is the sample size. It will certainly be appropriate to expand the sample and carry out more complex statistical analyzes.

5. Conclusions

Our study highlighted that the three neurodevelopmental disorders considered (Autism Spectrum Disorder level 1 ASD-HF, Attention Deficit/Hyperactivity Disorder—ADHD and Specific Learning Disorder—SLD) had a peculiar neuropsychological cognitive profile that distinguishes itself from the others and characterizes them in their functioning. The global intelligence was within the normal range in all the three groups, although ASD-HF scored higher than ADHD and SLD. The SLD subjects have weaknesses in working memory and in the processing speed skills. The ASD-HF had a strength in logical reasoning and a weakness in the processing speed (hand-eye coordination). ADHD subjects had a weakness in the verbal comprehension, working memory and processing speed abilities. Despite the heterogeneity of three the clinical conditions, the emotional-behavioral problems were very present in all groups compared to the controls, with greater problems of socialization, mood, and somatic problems in the ASD-HF. Compared to total stress, all the parents of ASD-HF, ADHD and SLD showed higher levels of stress than parents of typically developing children, despite the different clinical condition.

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An Exploratory Study of Emotional Dysregulation Dimensions in Youth With Attention Deficit Hyperactivity Disorder and/or Bipolar Spectrum Disorders

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Emotional dysregulation (ED) is currently the most frequently used term to describe children with an impaired regulation of emotional states. Recent research studies speculate whether ED may be a neurodevelopmental disorder itself, a shared risk factor, or a common key feature of several psychiatric disorders, including, among others, attention deficit hyperactivity disorder (ADHD), and bipolar spectrum disorders (BSD). The association between ADHD and ED is one of the main reasons of misconceptions in the definition of boundaries between ADHD and BSD, leading to the frequent misdiagnosis of ADHD as BSD. Since ED is a multidimensional concept, a novel instrument—the Reactivity, Intensity, Polarity and Stability (RIPoSt) scale—was recently developed to assess the different dimensions of ED, which could help in detecting specific ED profiles in clinical youths. Our study included 154 patients, aged 13.8 ± 2.3 years, diagnosed with either ADHD, BSD, or comorbid condition, and a school-based sample of 40 healthy control (HC) adolescents, aged 12.5 ± 1.2 years. The RIPoSt scale and the Child Behavior Checklist were administered to both groups. Our results indicate that affective instability and negative emotionality subscales, as well as negative emotional dysregulation, are higher in BSD, both pure and comorbid with ADHD, while emotional impulsivity is higher in the comorbid condition and similar in the ADHD and BSD alone group; all clinical groups scored higher than HC. Conversely, positive emotionality is similar among clinical groups and within them and HC. Our findings also support the validity of the RIPoSt questionnaire, since the instrument proved to have good-to-excellent internal consistency, and strongly significant positive correlations were found with the CBCL-Dysregulation Profile, which is a commonly used, indirect measure of

ED. Hence, the five subscales of the RIPoSt can be reliably used as an effective tool to study the emotional dysregulation in different clinical conditions, to help disentangle the complex relationship between ADHD and juvenile BSD and to provide clinicians with crucial evidence for better diagnostic characterization and therapeutic indications.

Keywords: emotional dysregulation, ADHD, bipolar disorder, children, adolescents

INTRODUCTION

Children with an impaired regulation of emotional states, including mood lability and instability, severe irritability, low tolerance to frustration, temper outburst, and hyperarousal, have become a diagnostic challenge in the last two decades (1, 2). The core features of emotional impairment, with possible different combinations, are low threshold, excessive intensity, inappropriate expression, and slow normalization (1). This clinical picture does not completely fit any of the current nosological categories, including attention deficit hyperactivity disorder (ADHD), mood disorders (MD) such as bipolar spectrum disorders (BSD) or disruptive mood dysregulation disorder, and impulse control disorders such as oppositional defiant disorder (ODD)/conduct disorder (CD), although they may share features of all these domains. Different definitions of this condition have been proposed (3), but the term emotional dysregulation (ED) is currently the most frequently used.

More recent advances tend to interpret ED as a neurodevelopmental, early-onset disorder of the regulation of emotions, often associated to other psychiatric disorders, strongly related with comorbidity between internalizing and externalizing disorders, suggesting that it could be a shared risk factor for both kinds of disorder (4), or a common key factor in the development of later psychopathology (5–8).

Most if not all descriptions in children are focused on the association with ADHD (1, 9). At least 40% of subjects with ADHD present an associated ED (9–14), particularly in the combined presentation (15, 16), with strong continuity in adults with ADHD (17–19). Symptoms of ED significantly and negatively impact quality of life (11), social functioning (20), acceptability by peers (21), need for interventions (11), and higher rates of persistence of irritability and impulsivity up to adulthood (10). Moreover, ED has been shown to predict risky behaviors in adolescents with ADHD, such as, for instance, substance use and abuse, especially amphetamine and cannabinoids, other addictive behaviors, self-harm, and suicidality (22, 23). Finally, ED is a negative predictor of short-term response to methylphenidate monotherapy in drug-naïve youth with ADHD, especially of changes in hyperactive–impulsive symptoms, and thus should be systematically assessed in ADHD at baseline (24).

The association between ADHD and ED is one of the main reasons of misconceptions in the definition of boundaries between ADHD and BSD, leading to the frequent misdiagnosis of ADHD as BSD, or to an overinflated rate of comorbidity between ADHD and BSD. The issue of the boundaries between ADHD and BSD is still difficult to solve, given the partial overlap of symptoms, namely when ED is a prominent feature. Whether ED is an associated feature or a specifier of ADHD—which defines a specific subtype of the disorder—or even a core feature of the disorder—additional to hyperactivity/impulsivity and inattention—or, finally, a comorbidity, is still a matter of discussion (9). Recent advances in ED research revealed that it can also be a specific feature of youths with BSD (25), and unaffected relatives of BSD youth can still present subthreshold deficits in emotion regulation and processing (26).

One of the most troublesome issues in the assessment of dysregulated children is the availability of cost-effective and reliable diagnostic measures. To date, the Child Behavior Checklist (CBCL), one of the most used instruments for the assessment of developmental psychopathology (27), has been considered a possible diagnostic tool for identifying children with these features. The CBCL-Dysregulation Profile (CBCL-DP) is an indirect index of ED, characterized by simultaneously high values [above two standard deviations (SD)] in three syndrome scales (anxious/depressed, attention problems, and aggressive behavior). Interestingly, this index was initially thought to be more closely related to the pediatric BSD, and thus, it was named CBCL-Pediatric Bipolar Disorder profile (CBCL-PBD) (28). Further research has questioned this relationship (5, 29–31), supporting the notion that it may be of a measure of a wider dysregulation profile (DP), rather than a proxy for a single disorder (32). Consequently, longitudinal studies have highlighted that higher CBCL-DP scores in at-risk subjects predict the risk for substance use, suicidality, and poorer overall functioning (5). Similarly, higher scores of DP in ODD patients predict a greater risk for ADHD and mood disorder in adolescence (33), while higher scores in ADHD patients predict impaired psychosocial functioning, psychiatric hospitalizations, and subsequent diagnoses of CD and BSD at the follow-up (34). In other words, research clearly suggests that ED, as indirectly assessed with an empirically derived measure (CBCL-DP), has high clinical relevance in different kinds of samples.

Although ED is a multidimensional concept, including emotional reactivity and impulsivity, affective intensity and polarity—both positive or elated and negative or irritable—and behavioral self-control, CBCL does not allow clinicians to disentangle these different components, which may be different in different subjects. Assessing all these components may need different measures, which are currently unavailable in youth (35, 36). However, a recently developed instrument to assess these different dimensions is the Reactivity, Intensity, Polarity, and Stability (RIPoSt) scale (37).

Starting from 60 items concerning reactivity, intensity, polarity of emotional responses, and affective stability, a first

validation in both clinical and non-clinical adult subjects led to a 40-item version with four scales (38). The four scales are the following: affective instability (AI), with 12 items exploring the presence of a cyclic pattern of sudden mood shifts between positive and negative polarity; emotional impulsivity (EI), with 8 items on the over-reactivity to negative or frustrating stimuli and the inability to inhibit impulsive behavioral responses; negative emotionality (NE), with 10 items evaluating the propensity for experiencing more often and more easily strong negative feelings, such as sadness, worry, anxiety and dissatisfaction; and positive emotionality (PE), with 10 items exploring the tendency to experience more often and more easily strong positive feelings, such as euphoria, joy, enthusiasm, and exuberance. The first three subscales also sum up to a negative ED (NED) scale, totally including 30 items. Measures of reliability (test–retest $r = 0.71$–0.84) and internal consistency (Cronbach's $\alpha = 0.72$–0.95) were high, and concurrent validity was also supported by correlations with the brief TEMPS-M subscales (39). Discriminant validity was finally significant ($p < 0.001$) since cyclothymic and ADHD patients exhibited higher scores than non-clinical controls for each subscale, except for PE.

In the present exploratory study, we employed, for the first time, the 40-item version of the RIPoSt questionnaire in a clinical and non-clinical sample of youths, providing initial psychometric assessment and thoroughly examining ED profiles in a sample of ADHD and/or BSD patients, in order to detect possible specificities. Our main hypotheses are that emotional regulation is more impaired in the comorbid condition (ADHD + BSD) than in ADHD or BSD alone patients and that all clinical groups score higher than a control group of healthy adolescents in all subscales of the questionnaire. We lack specific *a priori* hypotheses on each single dimension of the construct, since no previous clinical study applied the RIPoSt questionnaire in youths. Nonetheless, according to the theoretical model proposed by Banaschewski et al. (40) and Petrovic and Castellanos (41), we may only hypothesize a selective increase in EI scores in ADHD patients, both pure and comorbid with BSD, unless this specific subscale reflects the high sensitivity to emotionally salient stimuli with reduced self-control and behavioral inhibition described by the model.

MATERIALS AND METHODS

Recruitment and Diagnostic Procedures

Our study included 154 participants (104 males and 50 females, age range 9–18 years, mean age 13.8 ± 2.3 years) recruited in our third-level Department of Child and Adolescent Psychiatry and Psychopharmacology from 2017 to 2020 (clinical group; CG). Inclusion criteria were diagnoses of ADHD, BSD, or both, made according to the Diagnostic and Statistical Manual of Mental Disorders—fifth edition (DSM-5) (42), based on medical history, clinical observations, and a semistructured interview, the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime version (K-SADS-PL) (43), administered by trained child psychiatrists to both patients and parents.

Exclusion criteria for the CG were as follows: older than 18 years old or younger than 9 years old; presence of comorbid intellectual disability, as detected through formal psychometric assessment (either the Full-Scale Intelligence Quotient or the General Ability Index below 85 at the WISC-IV); and presence of comorbid autism spectrum disorders, schizophrenia spectrum, and other psychotic disorders.

Three clinical subgroups were identified in the CG: the ADHD group (namely, without comorbid BSD), consisting of 72 subjects (62 males and 10 females, mean age 12.9 ± 2.2 years); the BSD group (namely, without comorbid ADHD), consisting of 53 subjects (18 males and 35 females, mean age 14.9 ± 1.8 years); and the comorbid ADHD + BSD group, consisting of 29 subjects (24 boys and 5 females, mean age 13.8 ± 2.4 years).

A school sample of 40 healthy control adolescents (HC group) (8 boys and 32 females, age range 9–18 years old, mean age 12.5 ± 1.2 years) was recruited on a voluntary basis upon engagement of a nearby junior high school in Pisa. Exclusion criteria for the HC group were as follows: older than 18 years old or younger than 9 years old, presence of intellectual disability, and presence of any psychiatric disorder.

All participants and parents were informed about assessment instruments, and there was voluntary participation in the study after written informed consent was obtained for assessment procedures from the parents of all children. The institutional review board of our hospital approved the study.

Measures

A clinical questionnaire, the Child Behavior Checklist, was used in the both CG and HC samples to support clinical assessment and diagnostic procedures. The Child Behavior Checklist for ages 6–18 years (CBCL-6/18) (27, 44) is a 118-item scale, completed by parents or caregivers, with eight different syndromes scales, a total problem score, and two broad-band scores designated as internalizing problems and externalizing problems. In the current study, emotional dysregulation was assessed based on the CBCL-DP, using the sum of *t* scores of the following subscales, anxious/depression, attention problems, and aggressive behaviors. The reliability coefficients (Cronbach's α) were 0.82, 0.81, and 0.82, respectively.

CG and HC were also assessed by means of the Italian 40-item version of the Reactivity, Intensity, Polarity and Stability (RIPoSt-40) questionnaire (37, 38), a self-rated measure of emotional dysregulation. The RIPoSt-40 has been recently validated in an adult Italian sample of 174 cyclothymic and/or ADHD patients and 396 non-clinical subjects. The 40 items are unequally distributed across four subscales, respectively identified as measures of AI, EI, NE, and PE; the first three subscales also sum up to a NED score which includes 30 items. The instrument showed generally high test–retest reliability ($r = 0.71$–0.84) and good-to-excellent internal consistency (Cronbach's $\alpha = 0.72$–0.95). Concurrent and discriminant validity were also demonstrated to be significant. Thus, the RIPoSt-40 questionnaire proved to be a valid, reliable, and useful tool to assess emotional dysregulation, both in clinical and non-clinical contexts.

Statistics

Statistical analyses were performed by means of MATLAB® and RStudio® software. For each clinical variable with continuous distribution, outliers were defined as observations lying outside

the range between (first quartile − 2 * interquartile range) and (third quartile + 2 * interquartile range) and removed. Cronbach's alphas were computed as measures of internal consistency of each subscale of the RIPoSt-40 questionnaire. The χ^2 test was used to detect significant differences ($p < 0.05$) between the three clinical groups and the HC group in the distributions of demographic and clinical nominal categorical variables, such as gender and clinical comorbidities. When more than 20% of observations had expected frequencies <5, Fisher's exact test was performed. Analyses of covariance (ANCOVA) were conducted to assess significant differences ($p < 0.05$) between group means in the demographic and clinical variables with continuous distribution, such as subscale scores of the RIPoSt-40 questionnaire while controlling for gender as covariate. A Tukey *post hoc* test was used whenever ANCOVA led to a statistically significant result in order to identify significant comparisons between couples of groups.

Pearson's linear correlation coefficients were estimated to detect significant relationships of the RIPoSt-40 questionnaire subscales with each other and between these and the CBCL-6/18 subscales in the CG and HC group. The Bonferroni correction method for multiple comparisons was applied after assessing significant differences at a traditional significance level of 5%. Finally, linear multivariate regression models were applied to identify statistically significant associations between the RIPoSt-40 questionnaire subscales and the presence of psychiatric comorbidities, notably anxiety disorders and disruptive behavior disorders, while controlling for the principal diagnoses (ADHD and BSD) as covariates.

RESULTS

Our sample included 194 participants, of which 154 were in the CG (72 ADHD, 53 BSD, and 29 ADHD + BSD) and 40 in the HC group. Demographic and clinical characteristics of the four groups are reported in **Table 1**. As shown, gender and age were significantly different among the groups; *post hoc* comparisons are detailed in the table legend. Clinical comorbidities also significantly differed, with the BSD group exhibiting the greatest mean number of comorbid psychiatric conditions, followed by the ADHD + BSD, and then by the ADHD. Specific comorbidities, according to DSM-5, are listed in **Table 1**.

Internal consistency of the RIPoSt-40 questionnaire was initially assessed by computing Cronbach's α coefficients for each subscale. Cronbach's coefficients were generally high for most subscales (AI: $\alpha = 0.896$; EI: $\alpha = 0.870$; NE: $\alpha = 0.864$; AI: $\alpha = 0.896$), except for PE, whose internal consistency was still good (PE: $\alpha = 0.814$). An excellent reliability value was identified for the NED subscale (NED: $\alpha = 0.946$).

We then compared the RIPoSt-40 subscale scores between the three CG and the HC through ANCOVAs, while correcting for gender distributions as covariate. Age was also initially assessed through a linear multivariate model, though displaying no significant effects on any of the questionnaire subscales and not altering the effect of the other variables of the model; thus, we decided to remove it from the analyses. As shown in **Table 2** and **Figure 1**, the AI, EI, NE, and NED subscales demonstrated highly significant differences among the groups, while the analysis revealed no significant effect of diagnosis or gender on the PE subscale. *Post hoc* comparisons are detailed in the table legend. Notably, the BSD and ADHD + BSD groups scored the highest in the AI, NE, and NED subscales, without significant differences between the groups, and the ADHD group presented significantly lower scores in the three scales, but higher than the HC group. As for the EI subscale, the ADHD + BSD group scored the highest, followed by the BSD and the ADHD groups, which did not differ significantly between them, and finally the HC group, with significantly lower scores. *Post hoc* comparisons between males and females in the RIPoSt-40 questionnaire subscales revealed highly significant gender-related differences for the AI, NE, and NED subscales, with females scoring higher than males (data not shown).

As shown in **Table 3**, the AI, EI, and NE subscales were all highly significantly positively correlated in the whole sample, with coefficients *r* ranging between 0.660 for the correlation between AI and EI and 0.829 for the correlation between AI and NE. The PE subscale was also positively correlated, though less significantly, with the AI, EI, and NE subscales, with coefficients *r* between 0.184 for the correlation with NE and 0.227 for the correlation with EI. Significantly positive correlations were finally identified between the NED and other subscales of the questionnaire.

We also estimated linear correlation coefficients to detect significant relationships between the RIPoSt-40 and the

TABLE 1 | Demographic and clinical characteristics of the sample.

Total = 194	Group 1 ADHD	Group 2 BSD	Group 3 ADHD + BSD	Group 4 HC	*p*
N	72	53	29	40	–
Males, *N* (%)	62 (86.1)	18 (34.0)	24 (82.8)	8 (20)	<0.001***
Age, *M* (SD)	12.9 (2.2)	14.9 (1.8)	13.8 (2.4)	12.5 (1.2)	<0.001***
Comorbidities, *M* (SD)	0.8 (1.0)	2.7 (1.0)	1.8 (1.5)	0 (0)	<0.001***
Single AD, *N* (%)	9 (12.5)	13 (24.5)	6 (20.7)	0 (0)	<0.001***
Multiple AD, *N* (%)	7 (9.7)	20 (37.7)	7 (24.1)	0 (0)	
OCD, *N* (%)	2 (2.8)	6 (11.3)	2 (6.9)	0 (0)	0.017*
Tics, *N* (%)	5 (6.9)	1 (1.9)	3 (10.3)	0 (0)	0.134
ODD, *N* (%)	21 (29.2)	18 (34.0)	16 (55.2)	0 (0)	<0.001***
CD, *N* (%)	3 (4.2)	11 (20.8)	4 (13.8)	0 (0)	<0.001***
Eating disorders, *N* (%)	1 (1.4)	6 (11.3)	0 (0)	0 (0)	0.003**

*Post hoc comparisons: age: group 1–group 2: p < 0.001 < 0.001***; group 1–group 3: p = 0.208; group 1–group 4: p = 0.703; group 2–group 3: p = 0.061; group 2–group 4: p < 0.001 < 0.001***; group 3–group 4: p = 0.044*. Comorbidities: group 1–group 2: p < 0.001 < 0.001***; group 1–group 3: p < 0.001 < 0.001***; group 1–group 4: p < 0.001 < 0.001**; group 2–group 3: p = 0.005**; group 2–group 4: p < 0.001 < 0.001***; group 3–group 4: p < 0.001 < 0.001***. AD, anxiety disorder; ADHD, attention deficit hyperactivity disorder; BSD, bipolar spectrum disorder; CD, conduct disorder; HC, healthy controls; M, mean; N, number; OCD, obsessive–compulsive disorder; ODD, oppositional defiant disorder; SD, standard deviation. *p < 0.05; **p < 0.01; ***p < 0.001.*

TABLE 2 | RIPoSt-40 subscales: comparisons among the PAT and HC groups.

Total = 194	Group 1 ADHD	Group 2 BSD	Group 3 ADHD + BSD	Group 4 HC	*p*
N	72	49	28	38	–
RIPoSt-40 AI, *M* (SD)	30.7 (9.8)	41.4 (14.3)	37.6 (12.2)	23.4 (9.1)	<0.001***
RIPoSt-40 EI, *M* (SD)	25.3 (7.5)	28.0 (9.6)	30.5 (9.1)	16.8 (5.9)	<0.001***
RIPoSt-40 NE, *M* (SD)	27.4 (7.9)	37.6 (12.7)	32.7 (10.5)	23.8 (7.3)	<0.001***
RIPoSt-40 PE, *M* (SD)	37.8 (9.4)	36.8 (9.7)	38.8 (10.9)	39.1 (9.2)	0.702
RIPoSt-40 NED, *M* (SD)	83.4 (21.5)	107.1 (33.0)	100.8 (28.3)	64.0 (20.4)	<0.001***

*Post hoc comparisons: AI: group 1–group 2: $p < 0.001 < 0.001$***; group 1–group 3: $p = 0.027$*; group 1–group 4: $p = 0.007$**; group 2–group 3: $p = 0.464$; group 2–group 4: $p < 0.001 < 0.001$***; group 3–group 4: $p < 0.001 < 0.001$***; males < females: $p = 0.001$**. EI: group 1–group 2: $p = 0.279$; group 1–group 3: $p = 0.022$*; group 1–group 4: $p < 0.001 < 0.001$**; group 2–group 3: $p = 0.555$; group 2–group 4: $p < 0.001 < 0.001$***; group 3–group 4: $p < 0.001 < 0.001$***; males < females: $p = 0.087$. NE: group 1–group 2: $p < 0.001 < 0.001$***; group 1–group 3: $p = 0.056$; group 1–group 4: $p = 0.244$; group 2–group 3: $p = 0.119$; group 2–group 4: $p < 0.001 < 0.001$***; group 3–group 4: $p = 0.001$**; males < females: $p < 0.001 < 0.001$***. PE: group 1–group 2: $p = 0.952$; group 1–group 3: $p = 0.968$; group 1–group 4: $p = 0.903$; group 2–group 3: $p = 0.834$; group 2–group 4: $p = 0.698$; group 3–group 4: $p = 0.999$; males < females: $p = 0.409$. NED: group 1–group 2: $p < 0.001 < 0.001$***; group 1–group 3: $p = 0.011$*; group 1–group 4: $p < 0.001 < 0.001$***; group 2–group 3: $p = 0.719$; group 2–group 4: $p < 0.001 < 0.001$***; group 3–group 4: $p < 0.001 < 0.001$***; males < females: $p = 0.001$**. AI, affective instability; ADHD, attention deficit hyperactivity disorder; BSD, bipolar spectrum disorder; EI, emotional impulsivity; HC, healthy controls; M, mean; N, number; NE, negative emotionality; NED, negative emotional dysregulation; PE, positive emotionality; RIPoSt-40, 40-item Reactivity, Intensity, Polarity and Stability questionnaire; SD, standard deviation. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.*

CBCL-6/18 subscales. The AI, EI, NE, and NED subscales of the RIPoSt-40 questionnaire were highly significantly positively correlated with all syndromes and problems subscales and most DSM-oriented diagnostic category subscales, while the only significant negative relationships of the PE subscale were identified with the anxious/depressed, the withdrawn/depressed, and the affective problems subscales. Notably, the dysregulation profile index of the CBCL-6/18 was highly positively associated with the AI, EI, NE, and NED subscales, while no significant correlation was detected with the PE subscale. Correlation coefficients and statistics are detailed in **Tables 4A,B**.

Five linear multivariate regression models were finally applied to identify statistical associations between the subscales of the RIPoSt-40 questionnaire, as dependent variables, and the presence of psychiatric comorbidities [i.e., single and/or multiple anxiety disorder (AD) and ODD and/or CD], as independent variables, while controlling for the principal diagnoses (ADHD and BSD). As displayed in **Tables 5A–E**, significant positive associations were found between the AI, NE, and NED subscales and both BSD and multiple AD. Moreover, EI was significantly positively associated with both ADHD and BSD, while PE displayed no significant associations. Neither the presence of a single AD nor that of ODD/CD was significantly associated with any of the RIPoSt-40 subscales.

DISCUSSION

This is the first study aimed to explore ED in a clinical sample of children and adolescents using a specific measure, the RIPoSt questionnaire, which includes four dimensions of dysregulation, that is affective instability, emotional impulsivity, negative emotionality, positive emotionality, and the negative emotional dysregulation derived from the sum of the first three dimensions. The first aim of our study was to explore the different dimensions of ED in youth with ADHD, BSD, and the two comorbid conditions. The secondary aims of the study were to preliminarily explore the psychometric characteristics of the RIPoSt questionnaire and to compare this measure with a well-established dimensional measure of psychopathology in youth, the CBCL-6/18, and more specifically with the CBCL-Dysregulation Profile, derived from the three symptom scales of the instrument.

The boundaries between ADHD and BSD raised a controversy in the literature, given the partial overlap of symptoms, such as hyperactivity, impulsivity/aggressiveness, and distractibility, particularly when ED is associated. Indeed, when this latter is prominent, inflated rates of comorbidity between the two disorders have been reported in the literature (45). The greater awareness of ED in ADHD individuals (1, 14) has contributed to a better comprehension of the relationship between ADHD and BSD, but the lack of reliable and sensitive measures of ED significantly limited this exploration. Thus, the RIPoSt questionnaire may represent a possible new tool for exploring different dimensions of ED in ADHD, BSD, and the comorbid condition, compared with heathy controls, which helps to better understand the relationship between the two disorders and to finely disentangle the disorders, highlighting possible targets for a well-adjusted intervention.

Our findings indicate that AI and NE, as well as the combined NED scale, are mostly related to the BSD, both pure and with ADHD, and can reliably differentiate these conditions from pure ADHD. Similarly, these three dimensions are able to discriminate the dysregulated profile of ADHD youth compared with the heathy controls. A more nuanced difference was shown with emotional impulsivity, which was found to be similar in ADHD and BSD alone and higher in the comorbid condition, and notably, all clinical groups exhibited higher scores than the healthy controls.

On the other hand, PE is unable to differentiate clinical and healthy groups and seems a sort of temperamental dimension, which can be found in both patients and healthy individuals, without a significant impairing effect. Moreover, it seems more difficult to be detected, at least compared with NE, and would thus require larger sample size to achieve statistical significance (38). Also, differences among groups in PE may be more qualitative than quantitative, but even more reactive and transitory in clinical samples, and/or with different behavioral correlates. Further studies are hence needed to support the clinical utility of the PE subscale.

A comparison between these results and those reported in a parallel study, conducted on adult patients explored with the same diagnostic tool (38), is highly informative, given the strong

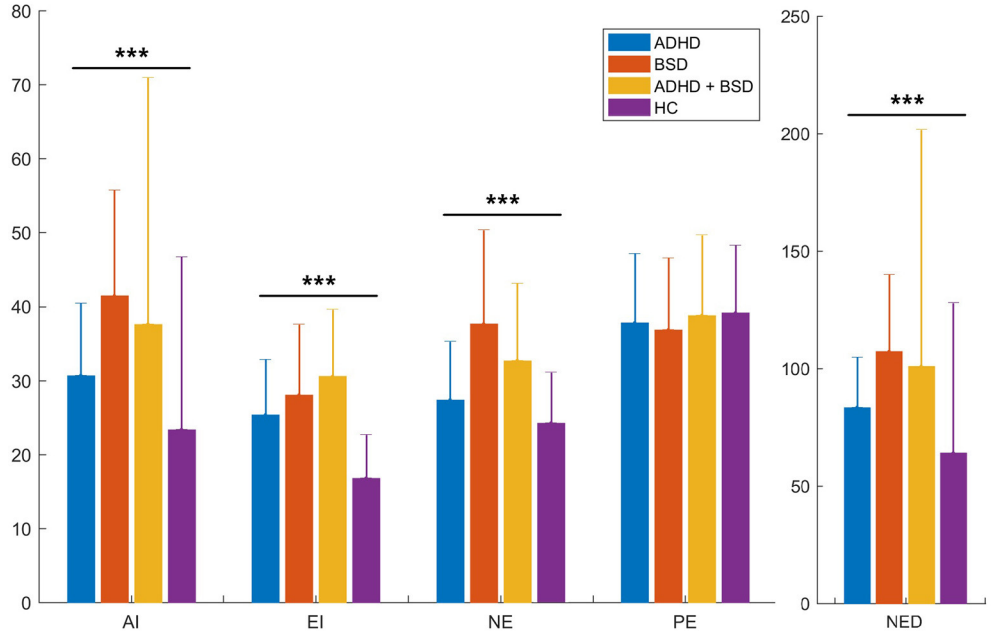

FIGURE 1 | RIPoSt-40 subscales: comparisons between clinical and non-clinical groups. Scores obtained by the four groups in our sample, namely the three clinical groups and the control group, in the five RIPoSt-40 questionnaire subscales—AI, EI, NE, PE, and NED—are here illustrated. Scores are compared between ADHD patients (blue bars), BSD patients (red bars), comorbid ADHD + BSD patients (yellow bars), and HC individuals (purple bars). Graphs represent means with standard deviation bars. ADHD, attention deficit hyperactivity disorder; AI, affective instability; BSD, bipolar spectrum disorder; EI, emotional impulsivity; HC, healthy controls; NE, negative emotionality; NED, negative emotional dysregulation; PE, positive emotionality; RIPoSt-40, Reactivity, Intensity, Polarity and Stability questionnaire. ***$p < 0.001$.

TABLE 3 | RIPoSt-40 subscale internal correlations.

	RIPoSt-40 AI	RIPoSt-40 EI	RIPoSt-40 NE	RIPoSt-40 PE	RIPoSt-40 NED
RIPoSt-40 AI	$r = 1$	$r = 0.660$	$r = 0.829$	$r = 0.184$	$r = 0.938$
	$p = 1$	$p < 0.001 < 0.001$***	$p < 0.001 < 0.001$***	$p = 0.012$*	$p < 0.001 < 0.001$***
RIPoSt-40 EI	$r = 0.660$	$r = 1$	$r = 0.667$	$r = 0.227$	$r = 0.835$
	$p < 0.001 < 0.001$***	$p = 1$	$p < 0.001 < 0.001$***	$p = 0.002$**	$p < 0.001 < 0.001$***
RIPoSt-40 NE	$r = 0.829$	$r = 0.667$	$r = 1$	$r = 0.158$	$r = 0.928$
	$p < 0.001 < 0.001$***	$p < 0.001 < 0.001$***	$p = 1$	$p = 0.031$*	$p < 0.001 < 0.001$***
RIPoSt-40 PE	$r = 0.184$	$r = 0.227$	$r = 0.158$	$r = 1$	$r = 0.207$
	$p = 0.012$*	$p = 0.002$**	$p = 0.031$*	$p = 1$	$p = 0.005$*
RIPoSt-40	$r = 0.938$	$r = 0.835$	$r = 0.928$	$r = 0.207$	$r = 1$
NED	$p < 0.001 < 0.001$***	$p < 0.001 < 0.001$***	$p < 0.001 < 0.001$***	$p = 0.005$*	$p = 1$

*AI, affective instability; EI, emotional impulsivity; NE, negative emotionality; NED, negative emotional dysregulation; PE, positive emotionality; RIPoSt-40, 40-item Reactivity Intensity Polarity Stability questionnaire. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.*

consistencies in the findings, with remarkable implications in a developmental perspective. In Brancati et al. (38), the RIPoSt questionnaire was administered to two clinical samples, namely cyclothymic and ADHD patients, along with a community-based sample of healthy controls. Consistent with our data, AI, NE, and NED lead to overlapping scores in cyclothymic and ADHD patients, and both groups scored higher than healthy controls, while PE failed to discriminate clinical patients and healthy individuals. Noteworthy, adult ADHD scored higher than both cyclothymic and healthy individuals in the EI subscale, suggesting that this dimension would be more likely related to the hyperactive–impulsive trait of ADHD rather than to the affective instability of BSD. On the contrary, in our youth, ADHD and BSD exhibited similar scores in EI, and only the comorbid condition was associated with higher scores. A possible explanation of this phenomenon may be related to the developmental divergences between juvenile and adult BSD, since among youth, impulsivity, both emotional and behavioral, is considered as a marker of earlier-onset juvenile BSD, which makes this condition more similar to

TABLE 4 | RIPoSt-40 and CBCL-6/18 subscale correlations.

	RIPoSt-40 AI	RIPoSt-40 EI	RIPoSt-40 NE	RIPoSt-40 PE	RIPoSt-40 NED
(A) Coefficients *r*					
CBCL AD	0.440	0.457	0.492	−0.171	0.502
CBCL WD	0.431	0.341	0.441	−0.240	0.445
CBCL SomP	0.382	0.249	0.427	−0.014	0.391
CBCL SocP	0.448	0.473	0.462	0.012	0.499
CBCL TP	0.381	0.439	0.386	−0.061	0.433
CBCL AP	0.322	0.430	0.279	−0.030	0.367
CBCL RBB	0.368	0.474	0.314	0.045	0.412
CBCL AB	0.331	0.482	0.322	0.042	0.402
CBCL DPI	0.428	0.530	0.426	−0.066	0.495
CBCL Int	0.463	0.480	0.495	−0.122	0.520
CBCL Ext	0.397	0.546	0.367	0.028	0.466
CBCL Tot	0.437	0.544	0.436	−0.049	0.507
CBCL Aff	0.310	0.298	0.323	−0.213	0.343
CBCL Anx	0.167	0.250	0.276	−0.180	0.250
CBCL Som	0.189	0.078	0.302	0.0172	0.219
CBCL ADHD	−0.048	0.208	−0.058	0.020	0.018
CBCL ODP	0.061	0.286	0.107	0.025	0.150
CBCL CP	0.098	0.338	0.054	0.040	0.161
(B) *p* values					
CBCL AD	<0.001***	<0.001***	<0.001***	0.045*	<0.001***
CBCL WD	<0.001***	<0.001***	<0.001***	0.004**	<0.001***
CBCL SC	<0.001***	0.003**	<0.001***	0.862	<0.001***
CBCL SP	<0.001***	<0.001***	<0.001***	0.881	<0.001***
CBCL TP	<0.001***	<0.001***	<0.001***	0.477	<0.001***
CBCL AP	<0.001***	<0.001***	<0.001***	0.726	<0.001***
CBCL RBB	<0.001***	<0.001***	<0.001***	0.600	<0.001***
CBCL AB	<0.001***	<0.001***	<0.001***	0.619	<0.001***
CBCL DPI	<0.001***	<0.001***	<0.001***	0.445	<0.001***
CBCL Int	<0.001***	<0.001***	<0.001***	0.156	<0.001***
CBCL Ext	<0.001***	<0.001***	<0.001***	0.745	<0.001***
CBCL Tot	<0.001***	<0.001***	<0.001***	0.569	<0.001***
CBCL Aff	0.001**	0.002**	0.001**	0.034*	<0.001***
CBCL Anx	0.096	0.012*	0.005**	0.074	0.012*
CBCL Som	0.061	0.441	0.002**	0.865	0.029*
CBCL ADHD	0.633	0.038*	0.566	0.840	0.858
CBCL ODP	0.547	0.004**	0.290	0.803	0.135
CBCL CP	0.331	<0.001***	0.590	0.688	0.109

*ADHD, attention deficit hyperactivity disorder; AB, aggressive behavior; AD, anxious/depressed; Aff, affective problems; AI, affective instability; Anx, anxiety problems; AT, attention problems; CBCL, Child Behavior Checklist; CP, conduct problems; DPI, dysregulation profile index; EI, emotional impulsivity; Ext, externalizing problems; Int, internalizing problems; NE, negative emotionality; NED, negative emotional dysregulation; ODP, oppositional defiant problems; PE, positive emotionality; RBB, rule-breaking behavior; RIPoSt-40, 40-item Reactivity, Intensity, Polarity and Stability questionnaire; SC, somatic complaints; Som, somatic problems; SP, social problems; Tot, total problems; TP, thought problems; WD, withdrawn/depressed. *p < 0.05; **p < 0.01; ***p < 0.001.*

ADHD (46). Conversely, adult BSD is less impulsive and more affective, while impulsivity of ADHD adult patients is much more prominent.

TABLE 5 | Linear regression models with clinical comorbidities.

	β	SE	*t* value	*p*
(A) RIPoSt-40 AI				
Intercept	26.099	1.626	16.051	<0.001***
ADHD	1.527	1.863	0.820	0.414
BSD	10.001	2.348	4.259	<0.001***
Single AD	4.147	2.653	1.563	0.120
Multiple AD	6.756	2.620	2.578	0.011*
ODD/CD	1.724	2.094	0.823	0.412
(B) RIPoSt-40 EI				
Intercept	18.105	1.134	15.969	<0.001***
ADHD	5.720	1.299	4.404	<0.001***
BSD	7.088	1.637	4.329	<0.001***
Single AD	2.265	1.850	1.224	0.223
Multiple AD	2.598	1.827	1.422	0.157
ODD/CD	0.426	1.460	0.292	0.771
(C) RIPoSt-40 NE				
Intercept	26.081	1.342	19.436	<0.001***
ADHD	−0.232	1.537	−0.151	0.880
BSD	9.137	1.938	4.714	<0.001***
Single AD	3.178	2.190	1.450	0.149
Multiple AD	5.672	2.163	2.623	0.006**
ODD/CD	−2.127	1.729	−1.231	0.220
(D) RIPoSt-40 PE				
Intercept	38.513	1.373	28.044	<0.001***
ADHD	−0.463	1.573	−0.294	0.769
BSD	−0.340	1.984	−0.172	0.864
Single AD	3.419	2.241	1.526	0.129
Multiple AD	−0.380	2.213	−0.172	0.864
ODD/CD	−0.624	1.769	−0.353	0.725
(E) RIPoSt-40 NED				
Intercept	70.285	3.629	19.369	<0.001***
ADHD	7.015	4.157	1.687	0.093
BSD	26.226	5.241	5.004	<0.001***
Single AD	9.587	5.921	1.619	0.107
Multiple AD	15.026	5.848	2.569	0.011*
ODD/CD	0.023	4.674	0.005	0.996

*ADHD, attention deficit hyperactivity disorder; AD, anxiety disorders; AI, affective instability; BSD, bipolar spectrum disorders; CD, conduct disorder; EI, emotional impulsivity; NE, negative emotionality; NED, negative emotional dysregulation; ODD, oppositional defiant disorder; PE, positive emotionality; RIPoSt-40, 40-item Reactivity, Intensity, Polarity and Stability questionnaire; SE, standard error. *p < 0.05; **p < 0.01; ***p < 0.001.*

Our findings also provide a preliminary support to the construct and concurrent validity of the 40-item version of the RIPoSt questionnaire to assess ED. Indeed, the instrument proved to have good-to-excellent internal consistency in both clinical and non-clinical samples. Cronbach's coefficients were high for all subscales and for their combination in the NED subscale, while they were lesser, though still good, for the PE subscale. Furthermore, consistent with clinical findings, the AI, NE, and NED subscales were strongly and positively correlated with each other, while PE was more feebly correlated with the other three dimensions.

Construct validity was also assessed in terms of gender-related differences. Indeed, males and females significantly differed in both clinical and non-clinical samples. As expected, girls scored higher in most ED dimensions, namely the AI, NE, and NED subscales, while EI was similar across gender. Moreover, gender differences were also detected in the relative distribution among groups, with ADHD exhibiting strong male prevalence and BSD with an even gender distribution. On the contrary, no age effect was found for any of the dimensions of dysregulation.

Correlations between RIPoSt and CBCL subscales further supported the concurrent validity of the new instrument. Indeed, the significant positive correlation between the AI, EI, NE, and NED subscales of the RIPoSt-40 and all syndromes and problems subscales and most DSM-oriented diagnostic category subscales of the CBCL-6/18, but especially their strongest and most significant correlations with the CBCL-DP, indicates that the four subscales and their combination can be used as an effective tool for studying ED in different clinical conditions. On the contrary, PE was limitedly correlated with the anxious/depressed, withdrawal/depressed, and affective problems subscales; thus, it seems to be only related with the affective dimensions of the CBCL, and notably, it did not exhibit a significant correlation with CBCL-DP.

Finally, when comorbidities were also taken into account, the AI, NE, and NED subscales presented a positive significant association with multiple anxiety disorder, which has been repeatedly found as a possible precursor of and frequently associated with BSD (47–49). Unexpectedly, disruptive behavior disorders did not show such an association, not even with the EI subscale. This result is in apparent contrast with previous findings from the available literature on the topic (22, 33) and would need further research. Indeed, disruptive behavior disorders are heterogeneous conditions, according to associated emotional features, in which ED, present in a strong minority of disruptive patients, may be specifically characterized by a deficit in emotional and behavioral self-control, with a greater risk of externalizing and aggressive behaviors (41).

This study should be considered preliminary, given some significant limitations: first of all, the lack of a formal standardization of the RIPoSt questionnaire in young people. Indeed, psychometric validation of multiple-item scales is considered to be an integral part, if not a crucial step, of data analysis in most substantive research studies (50). We largely based our study on the recent validation of the instrument in an adult sample of both clinical and non-clinical individuals (38), but future studies aimed at robustly validating and psychometrically assessing the RIPoSt in youth will be definitely required. Moreover, despite replicating common male-to-female ratio distributions in clinical samples of ADHD and BSD as ordinarily reported in literature (51) and correcting for gender whenever required in statistical comparisons, our samples significantly differed in terms of gender distribution. Future studies with more homogeneous distributions, or rather with larger proportions of the lacking sex, are warranted. Other limitations also include that we recruited modestly sized clinical samples and compared them with a school-based control group; nonetheless, we supposed this latter to be representative of the general population and applied strict exclusion criteria to prevent non-healthy controls to be recruited. Finally, we could not control for medication use and current interventions as potential confounding factors, which may affect our results, since full data were not available.

Despite these limitations, our study paved the way for future directions of research in clinical practice. Indeed, a thorough validation of the RIPoSt questionnaire along with an assessment of its psychometric properties is warranted. Our results also need to be further corroborated in larger samples. As pointed out before, the RIPoSt represents a potential clinical tool that may help in disentangling the complex relationship between ADHD and juvenile BSD for better diagnostic characterization and therapeutic indications. Future studies may further explore the longitudinal course of emotional dysregulation in these two partially overlapping disorders and assess the changes in their ED profile after psychopharmacological interventions. Moreover, the questionnaire may be used in the frame of evidence-based psychotherapeutic settings for psychopathological conditions characterized by ED to monitor the clinical course of its different dimensions and provide further evidence of effectiveness. Finally, the assessment of ED dimensions may be also useful in adolescents with conduct disorders, especially comorbid with ADHD, to further characterize the complex relationship between emotional regulation and executive functioning.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS Stella Maris Scientific Institute of Child Neurology and Psychiatry, Pisa, Italy. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GM and AMi: conceptualization. GM, AMi, GS, and SP: methodology. CP, EV, AMo, FP, SB, NL, FD, and ARM: data collection and discussion on the first draft and conclusions. GS and SP: statistical analyses. GM, GS, AMi, and SP: writing first draft. All authors have read and agreed to the published version of the manuscript.

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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Lifetime evolution of ADHD treatment

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Abstract
Attention-deficit hyperactivity disorder (ADHD), has been traditionally considered a neurodevelopmental disorder affecting children and adolescents characterized by inattention, hyperactivity, disruptive behavior, and impulsivity. Although still debated, it is evident that ADHD is also present in adulthood, but this diagnosis is rarely carried out, mainly for the frequent comorbidity with other psychiatric and/or substance abuse disorders. Given the need to shed more light on the pharmacological treatment of ADHD, we performed a naturalistic review to review and comment on the available literature of ADHD treatment across the lifespan. Indeed, stimulants are endowed of a prompt efficacy and safety, whilst non-stimulants, although requiring some weeks to be fully effective, are useful when a substance abuse history is detected. In any case, the pharmacological management of ADHD appears to be still largely influenced by the individual experience of the clinicians. Further longitudinal studies with a careful and detailed characterization of participants across different phases of the lifespan are also required to provide relevant confirmations (or denials) regarding pharmacological treatments amongst the different age groups.

Keywords ADHD · Pharmacological treatment · Lifespan management · Stimulants · Non-stimulants

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined as "a persistent pattern of inattention and/or hyperactivity and impulsivity that interferes with functioning or development" (APA 2013). Although in the past it was considered a purely childhood disease, with a prevalence rate ranging from 4 to 7% (Spencer et al. 2007; Katzman et al. 2017), it is now evident that it may persist into adulthood in about two thirds of the cases (Kessler et al. 2005; Wender et al. 2001; Caye et al. 2016; Agnew-Blais et al. 2016). Given the mounting awareness regarding this disorder and the improved diagnostic tools, currently there is an increasing rate of ADHD diagnosis amongst both children and adults (Polanczyk et al. 2014). The Diagnostic and Statistic Manual of Mental Disorder (DSM-5, American Psychiatric Association, 2013) recognizes three different ADHD subtypes: a predominantly hyperactive-impulsive type (ADHD-PH), a predominantly inattentive type (ADHD-PI) and a combined type (ADHD-C) for those showing both hyperactive/impulsive and inattentive symptoms. It is noteworthy that no agreement does exist on the prevalence of these subtypes that results quite heterogeneous in the available studies. Generally, ADHD girls show a higher rate of ADHD-PI than ADHD-C (Carlson et al. 1997; Biederman et al. 2002). On the contrary, ADHD-PH and ADHD-C, frequently associated with conduct problems, are the most prevalent subtypes amongst boys (Milich 2001), while ADHD-PI is less common and often comorbid with learning disabilities, or anxiety and mood disorders (Gaub and Carlson 1997a, b).

Furthermore, clinical symptomatology and comorbidity tend to differ accordingly to the age. Adults are more likely

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to be emotionally disregulated (Retz et al. 2012), to show a higher distractability, working memory deficit and poorer sustained attention, reduced focusing (Goodman 2007a, b; Bálint et al. 2009), and a consequent greater impairment in completing specific tasks (APA 2013). On the other hand, children more often present motor symptoms than adults (like excessive talking, squirming or fidgeting) (Klassen et al. 2010; Bond et al. 2012), in parallel with the observed decrease of hyperactivity and impulsivity with aging, while inattentive symptoms remain relatively constant (Biederman et al. 2000; Weyandt et al. 2003; Larsson et al. 2011; Asherson et al 2014). Finally, functioning in social, educational or occupational field is significantly more impaired in ADHD patients, compared with their peers (Asherson et al 2014), together with the presence of risky or criminal behaviors, and substance abuse disorders (SUDs) (Katzman et al. 2017).

In addition, while the so-called "sluggish cognitive tempo" syndrome (SCT) was previously considered to affect only a subset of ADHD-PI patients, recent studies would indicate that it is also present in the other ADHD subtypes and even in patients without ADHD. Symptoms of SCT are hypoactivity, general slowness and slow working speed, dreaminess, mental fogginess and inconsistent alertness (Becker et al. 2014; Flannery et al. 2017). It is still debated whether SCT could be or not a distinct mental disorder. It is interesting to underline that SCT could add a further complication in assessing ADHD diagnosis, so that several specialists also suggested to consider it as a fourth different subtype (Flannery et al. 2016, 2017; Becker et al. 2014, 2018).

While reflecting on ADHD treatment, current guidelines are almost focused on children and adolescent where they are mostly accepted worldwide (Mucci et al. 2019). On the contrary, given the ongoing debate on the nosological autonomy or even existence of ADHD in adulthood, its treatment in this age group is still empirical, quite different from one country to another and often off-label (Mucci et al. 2019).

Given the substantial lack of general consensus on the management of this condition (especially in adulthood) and heterogeneous psychopharmacological approach in different countries, the present paper aimed at reviewing and commenting on the available literature of ADHD treatment across the lifespan.

Methods

We performed a narrative review by searching the databases of PubMed, Scopus, Embase, PsycINFO and Google Scholar to collect English language papers published between January 1st, 1980 and July 31st, 2020. Free text terms and MeSH headings were combined as it follows: "(ADHD OR ADD OR Attention-Deficit Hyperactivity Disorder) AND (Treatment OR Stimulants OR Non-Stimulants OR Metylphenidate OR Lisdexamfetamine OR Amphetamines OR Atomoxetine OR Bupropion OR Guanfacine OR Clonidine OR Novel treatments OR Lifetime OR Adulthood). All the authors agreed to include in the review conference abstracts, posters and case reports if published in indexed journals. We adopted the following inclusion criteria: studies carried out in clinical sample of adults and children/adolescents; reliable diagnosis of psychiatric disorders according to structured interviews and standardized criteria; reliable assessment of outcome measures. All the authors equally contributed in identifying potential information specific to this topic amongst the titles and abstracts of the publications.

Results

The first selection excluded 11,732 titles because: (a) duplicates; (b) not concerning the scope of the paper; c) not informative enough. The second selection excluded 433 abstracts after being read and reviewed, as the information reported did not fulfill the scope of our paper and/or the presented information did not seem relevant to the discussed topic. Subsequently, 118 publications were excluded after being completely read and evaluated, as they did not provide enough information and/or resulted sufficiently in line with our review. Finally, 150 papers were included in the present review (Fig. 1).

Metylphenidate

Metylphenidate (MPH), synthesized in 1944, belongs to the phenethylamine and piperidine classes. It is considered a presynaptic reuptake inhibitor of dopamine (DA) and norepinephrine (NE), although it blocks the NE transporter (NET) less effectively than the DA transporter (DAT), with the inhibition constant [Ki] of 160–341 for DAT and 40–238 nM for NET (Markowitz et al. 2003, 2006, 2009; Panizzon 1944; Williard et al. 2007; Dell'Osso et al. 2014). Its action results in a strongly increase in DA and NE in the synaptic cleft, particularly in the dorsolateral prefrontal cortex and striatum (Volkow et al. 2002; Heal et al. 2006; Iversen 2006; Hodgkins et al. 2012). Metylphenidate is a racemic mixture, but the affinity of dexmethylphenidate for the NET is significantly higher than the levorotaroty counterpart (Markowitz et al. 2009). A significant receptor affinity for the serotonin (5-HT) receptors of type 1A (5-HT_{1A}) and 2B (5-HT_{2B}) was reported for both enantiomers, with no blockade of the 5-HT transporter (SERT) (Chan et al. 1983; Markowitz et al. 2006, 2009; Lehmann et al. 2016).

After its oral intake (Chan et al. 1983), DA and NE rapidly increase in the central nervous system (CNS), while

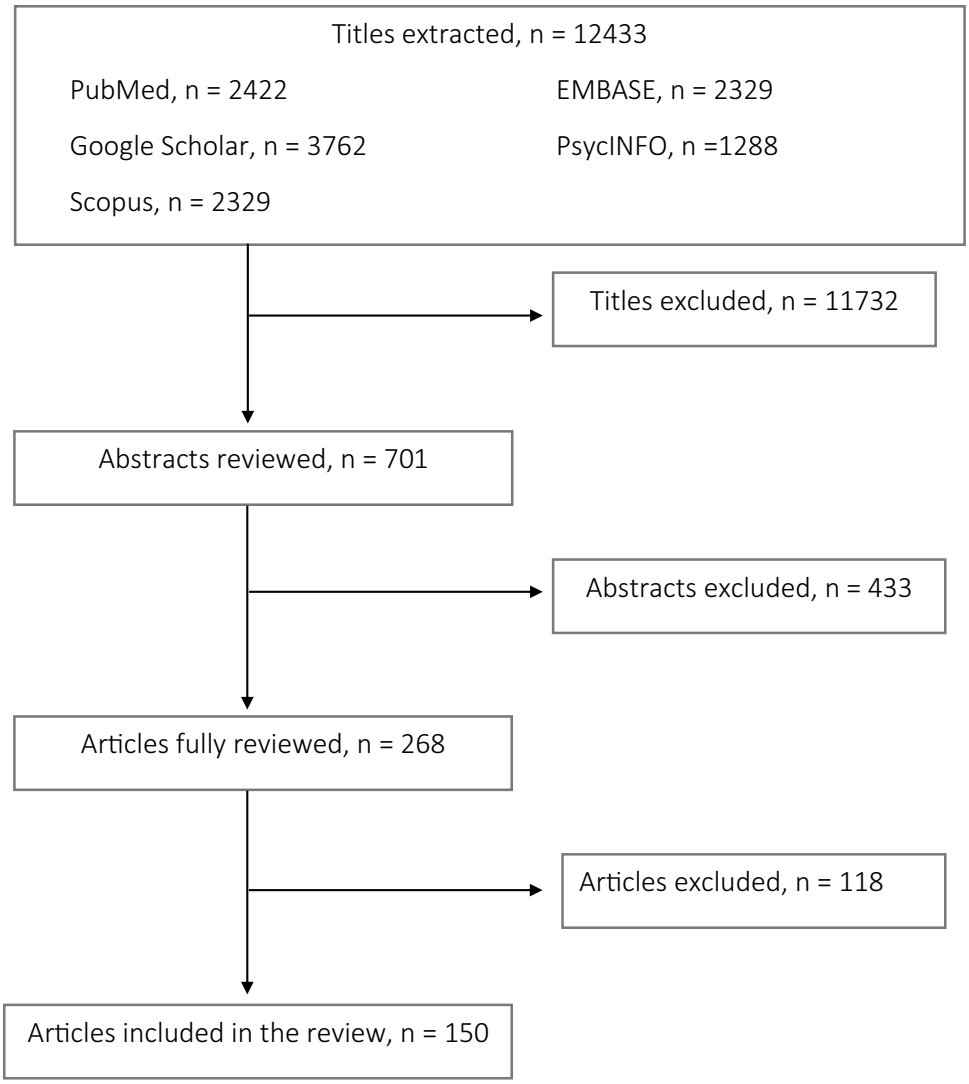

Fig. 1 Article selection flow chart

developing their effects on different brain areas (Volkow et al. 2002; Hodgkins et al. 2012). It is generally believed that planning, problem solving, inhibiting behaviors and other executive functions result from an improved activity of the dorsolateral prefrontal cortex; depressive symptomatology, fatigue and hypoactivity derive from a strengthened activity of the medial prefrontal cortex and hypothalamus; improvement of hyperactivity is possibly due to the DA and NE activity in the striatum (Volkow et al. 2002; Iversen et al. 2006; Berridge et al. 2006; Stahl et al. 2017; Hodgkins et al. 2012).

Although there is no doubt in considering MPH a first-line treatment in children, its approval in adults is more controversial. While FDA in the US approved of this medication in adults, in Europe its prescription is differently approved depending on the country. In Italy, prescription of MPH in adults and minors depends on different regulations (Migliarese et al. 2017). In children and adolescents up to 18 years of age, MPH is considered "on-label" when psychotherapeutic and/or psychosocial interventions have proved ineffective. As for adults, MPH use is considered off-label in both "naive" patients and those who had undergone treatment before 18 years of age. However, similarly to other medical branches, it is possible to carry out off-label prescriptions for those drugs with scientific evidence of efficacy and tolerability beyond the indications approved by the regulatory agencies, in this case also to ensure adequate therapeutic continuity in subjects previously treated with MPH (Agenzia Italiana del Farmaco 2015a, b).

According to the National Institute for Health and Care Excellence (NICE) and to the Canadian ADHD Resource Alliance (CADDRA) guidelines, MPH is recommended as the first-line treatment of moderate or severe levels of impairment in adults affected from, although the latter consider only the long-acting formulation as the first-line, and the short-acting one as the third-line (CADDRA 2011). Short-acting formulation is, however, globally considered to be the best treatment, as compared with other medications,

according to a recent review and meta-analysis (Stahl 2017; Kooji et al. 2019). In both adults and children, the average daily dose of MPH is assumed to be 10–30 mg per day, albeit in some cases it is possible to titrate the dose up to 60 mg/day (CADDRA 2011).

A warning on MPH, because of its potential misuse, should be taken into account when prescribing it (NICE 2018). Although MPH is metabolized by liver carboxylesterase 1 enzyme (CES1A1), rather than liver cytochromes, caution is necessary when MPH is co-prescribed with valproate as this association might possibly elicit dyskinesia and bruxism (Bond et al. 2012; Findling et al. 2007). On the other hand, MPH is able to inhibit the metabolism of warfarin-like anticoagulants and antidepressants like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). For this reason, it is generally required a careful drug's plasma level monitoring and dose adjustment. (Bodner et al. 1995; Ishii et al. 2008; Türkoğlu 2015; Stahl 2017). Moreover, the association with monoamine oxidase inhibitors (MAOIs) is contraindicated for the possible risk of a serotonergic syndrome or a hypertensive crisis. Glaucoma is another contraindication as well as the presence of anxiety and agitation, that could also develop during treatment with MPH as side effects (Hardy et al. 2009; Huss et al 2014; Dell'Osso et al. 2014; Stahl 2017). Although extremely rare, liver toxicity could be a possible result of associating MPH with β-adrenergic agonists (Roberts et al. 1997). Regarding special populations, MPH is well tolerated in older adults (Manor et al. 2011).

In patients suffering from other significant neurodevelopmental disorders, MPH prescription needs to be carefully evaluated (Türkoğlu 2015), although some studies conclude that MPH could be safely prescribed in patients affected from both ADHD and autism spectrum disorders (ASD) (Santosh et al 2006; Muit et al. 2020).

Finally, some case-reports describe episodes of stimulant-induced mania or psychosis (Ross 2006), so that MPH should be not prescribed in patients affected by untreated severe affective disorders or psychosis. However, in absence of a clear vulnerability, or a positive family history for affective, or psychotic disorders, or treated with mood-stabilizers and/or antipsychotics, MPH is not considered to induce those adverse events (Wingo et al. 2007; Findling et al. 2007; Zeni et al. 2009; Manor et al. 2011).

Amphetamines

Amphetamines (AMPs) are sympathomimetic amines belonging to the phenethylamine class, together with this endogenous neurotransmitter. They are chemically different from catecholamines, although they share with these latter the ability to stimulate both the CNS and the peripheral nervous system (Goodman et al. 2011; Heal et al. 2013; Stahl 2017). Since AMP exists in two enantiomers forms, the levoamphetamine (l-AMP) and the dextroamphetamine (d-AMP), different pharmacological formulations are clinically available (Foye et al. 1996; Goodman et al. 2011; Heal et al. 2013). They include a racemic pharmacological formulation called mixed amphetamines salts (MAS), singular enantiomers formulations (dextroamphetamine sulfate) and lisdexamphetamine dymesilate (LDX), the dextroamphetamine pro-drug (Goodman 2007a, b). Short-acting and long-acting formulations are also available for this AMP, with different daily doses (up to 40 mg per day for the former and 60 mg for the latter) (CADDRA 2011; Kooji et al. 2019).

The AMPs stimulate the release of DA, NE and, to a lesser extent, of 5-HT in the synaptic cleft by inhibiting DAT, NET, vesicular monoamine transporter of type 2 (VMAT-2) and MAOs (Broadley 2010; Bidwell et al. 2011; Miller 2011; Faraone 2018). The AMP is considered to heighten CNS levels of other neurotransmitters, as histamine, glutamate, epinephrine, endogenous opioids, corticosteroids, adrenocorticotropic hormone, cocaine-amphetamine regulated transcript (CART) peptides, through the same pathway (Underhill et al. 2014). Similarly to MPH, AMPs are able to enhance the functioning of dorsolateral prefrontal cortex, with increased DA and NE stimulating DA receptors of type 1 (D1) and α2-adrenoceptor. As a result, cognitive functions, attention, arousal and vigilance are enhanced, together with goal-directed behaviors, even at low doses (Wood et al. 2013; Bagot et al. 2014; Spencer et al. 2015; Ilieva et al. 2015). The improved task salience is strengthened by the increased motivation due to the effect of AMP in the mesolimbic cortex, while reinforcing behaviors are increased; finally, psychomotor activation is the result of increased DA and NE in the basal ganglia (Philpot et al. 2006; Ashok et al. 2017). On the other hand, euphoria, higher libido and reduced sense of fatigue are common consequences, although more frequent in healthy controls than in ADHD individuals (Foye et al. 1996; Goodman et al. 2011; Heal et al. 2013; Castells et al. 2018; Stahl 2017).

To date, amphetamines are neither marketed nor marketable in Italy. Therefore, not considered for the treatment of the disorder neither in children nor in adults. Guidelines differ in recommending AMPs in ADHD patients. The NICE guidelines suggest to prescribe d-AMP as a second-line treatment whenever MPH, the first-line treatment, results to be not effective (NICE 2018); on the other hand, long-acting formulation of AMPs is the first-choice treatment for ADHD in adults according to the CADDRA guidelines, while short-acting formulations are recommended as the third-line treatment (CADDRA 2011). Similar contraindications to MPH are reported for AMPs: hyperthyroidism, history of cardiovascular diseases, glaucoma, anxiety and agitation (Westover et al. 2012; Hodgkins et al. 2012). The

risks of hypertensive crises or malignant hyperpyrexia are also well known when AMPs are associated with MAOIs (Feinberg 2004).

Similarly to MPH, it is worth noting that several case-reports and case-series report episodes of stimulant-induced mania or psychosis (Ross 2006). Same warnings regarding the potential misuse and addiction of AMPs should be underlined (Kessler 1996; Heal et al. 2013). However, some authors questioned the evidence of long-term efficacy of AMPs in children, adolescents and adults in a recent meta-analysis (Xavier et al. 2018). Specifically, because of the elevated rate of adverse side effects, AMPs would show a significantly higher discontinuation rate than non-stimulants in short-term studies. Furthermore, it is speculated that the efficacy of AMPs might be overestimated precisely in the light of the fact that the majority of available studies have been carried out in the short term (Xavier et al. 2018).

Atomoxetine

Atomoxetine (ATX) is a non-stimulant medication recently approved for ADHD children and adults. It is a selective NET inhibitor (Ghuman and Hutchison 2014) increasing NE levels together with a minor effect on DA concentrations in the prefrontal cortex (Sauer et al. 2005; Koda et al. 2010; Taylor et al. 2012; Ghuman and Hutchison 2014). At variance with other stimulants (MPH, AMPs), the clinical effect of ATX is usually expected within two or four weeks, with other two weeks often required to reach the full effect (Taylor et al. 2012) that, however, is possibly lower than that of other stimulants (Ghuman and Hutchison 2014). However, a recent meta-analysis highlighted the significant effectiveness of ATX in improving symptoms, such as irritability, low tolerance to common stressors and affective instability, especially in ADHD adults (Lenzi et al. 2018; Kooji et al. 2019).

According to both the CADDRA and NICE, ATX is generally considered a second-line treatment in children and adults (NICE 2018; CADDRA 2011), with therapeutic doses ranging between 18 and 100 mg per day (CADDRA 2011). In the country (Italy) of the authors of the present paper, atomoxetine is approved for the treatment of ADHD in children older than 6 years, adolescents and adults, if included in a multimodal treatment program. Similarly to MPH, in adults the presence of ADHD symptoms that were pre-existing in childhood should be confirmed and patients must have moderate functional impairment in two or more settings (e.g. social, academic and/or occupational) affecting different aspects of the individual's life (Agenzia Italiana del Farmaco 2007).

Regarding pharmacological associations, to prevent problems possibly due to increased NE levels in CNS, the co-administration of direct and indirect noradrenergic agonists, such as phenylephrine, dobutamine, pseudoephedrine or NET and MAOIs, should be carefully avoided (Sauer et al. 2005; Stahl 2017). The possible association of ATX at therapeutic doses with a QT interval prolongation, warns for its use with other QT-prolongating drugs (Sauer et al. 2005; Kasi et al. 2011; Stahl 2017).

Since ATX is metabolized by the isoform CYP2D6 of the cytochrome P450, attention should be also paid to the simultaneous intake of cytochrome inducers, such as haloperidol or dexamethasone, or inhibitors, such as bupropion or SSRIs (Todor et al. 2016; Kasi et al. 2011; Belle et al. 2002).

The contraindications of ATX are similar to those of other stimulants and include: pheochromocytoma, glaucoma, cardiac arrhythmias, cardiovascular diseases and hypertension (Stahl 2017). ATX may also provoke erectile dysfunction or decrease libido, as the most common antidepressants (Stahl 2017).

Regarding psychiatric adverse effects, monitoring of young patients taking ATX is recommended even in children with no psychiatric comorbidity, since ATX may trigger the onset of manic and mixed symptoms (Steinberg and Choinard 1985; Henderson and Hartman 2004). Although uncommon, FDA warns for the risk of possible suicide-related events (Reed et al. 2016). On the other hand, ATX carries a lower risk of abuse with respect to other stimulants, while suggesting that it could be a preferred choice in adult patients with past or current history of substance use disorder (SUD) (Michelson et al. 2003; Jasinski et al. 2008; Wilens et al. 2008).

Guanfacine

Guanfacine (GFC), a phenylacetyl guanidine derivative acting as selective agonist of central α-2 adrenergic receptors, is another non-stimulant medication indicated for the treatment of ADHD (Alamo et al. 2016). Its affinity for α-2a receptors is approximately 60 and 20 times greater than for α-2b and α-2c receptors, respectively (Mucci et al. 2019).

In the last decades of the previous century, GFC was initially used as an antihypertensive medication (Belkin and Schwartz 2015), although often off-label prescribed in migraine, nicotine dependence, sleep disorders, behavioral problems in children, Tourette's syndrome or opioid withdrawal syndrome (Rubio et al. 1998; Martinez-Raga et al. 2015). In 2010, the FDA approved GFC for ADHD treatment in both children and adolescents, with a therapeutic dose ranging from 1 to 4 mg per day (Strange 2008), but it is considered a second-line agent useful in some patients with comorbidity. GFC, that is available in immediate-release and in extended-release formulations, should be taken orally, and it is effective in monotherapy and as augmentation strategy (Agnew-Blais et al. 2016). The extended-release formulation

shows delayed bowel absorption and can be prescribed in a single daily dose (Alamo et al. 2016).

Currently, there is no regulatory agencies' approval for GFC use in adults, so that it should be prescribed in resistant cases only, after the patient's informed consent and assumption of responsibility by the clinician (Kolar et al. 2008). The GFC has been demonstrated to improve working memory and attention, as well as behavioral inhibition, through the increase of the delay in neuronal discharges in dorsolateral prefrontal cortex (Wang et al. 2007; Arnsten and Pliszka 2011; Arnsten and Jin 2012). The great ability to significantly increase cortical activities is due to the strong selectivity for postsynaptic α2-adrenoreceptors (Ramos and Arnsten 2007), with the consequent inhibition of the excitatory glutamate transmission in pyramidal cells in prefrontal cortex (Ji et al. 2008). However, GFC is not a strong enhancer of salience, as suggested in a clinical trial, but not confirmed subsequently (Taylor and Russo 2001).

Fatigue and sedation are common side effects of GFC (with a prevalence of 12–60% and 16–35%, respectively) (Strange 2008), while hypotension, bradycardia and syncope (Strange 2008; Stahl 2017), decreased libido and sexual dysfunctions (Markowitz et al. 2006) are less frequent.

Reported cases of manic symptoms or hallucinations due to GFC are rare (Horrigan and Barnhill 1999; Boreman and Arnold 2003; Kim and Chayer 2015; Elbe et al. 2016).

Clonidine

Clonidine (CLN), is another α2-adrenoreceptor agonist, ten times stronger than GFC, used for the treatment of ADHD (Stahl 2017). However, unlike GFC, CLN is not a selective α-2a agonist, as it also binds to α1-adrenergic, β-adrenergic, histamine and imidazoline receptors (Engberg and Eriksson 1991; Arnsten and Jin 2012). Similarly to GFC, some decades ago, CLN was initially used as an anti-hypertensive medication, and then in the treatment of migraine, diarrhea, general pain, menopausal flushing, restless legs syndrome, and to reduce craving in nicotine and alcohol abuse, opioid withdrawal syndrome, post-traumatic stress, borderline personality disorder and Tourette's syndrome (Strange 2008; Belkin and Schwartz 2015). The FDA approved CLN as a second-line agent medication for ADHD in children and adolescents in 2010, with therapeutic doses ranging between 0.1 and 0.4 mg per day (Strange 2008; Croxtall 2011; Stahl 2017).

Although it appears safe and well tolerated in children and adults, there is no official approval for its prescription in adults. Similarly, to other second line-compounds, therefore, its use appears only possible out of the therapeutic indication, in the presence of the patient's informed consent and clinician's responsibility (Kolar et al. 2008). CLN is helpful in reducing hyperactivity and impulsivity, with a mild effect on attention deficit. The maximum clinical potential is reached when CLN is administered in augmentation to stimulants not only in children suffering from ADHD, but also from conduct disorders, tic disorder and oppositional defiant disorder (Molina-Carballo et al. 2016). Hypotension, drowsiness and sedation are common side effects of CLN (Abela et al. 2014; Bello 2015).

Abuse of CLN is reported in the literature, mainly due to its anxiolytic and sedative effects (Seale et al. 2014). Cases of abuses of CLN together with benzodiazepines or opioids are also reported, possibly explained by the effect of CLN to enhance and prolong the benzodiazepine-induced sedation, as well as the opioid-induced euphoria (Gahr et al. 2014).

Modafinil and Armodafinil

Modafinil (MOD) is a racemic compound constituted by the two chemical enantiomers, s-MOD and r-MOD, while armodafinil (ARM) is exclusively composed by r-MOD (Stahl 2017). Despite the unconclusive data on their mechanism of action, it is accepted that MOD and ARM might inhibit the DAT and increase the levels of histamine and orexin-related neuropeptides (Ishizuka 2012). MOD and ARM are defined as atypical DA reuptake inhibitors, since their blocking of DAT is weak, and their other pharmacodynamic properties are considerably different from those of common DAT-inhibitors antidepressants (Robertson et al. 2000; Chatterjie et al. 2004; Reith et al. 2015).

They show a significantly different pharmacokinetics, since, despite the similar range of therapeutic doses (from 100 to 600 mg per day for MOD, from 50 to 400 mg per day for ARM), ARM ensures a quite four-time longer half-life than the s-MOD, with a different clinical effectiveness particularly on attention levels and arousal (Goodman et al. 2011; Loland et al. 2012; Dell'Osso et al. 2014).

The FDA approved MOD and ARM for the treatment of narcolepsy, daytime sleepiness associated with obstructive-sleep apnea syndrome (OSAS) and shift work sleep disorder (Ishizuka et al. 2012). However, MOD and ARM are both used off-label in treating ADHD, mood disorders and schizophrenia, as well as cocaine and methamphetamine addiction (Ishizuka et al. 2012; Goss et al. 2013). Other minor off-label uses include the treatment of chronic fatigue syndrome, fibromyalgia, myotonic dystrophy, spastic cerebral palsy and Parkinson's disease (Menza et al. 2000; MacDonald et al. 2002; Hurst and Lajara-Nanson 2002; Nieves and Lang 2002; Abbas et al. 2010; Ketter et al. 2015). MOD and ARM have currently no indication for the treatment of the subject with ADHD and their use therefore appears only possible out of the therapeutic indication, in the presence of the patient's informed consent and assumption of responsibility by the clinician.

According to the finding of a recent study on short-term treatment of ADHD, MOD appeared less effective and less tolerated than placebo (Cortese et al. 2018).

Bupropion

Bupropion (BPN), an aminoketone synthetized in 1969, is a strong DAT reuptake blocker, with a weak activity on NET reuptake (Paccosi et al. 2020). BPN also binds to a lesser degree to α1-adrenergic, H1-histamine and nicotine receptors, and it is a negative allosteric modulator of 5-HT_{3A} receptor. The therapeutic effect of BPN is mostly due to increasing levels of DA and NE in CNS in the prefrontal cortex (Stahl 2017).

BPN is metabolized in the liver by CYP2B6 and its metabolites are active, with their potency ranging from 20 to 50% of the BPN; however, the onset of its therapeutic effect usually occurs in the second week after the first administration (Paccosi et al. 2020). Immediate-release, sustained-release (12 h) and extended-release forms (24 h) of BPN are available, both to be orally taken (Paccosi et al. 2020).

The FDA approved BPN for the treatment of adult depression, seasonal affective disorder, and smoking cessation, and it is one of the most used antidepressants, in both monotherapy and in augmentation (Perrine et al. 2000; Fava et al. 2005).

In any case, BPN is not included for the treatment of ADHD in CADDRA and NICE guidelines (CADDRA 2011; NICE 2018), but its off-label use, especially in pediatric populations is common (Paccosi et al. 2020). Unfortunately, reported cases of worsening of suicidal ideation and suicidal behaviors in children, adolescents and young adults led to a warning for BPN, with the need of monitoring patients especially during the first period of treatment (Kriikku and Ojanperä 2016).

Desipramine

Desipramine (DIP) is a metabolite of both imipramine and lofepramine belonging to the class of TCAs (Kolar et al. 2008), with a higher activity as NET blocker than the parent compounds (Riediger et al. 2017). DIP may also block the SERT at a lesser extent and several other receptors similarly to other TCAs (Riediger et al. 2017; Stahl 2017).

DIP shows typical side effects of TCAs, such as excessive sweating, dry mouth, constipation, blurred vision, hypertension or orthostatic hypotension and prolonged QT interval (Foye et al. 1996; Goodman et al. 2011; Stahl 2017), although it is better tolerated than TCAs in terms of sedation and weight gaining (Stahl 2017).

DIP is approved for the treatment of depression (Goodman et al. 2011), but it is also used in other conditions, such as neuropathic and chronic pain and anxiety. Although different authors emphasize the role of DIP in the treatment of ADHD due to the effectiveness of TCAs in decreasing hyperactivity (Kolar et al. 2008), others questioned its role with respect to stimulants, because it does not seem to improve concentration and cognitive tasks (Spencer et al. 2004; Kolar et al. 2008).

Mood stabilizers

Only a few studies explored the use of mood stabilizers in the treatment of ADHD (Dorrego et al. 2002), while the majority of trials evaluated the effect of these drugs in ADHD patients suffering from comorbid affective disorders (Scheffer et al. 2005; Bond et al. 2012). Therefore, although the available data should be considered inconclusive, valproic acid and lithium showed, respectively, no or just a weak improvement (37%) (Dorrego et al. 2002).

Other medications

Different drugs have been proposed for the treatment of ADHD, but current data are limited and should be considered mere suggestions. Three ADs, specifically viloxazine, venlafaxine and reboxetine attracted some interest for their possible treatment in ADHD. Viloxazine, an inhibitor of NET, seems to increase vigilance and attention in adults with ADHD, similar to stimulant medications (Molina-Carballo et al 2016). Venlafaxine, an inhibitor of NET and SERT, seems to be effective in general symptoms of ADHD (Adler et al. 1995; Amiri et al. 2012). The effectiveness of reboxetine, a NET inhibitor, is controversial (Hashemian et al. 2011), although this molecule has a pharmacodynamics profile similar to that of ATX (Sauer 2005).

Further, metabolites of SSRIs were also tested in ADHD, such as a steroisomer of the desmethylsertraline, called dasotraline, a NET, SERT and DAT inhibitor (Chen and Skolnick 2007). Preliminary data on this drug seem promising for the treatment ADHD (Koblan et al. 2015).

Finally, some studies investigate droxidopa, a synthetic derivative of dihydroxyphenylalanine, currently approved for the treatment of neurogenic orthostatic hypotension. This drug seems to reach the CNS through the blood–brain barrier and to be directly converted to NE (Kaufmann et al. 2014). According to preliminary data, it could be effective as a medication for ADHD at a dose of 1800 mg per day, while provoking very few side effects (Adler and Gorny 2015).

Discussion and conclusions

Attention-deficit hyperactivity disorder is a common neurodevelopmental disorder, considered for decades affecting only children and adolescents. However, although

disagreement exists, it is generally believed that it may persist or even begin in adulthood. Pharmacological treatment of ADHD includes a variety of psychotropic drugs that demonstrated to be effective not only in improving specific symptoms, but also patient's overall functioning and family, educational, work and relationship adjustment. In our opinion, it is fundamental that clinicians might promptly recognize the clinical features of ADHD, make the correct diagnosis/assessment and adequately treat the patients with tailored interventions across age groups. Indeed, different factors, such as the lack of well-defined diagnostic assessments, an extremely heterogeneous amount of screening instruments, variability of diagnostic criteria throughout the years, vulnerability to recall biases in retrospective studies, a high frequency of misdiagnosis and the phenomenon of malingering, may lead to variable and inconclusive findings.

In children, stimulants (namely MPH and AMPs) are acknowledged as the safest and most effective therapeutic options by both the main guidelines and the majority of available reviews and, as such, considered the first-line treatment. On the other hand, non-stimulant drugs (ATX and alpha-2 receptor agonists) fall into the second line of treatment due to the evidence of weaker efficacy than stimulants. In any case, it may be preferable to undertake treatment with these drugs when the parents or caregivers of the children express a firm position against the use of stimulants, concern about drug diversion, or in case of comorbidities that that make the clinical picture more complicated to disentangle (such as an anxiety or tic disorders) (Wolraich et al. 2011). Indeed, other medications may be used for treating ADHD in children (i.e. BPN, mood stabilizers, antidepressants) when stimulants, ATX and alpha-2 receptor agonists have resulted ineffective, or in the presence of comorbidities, while keeping in mind that are not approved by the U.S. Food and Drug Administration and their use is strictly off-label (Felt et al. 2014).

Unlike in children, the treatment in adults still suffers from the "original sin" of ADHD being considered a pediatric disease and, although guidelines are identifiable, these are not yet completely recognized unanimously across different countries. For this reason, the treatment of this disorder in adults relies on both the international scientific literature reports, but also, and above all on the clinical experience gained by mental health professionals who have specifically dedicated themselves to the study of adult ADHD (Migliarese et al. 2017). Furthermore, even if available pharmacological arsenal is still limited, the differences can be significant from country to country. For example, in Italy, ATX is the drug of first choice for its recognized clinical efficacy and in spite of representing the only one compound endowed of "on-label use" amongst the so-called drug-naïve patients. Furthermore, ATX appears the safest choice in case of suspect or overt comorbidity with a substance use disorder or a malingering/misuse, that is to say the two conditions particularly frequent in this type of patients (Mucci et al. 2019). MPH, as already mentioned, is suggested as a second-line choice, namely in case of previous effective treatment with the same compound as well as in subjects who are not suitable for the use of ATX or if this or other treatments were ineffective. In this case, however, the prescription is off-label and requires informed consent from the patient. Although considered second (if not third) choice, bupropion appears to represent a good therapeutic compromise particularly in specific cases of ADHD, for example when associated with anxiety, depressive or bipolar disorder. In these cases bupropion can be used successfully both alone and in combination with other drugs, especially mood stabilizers (Migliarese et al. 2017; Mucci et al. 2019).

Finally, regarding old age, it is noteworthy to mention that, as underlined in a recent review by some scholars, the diagnosis and the therapeutic strategies in the elderly population currently represents a "blind spot" in ADHD research (Franke et al. 2018). Although more than five decades have passed since the first description of the pervasiveness of ADHD from infancy to adulthood, it seems difficult to find any trace of studies exploring the management of this disorder beyond middle adulthood in the available scientific literature, thus making it difficult to carry out a complete overview over the entire life span (Franke et al. 2018). Furthermore, in older age groups an important confounding factor is the frequent comorbidity with other, much better known, neuropsychiatric problems such as mild cognitive impairment and dementia (Marazziti et al. 2020). To complicate this already obscure "clinical tangle", it should be noted that even some of the symptoms of the ADHD diagnostic criteria described in the DSM could overlap and be (possibly better?) explained by another functional / organic pathology. For this reasons, it seems reasonable to recommend caution when attempting to identify ADHD in the elderly without a prior, careful, investigation of the neuropsychological history of childhood, paying also attention to treatments, given the frequent comorbidity with cardiovascular diseases. On the other hand, albeit the substantial lack of studies, there is agreement that stimulants do not appear to be sufficiently effective for behavioral or cognitive symptoms of dementia with the notable exception of MPH as a possible treatment for apathy in patients with dementia (Dolder et al. 2010).

The main limitation of the present study is that it is a narrative review. Indeed, systematic reviews are considered to significantly limit authors' bias, as they use specific criteria to select important publications and analyze their validity. However, as already underlined (Collins and Fauser 2005) "the strengths of systematic reviews may turn into weakness". For these reasons, narrative reviews are more comprehensive and include more issues of a given topic, although they do not follow specific rules for searching the literature.

In any case, although we decided to perform a narrative review, we adopted explicit specific selection and exclusion criteria, as stated in the methods sections.

In conclusion, at the present time, there are more treatment options for the same disorder in children than in adults, and, with no doubt, depriving adults of proven effectiveness drugs represents an unmet need and an important challenge of psychiatry in 2021. As already highlighted by different scholars, there is still a substantial lack of longitudinal and long-term studies with a careful and detailed characterization of participants across different phases of the lifespan. Such studies would serve to shed light on the clinical presentation of ADHD amongst the different age groups, as well as on the possibly important role of life events and environmental factors in individual patients. A major question that should be answered in controlled studies is the following: is there any heterogeneity in the pharmacological response or resistance to treatment in ADHD patients of different ages? Furthermore, future trials should also deepen, and possibly implementing, the role of non-pharmacological strategies (i.e., deep brain stimulation, trans-magnetic stimulations, neurofeedback, and nutritional intervention), while also providing more information on their long-term effects. The hope for the future is to implement this type of naturalistic studies to try to better predict the evolution of ADHD during its course, as well as to tailor the best-personalized medicine for individual patients.

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Declarations

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approval This review of the literature does not contain any studies with human participants or animals performed by any of the authors.

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pediatric reports

MDPI

Case Report

Poly-Unsaturated Fatty Acids in ADHD and in Other Neuropsychiatric Conditions: A Multiple Case Presentation

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Abstract: Neurodevelopmental disorders are seen quite commonly by general pediatricians. They should be managed with a multi-professional approach. The potential beneficial effect of poly-unsaturated fatty acids (PUFAs) has been reported in recent literature, but guidelines describing their use in everyday practice are still lacking. We describe four cases as examples of the possible integration of a supplementation with PUFAs in the management of four relatively common clinical situations (i.e., children too young to receive pharmacological treatment for ADHD, children with nonspecific neurodevelopmental disorders, children whose parents refuse consent for pharmacological treatment of ADHD, and children for whom methylphenidate is not sufficient to achieve expected results).

Keywords: ADHD; omega3; omega6; PUFAs; neurodevelopmental disorders

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1. Introduction

According to the DSM-5 [1], neurodevelopmental disorders are "a group of conditions with onset in the developmental period ... often before the child enters grade school ... characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning". This definition includes a number of well-defined disorders, including e.g., Autism Spectrum Disorder, Intellectual Disability, and Attention-Deficit/Hyperactivity Disorder. It is, however, anticipated the possibility to see in clinical practice a number of patients having signs and symptoms of a neurodevelopmental disorder which cause clinically significant distress or impairment but do not reach the diagnostic threshold for any specific diagnostic class.

The prevalence of these disorder is debated in current literature, but as a whole in Italy (and possibly in all developed countries) their symptoms represent a non-negligible reason for consultation with the general pediatrician and of referral to a child neuropsychiatrist.

All neurodevelopmental disorders require a multi-factorial diagnostic approach and treatment. Key factors are an accurate diagnosis, the involvement of families and the availability of evidence-based interventions [2,3]. Psychopharmacological strategies actually available are considered to be only partially useful to manage some more disturbing symptoms, with the notable exception of ADHD where methylphenidate has proven to be highly effective, at least in the short-to-medium term [4]. As in all other neuropsychiatric disorders, the use of complementary and alternative medicine has been considered [5], more often in association with other therapeutic approaches.

Among others, the use of poly-unsaturated fatty acids (PUFAs) has received a significant attention and has been studied in detail, especially in ADHD [6] but also in other neurodevelopmental disorders [7]. PUFAs are one of the main cellular building blocks. A loss of their balance, due to dietary issues, has been considered as a risk factor for many neuropsychiatric disorders [8]. Actual evidence of a possible role of a supplementation of PUFAs in the treatment of neurodevelopmental disorders has provided promising but not conclusive results [9], possibly due to the use of single fatty acids or of omega-3 fatty acids alone; in fact, given the physiological regulation between the different PUFAs in a dynamic

equilibrium, it is possible that the utility of this approach relies on the possibility to obtain or restore a correct balance between the different PUFAs (and, therefore, their optimal functionality) [10]. This equilibrium is one of the factors which is altered as a consequence of neuroinflammation, a factor which as been reported as a major shared mechanisms in neurodevelopmental disorders and in other psychiatric disorders [11]; it is possible that the restoration of the omega-3:omega-6 ration could contribute the reducing the dysfunctional activation of metabolic pathways leading to behavioral symptoms [12]. Moreover, there are no guidelines available regarding the use of PUFAs in everyday pediatric practice.

Considering this framework, four case reports are presented to offer insights about the possible use of PUFAs in different commonly seen clinical conditions.

2. Case Reports

2.1. Case 1—Too Young to Receive Methylphenidate

G. was first seen by a child neuropsychiatrist when he was four years and seven months old. Their parents stated that their child was always moving, like he was driven by a motor. He was unable to play with peers but also with adults because he could not respect his turn and was frequently asking to change the activity, declaring to be "bored". He had been described by some parents as "uneducated", because of his tendency to intrude on others and to talk excessively. This description was also confirmed by his general pediatrician, who added a tendency to have falls and minor injuries due to his lack of attention, combined with a too high level of motor activity and a tendency to underestimate risks taken while making motor activities.

A carefully taken history revealed normal pregnancy and term birth without any significant problem. In the first months of life he was described as "always trying to move", with reduced sleep necessities and short feeding times (leading to multiple small meals). Developmental milestones were reached at normal age, with a slight tendency to be more skilled in motor performances than in language use. In kindergarten, he was considered far too active, with highly developed gross- but reduced fine-motor skills. No treatment or specific counselling had been offered to him or his family before that moment.

Clinical examination was in line with the description provided by parents and teachers. A cognitive evaluation confirmed a normal functioning, with only a frailty in short-term memory and a significant difficulty in both fixing and maintaining attention. This also offered an explanation to the difficulty in completing requests involving sequential tasks described by the parents during the evaluation.

Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime (K-SADS-PL, DSM-5 version) was administered and a diagnosis of Attention-Deficit/Hyperactivity Disorder was confirmed [13]. Conners' Parent Rating Scales (CPRS) [14] and Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) [15] were filled by the parents, confirming the diagnosis and a significant level of symptoms in terms of inattention as well as of hyperactivity and impulsivity (CPRS: Cognitive problems due to attention deficit raw score 17 (T score: 75), hyperactivity raw score 19 (T score: 74), ADHD symptoms raw score 24 (T score 77); SNAP-IV: attention deficit 2.12 (cut off 1.78), hyperactivity 2.33 (cut off 1.44), no significant oppositional-defiant functioning). The final diagnosis was, therefore ADHD, combined presentation, moderate-to-severe.

Parents, who had previously searched the Internet for information, requested the possibility to start a pharmacological treatment to help their child. Due to existing regulations for the prescription of methylphenidate in Italy, however, we had to deny their request due to the child's age (as he was less than six years old). We proposed as an alternative, at least pro-tempore, the use of PUFAs; the parents accepted this, although not happily (as they had read of the effects of methylphenidate and had great expectations from its use in G.).

G. was administered eicosapentaenoic acid (EPA) 558 mg + docosahexaenoic acid (DHA) 174 mg + gamma-linolenic acid (GLA) 60 mg per day in the form of chewable capsules taken twice per day. The parents were informed that it was necessary to allow a sufficient amount of time before assessing the efficacy of this approach. An appointment

was booked after two months of treatment. We provided counselling both to the parents and the teachers, and scheduled periodic monitoring phone contacts.

The first month was described as difficult, possibly because parents and teachers were more informed and tended, therefore, to observe and report more behaviors typical of ADHD. Then, in the parent's words, "he started to change" towards a better functioning: He was able to pay attention for a longer time both at kindergarten and at home, he was easier to stop when starting to be too active, and had less tendency to intrude on other's conversations. His drawing skills started to improve, possibly as a consequence of a much longer exercise and attention paid to the task. The general pediatrician confirmed the parent's reporting of a significant reduction of the previously frequent minor injuries following motor hyperactivity.

All questionnaires and interviews showed a reduction of both symptoms and impairment (CPRS: cognitive problems due to attention deficit raw score 14 (T score: 68), hyperactivity raw score 16 (T score: 68), ADHD symptoms raw score 21 (T score 72); SNAP-IV: attention deficit 1.89.12 (cut off 1.78), hyperactivity 2 (cut off 1.44)), so that the severity of expression was changed to moderate. We suggested to maintain the treatment as in use, a fact that the parents were at this time happy to accept.

Treatment was continued for six months, without any significant side effect; G. only reported to prefer not to chew the capsule because "they don't taste good". The improvement was lasting and substantially stable. No longer was follow up possible because the family moved quite far from our medical center.

2.2. Case 2—Dysregulated but Not Specific

M. was seen at the age of eight years and three months. His parents reported significant concerns expressed by his teacher: He was not obtaining expected results, he was messy and his handwriting was hard to read, despite his efforts and some specific training provided by the school and the parents. Moreover, according to the parents he was often a bit slow in following orders, despite not refusing to obey. He had some "tantrums", appearing suddenly and without connection with significant events, and sometimes his mood was unstable.

He was a second son and had no significant family history of any neuropsychiatric disorder. Pregnancy was described as fully normal, while birth had been characterized by a delay of the expulsive phase, without detectable signs of perinatal brain problems. He had reached developmental milestones in typical times, although parents described him as always clumsy and somewhat "unstable" in his behavior.

The clinical examination was in line with the description provided. Cognitive functioning was normal, but writing skills and global praxic abilities were slightly below average when formally tested; he was able to stay focused for an adequate time, but his ability to shift attention to a target proposed by the examiner was below average. During the testing, he had two moments of loss of emotional control, apparently caused by minor problems (one time he misread a word, the other time apparently his drawing was not up to his expectations). All his neuropsychological parameters related to academic skills (i.e., reading fluency and correctness, writing fluency and correctness, ability to manipulate numbers and to calculate) were at the lower limit of the normal range (indicating a widespread frailty of these aspects without a significant deficit in any of them).

A diagnosis of "mixed specific developmental disorder" was proposed, with an added indication of a frailty in emotion regulation. The parents, preoccupied with the possibility of academic failure, accepted the proposal of a psychomotor treatment aiming at improving praxic skill, but posed the question of the possibility to support this with a pharmacological approach to make M. "more stable".

Parents were offered a structured counselling to help them cope with the peculiarities of their child, but given their explicit request, M. was also started eicosapentaenoic acid (EPA) 837 mg + docosahexaenoic acid (DHA) 261 mg + gamma-linolenic acid (GLA) 90 mg per day in the form of capsules taken twice per day.

The child was re-evaluated after four months of treatment. Reports by the parents, the teacher and the general pediatrician were highly consistent in describing a significant improvement. The frequency of tantrums decreased from the third month of treatment. Academic and praxic skills began to increase from the second month of treatment (it was not possible to differentiate the effect of the psychomotor treatment from that of PUFA supplementation). The child remained able to focus his attention, but became "easier to guide" towards adult-established goals.

Treatment with PUFAs was continued for six months, then a four-months break was given, followed by a second period of treatment (this time lasting two months). Benefits obtained were stable, both during the suspension and after the second period of treatment. The child was able to improve his proficiency at school although with some aspects of "slowness" which were easily managed with didactic strategies. No side effects were reported. As a precaution, a blood sample was collected and all exams executed were unremarkable.

2.3. Case 3—Everything but Drugs, Please!

At the age of nine years and two months F. was sent for a consultation by the general pediatrician, who also wrote a short note describing the typical symptoms of ADHD he had observed and that had already been confirmed by both parents and teachers. F. was described as a restless child, unable to stay still or to keep sitting for more than a minute or so. He was also unable to pay sufficient attention to any activity, therefore, not completing his schoolwork nor any task proposed by his parents and adequate for his age. He was unable to make friends, because he easily got distracted during games and was therefore rejected as a "sandbag".

Term born after a fully normal pregnancy, F. had been always seen as a child with poor attentive skills and high level of motor activity. As far as the parents could tell, he had always been seen as needing significant attention from the adults to be kept focused on the ongoing activities and to prevent him from moving around without an apparent reason but to keep moving. His father declared that he expected F. to improve spontaneously. The mother explained that almost all males in the paternal family were roughly similar to F., although apparently with less severe behaviors.

K-SADS-PL (DSM-5 version) [13] was administered and a diagnosis of Attention-Deficit/Hyperactivity Disorder was confirmed. Conners' Parent Rating Scales [14] and Swanson, Nolan, and Pelham Rating Scale [15], filled by the parents, evidenced a significant level of symptoms in terms of hyperactivity and inattention (CPRS: cognitive problems due to attention deficit raw score 22 (T score: 73), hyperactivity raw score 15 (T score: 73), ADHD symptoms raw score 25 (T score 78); SNAP-IV: attention deficit 2.33 (cut off 1.78), hyperactivity 2.56 (cut off 1.44), no significant oppositional-defiant functioning). Global cognitive functioning was in the normal range as well as learning skills. The final diagnosis was, therefore, ADHD, combined presentation, moderate-to-severe.

Given the impact that ADHD symptoms were having on F.'s life, methylphenidate was offered, in the context of a more global intervention including parent and teacher training. Indication and possible side effects of this approach were thoroughly discussed. However, possibly after looking for additional information on the Internet, parents refused consent to the administration of methylphenidate, expressing their preoccupation with the biochemical similarities between methylphenidate and cocaine.

At the same time, however, parents expressed their preoccupation with the time needed for psychoeducational interventions to be effective and asked for alternative solutions. Since they were ready to accept it, F. was started eicosapentaenoic acid (EPA) 837 mg + docosahexaenoic acid (DHA) 261 mg + gamma-linolenic acid (GLA) 90 mg per day in the form of capsules taken twice per day.

Teachers were the first to evidence some improvements after 2.5 months: F. was described as more able to participate to everyday school activities, with a small but clear improvement in his academic results. One month later, he received his first invitation for a

sleepover with his newly acquired "best friend" and after five months of treatment he was accepted in a local soccer team, where he was described by his coach as "a nice lad, even if not always focused during the matches, when his fellows have to help him sometimes".

Treatment was continued with the same dose for one year. Parents recognized that the use of PUFAs had been useful and without side effect, but decided to change their mind as to the use of methylphenidate because they wanted to try it before their child becoming an adolescent. The administration of the drug under medical control (so called "dose test") provided clear evidence of efficacy and methylphenidate was then started following standard protocols in keeping with the Italian laws (i.e., a therapeutic plan was defined by our Center and regularly monitored with clinical, ECG, blood examinations as prescribed by the Italian laws concerning the use of methylphenidate and of other drugs to treat ADHD). Following parental request, PUFAs were suspended.

2.4. Case 4—Methylphenidate Is Not Enough

F. (the patient whose story was previously reported as "case 3") had a significant improvement using methylphenidate. He was started using immediate-release methylphenidate, first once per day and then twice per day. After a couple of months, he was given delayed-release methylphenidate to optimize the efficacy and to eliminate the need of a second dose after lunch (which required the parents to go to school to have F. take his pills, as the school had no nurse or similar facilities).

As F. grew, the dose of methylphenidate was adapted to his weight and kept around 0.5 mg/kg/dose (or equivalent for delayed-release methylphenidate). When F. reached 12 years and eight months, parents started to report some unusual movements of the shoulders. During the neurological examination, this was understood as a motor tic and other tics were noted, both motor (eye blinking, movements of the wrists) and occasionally vocal (one episode of repetitive throat clearing, without evidence of any relevant medical condition). Since this was a possible side effect of methylphenidate, and considering parental concerns (both in the past and at present) towards this drug, the dosage was reduced to the equivalent of 0.4 mg/kg/dose. This led to an almost immediate disappearance of tics, but also to a reduction of the positive effects of methylphenidate: F. was described as less able to pay attention, with an apparent shorter efficacy of the delayed-release formulation he was taking.

After discussion with the parents, it was decided to re-introduce PUFAs in an attempt to strengthen the effect of methylphenidate without increasing the pro-kilo dose of the drug. F. was started eicosapentaenoic acid (EPA) 558 mg + docosahexaenoic acid (DHA) 174 mg + gamma-linolenic acid (GLA) 60 mg per day in the form of chewable capsules taken twice per day. After about two months of this regimen, all adults around F. (parents, teachers, soccer coach) agreed that his functioning was almost identical to that seen when he was taking a higher dose of methylphenidate.

Both methylphenidate and PUFAs were continued for roughly one year, without further side effects. Since F. had improved, a suspension was attempted and was successful, since F. was able to continue his life no longer needing pharmacological or nutraceutical support.

3. Conclusions

The cases depicted are examples of clinical situations, frequently occurring in real-life pediatric and neuropsychiatric practice, where the use of PUFAs contributed to the results obtained as a significant part of a multi-modal therapeutic strategy. They are not meant to demonstrate the utility of PUFAs in these situations, which has been studied in far more detail [16]. They are intended to offer real-life examples about how to use them in lack of published guidelines.

To summarize, the clinical situations were as follows:

(1) when a treatment could be useful, but the standard drug (i.e., methylphenidate) cannot be prescribed due to existing regulations;

(2) when the clinical situation is atypical, but dominated by dysregulation (both of mood and behavior);
(3) when parents refuse consent to administration of methylphenidate, despite medical advice suggesting to use it; and
(4) when methylphenidate is effective but not fully, and dose cannot be safely increased.

Given that PUFA administration is a highly safe intervention, it is important for the general pediatrician, to be aware of this option, of its possible use, of the differences existing between different products in order to best serve the interest of the patient and of his/her family, considering the increasing use of nutraceuticals in psychiatric e neuropsychiatric disorders [17]. It is also important to consider PUFAs as part of a more comprehensive approach towards neurodevelopmental difficulties, as evidenced by the clinical vignettes described. We used a formulation providing a specific ratio (9 EPA:3 DHA:1 GLA), in line with existing studies evidencing its peculiar efficacy [18], its effect on neuronal viability [19] and its ability to improve fatty acid plasma profile [20]. Given their "real-life" nature, these case reports could be a useful source of inspiration despite the limitation connected with the nature of the case reports and with the lack of published guidelines.

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Institutional Review Board Statement: Ethical review and approval were waived for this study, due to the retrospective nature of the case description and the use of data deriving from everyday Good Clinical Practice in the specific field.

Informed Consent Statement: Informed consent was obtained from all legal guardians of subjects involved in the study to use data also for research purposes (including publication).

Data Availability Statement: Raw data are available from the author upon reasonable request.

Conflicts of Interest: The author declare no conflict of interest.

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Traiettorie evolutive: una lezione dall'ADHD

Guardarsi indietro per gestire il futuro

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La storia di una adolescente con diagnosi tardiva di ADHD che si presenta con la concomitante presenza di un disturbo oppositivo provocatorio. Il pediatra è la figura centrale nel sospettare una diagnosi precoce di ADHD che è fondamentale per modificare le possibili traiettorie neuroevolutive. E il ruolo del pediatra è determinante anche per sostenere il neuropsichiatra infantile e la famiglia nella verifica della compliance agli interventi proposti e per rilevare precocemente l'insorgenza di comorbidità (vedi anche Appunti di Neuropsichiatria).

CASO CLINICO

Silvia, 12 anni, viene inviata dal pediatra in Clinica di Neuropsichiatria dell'Infanzia e Adolescenza con richiesta di visita urgente per "disturbi comportamentali, con minaccia di suicidio". I genitori si sono allarmati dopo aver letto alcuni messaggi nei quali la ragazza ha espresso ai coetanei l'intenzione di defenestrarsi. Viene effettuato un colloquio con i genitori e con Silvia e viene indagata l'ideazione suicidaria con la scala Columbia (C-SSRS)[1]. Considerata la presenza di generici pensieri suicidari, in assenza di reale intenzionalità e pianificazione, il rischio di suicidio risulta basso, ma appare opportuno predisporre un breve ricovero in *Day Hospital* per gli approfondimenti diagnostici. All'anamnesi familiare e personale emerge familiarità per depressione e demenza tipo Alzheimer. Sviluppo psicomotorio e del linguaggio riferito nella norma.

All'esame psichico si evidenziano scarso orientamento temporale, logorrea, distraibilità, irrequietezza motoria, avversione per l'attesa e difficoltà nel rispetto dei turni conversativi, critica e *insight* parziali.

Silvia è stata una bambina molto vivace sin dall'asilo nido e, già dalle scuole elementari, presentava difficoltà di attenzione, iperattività, impulsività, bassa soglia di tolleranza alle frustrazioni, difficoltà nel rispetto delle regole e mancanza di *savoir-faire* sociale. Questi sintomi ne compromettono anche attualmente il funzionamento globale, in particolare la socializzazione: Silvia ha cambiato diversi sport e i coetanei tendono a escluderla o evitarla. Le ripetute esperienze di fallimento in diversi contesti di vita hanno determinato, da circa un anno, a fronte di un'apparente spavalderia, la comparsa di profondi sentimenti di demoralizzazione, bassa autostima e saltuarie idee di morte.

Presenta, inoltre, facile irritabilità, labilità emotiva e difficoltà nella regolazione delle emozioni, tanto che in alcune occasioni, reattivamente a frustrazione o esclusione, ha messo in atto comportamenti potenzialmente autolesivi (sporgersi dalla finestra, sedersi sul davanzale) dal carattere prettamente dimostrativo.

DEVELOPMENTAL TRAJECTORIES: A LESSON FROM ADHD TO LOOK BACK TO THE PAST IN ORDER TO FACE THE FUTURE
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Key words
Attention-Deficit Hyperactivity Disorder (ADHD), Neurodevelopmental disorders, Comorbidities, Suicidal ideation, Developmental trajectories

Summary
A 12-year-old girl was urgently sent by her paediatrician to the Child and Adolescent Neuropsychi-atry ward for behavioural disorders and suicide threat. At the time of the visit the suicide risk was low. Nevertheless, considering a possible underlying psychopathology, a short Day Hospital admis-sion for appropriate diagnostic investigations was warranted. Developmental trajectory showed several symptoms of inattention, hyperactivity, impulsivity, poor tolerance to frustrations, emotional lability, irritability, emotional dysregulation, rule breaking be-haviours and impaired socialization with her coevals from early childhood. The diagnostic delay may have led to demoralization and then to depressive feelings. This led to the diagnoses of Attention - Deficit Hyperactivity Disorder and Oppositional-Defiant Disorder. Pharmacological therapy with Methylphenidate was prescribed as well as cognitive-behavioural therapy and parent training intervention.

Ripercorrendone la traiettoria evolutiva, sono stati rintracciati degli elementi di continuità che, in associazione alle opportune valutazioni strutturate, hanno permesso di formulare le diagnosi di disturbo da deficit di attenzione e iperattività (ADHD), presentazione combinata, e disturbo oppositivo provocatorio di grado moderato.

Con la restituzione clinica, considerata la severità del caso, viene proposto di intraprendere una terapia farmacologica con metilfenidato e psicoterapia cognitivo-comportamentale, oltre al *parent training*.

I genitori hanno rifiutato la terapia farmacologica e intrapreso gli altri interventi.

Attualmente risultano ridotti i comportamenti oppositivi e migliorata la gestione dell'emotività, persistono tuttavia i sintomi di inattenzione, di iperattività/impulsività e la compromissione della socializzazione. È stata riproposta la terapia farmacologica ai genitori, che appaiono ancora incerti.

COMMENTO

Le traiettorie evolutive

Per traiettoria evolutiva, o di sviluppo, si intende il percorso evolutivo individuale, orientato da fattori genetici, neurobiologici, ambientali e culturali, nel quale si susseguono, nel corso della vita, una serie di cambiamenti psico-comportamentali. Si tratta di un processo dinamico, in cui ogni cambiamento influenza le successive tappe di sviluppo e condiziona, determinandolo, l'evolversi del percorso. Si distinguono uno sviluppo tipico, in cui il *trend* di sviluppo procede senza alterazioni, in maniera sovrapponibile a quanto atteso per età cronologica, e uno atipico, in cui una compromissione evolutiva di varia natura altera il percorso.

Il caso di Silvia ci ha mostrato come ricostruire la traiettoria di sviluppo sia fondamentale in Neuropsichiatria dell'infanzia e adolescenza, dove la psicopatologia va inquadrata secondo una dimensione evolutiva. Se ciò è particolarmente vero per i disturbi del neurosviluppo, come l'ADHD, che si caratterizza per una presentazione clinica diversa nelle differenti età, è altresì vero che questa riflessione può essere estesa a tutta la psicopatologia dell'età evolutiva[2-4].

La prospettiva del neurosviluppo consente di rintracciare la storia naturale dei disturbi, la loro evoluzione e transizione, permettendo di dare ordine e senso a quelle che, altrimenti, potrebbero diventare liste di etichette diagnostiche.

Tale prospettiva consente di riconoscere i segnali di allarme nella prima infanzia e di fare diagnosi e interventi precoci, al fine di proteggere il bambino da un'evoluzione peggiorativa dei suoi disturbi; in adolescenza, essa permette di rintracciare, retrospettivamente, le modalità e le tempistiche di esordio delle patologie, consentendo di formulare diagnosi più accurate, di scegliere interventi più specifici e appropriati e di prevenire lo sviluppo di psicopatologia successiva.

L'ADHD ha una presentazione clinica eterogenea che varia con l'età e il sesso

L'ADHD è caratterizzato da un *pattern* persistente di inattenzione e/o di iperattività/impulsività presente in almeno due contesti di vita e interferente con il funzionamento globale dell'individuo[5].

Vi sono tre principali modalità di presentazione clinica: una prevalentemente inattentiva; una prevalentemente iperattiva/impulsiva e una, quella di Silvia, combinata[5]. Ai sintomi nucleari possono frequentemente aggiungersi, tra gli altri, come nel caso descritto, alterata percezione temporale e disregolazione emotiva[6].

In età evolutiva, l'ADHD è diagnosticabile nel 2-3% dei maschi e nell'1-1,5% delle femmine, con un picco in età scolare[7]. Il dato della maggiore prevalenza nel sesso maschile potrebbe, tuttavia, essere falsato dal fatto che i campioni utilizzati negli studi clinici sono principalmente o esclusivamente costituiti da maschi, con conseguente possibile strutturazione di un "prototipo maschile" di ADHD su cui sono stati definiti i criteri diagnostici stessi[8].

Come rintracciabile nella storia evolutiva di Silvia, le manifestazioni cliniche dell'ADHD variano con l'età.

- In *età prescolare* rileviamo marcata iperattività, crisi di rabbia, gioco caotico, litigiosità, provocatorietà, assenza di paura e incidenti frequenti, comportamenti aggressivi e disturbi del sonno.
- In *età scolare* è più facile riscontrare disattenzione, difficoltà scolastiche, evitamento di compiti cognitivi, impulsività, iperattività, comportamenti oppositivo-provocatori e difficoltà relazionali.
- In *età adolescenziale* l'iperattività tende a ridursi per lasciare spazio a una sorta di tensione emotiva interna, mentre i sintomi di inattenzione persistono, con difficoltà di organizzazione e pianificazione in diversi ambiti (ad esempio, difficoltà nel rispettare scadenze e appuntamenti). Gli adolescenti con ADHD presentano spesso instabilità nelle scelte scolastiche o relazionali, condotte a rischio, ricerca di sensazioni forti e novità, problemi emotivi e conflittualità intrafamiliare. In adolescenza, inoltre, diventa ancor più evidente e impattante la mancanza di *savoir-faire* sociale, con compromissione della socializzazione[2,5].

Nelle bambine e nelle ragazze, l'ADHD si manifesta più frequentemente con la disattenzione o con sintomi internalizzanti (ansia, tristezza): questo può portarle a essere "meglio accettate" nei vari contesti e quindi a non arrivare alla diagnosi, o ad arrivarci solo se la presentazione clinica è simile a quella maschile o solo quando l'ADHD si è evoluto in altri disturbi più gravi.

Inoltre, anche quando iperattive e/o impulsive, come nel caso di Silvia, le bambine e le ragazze possono manifestare tali sintomi in maniera peculiare: possono esprimere l'iperattività parlando eccessivamente e ridacchiando, e manifestare l'aggressività più sul piano verbale e relazionale (minare le relazioni altrui) che fisico.

L'apparente spavalderia, che abbiamo riscontrato in Silvia, può infine, nelle adolescenti, mascherare un forte

malessere derivante dalle difficoltà relazionali e interpersonali[2,8-10].

Avere presente questa eterogeneità clinica riduce il rischio di mancate o tardive diagnosi.

La storia naturale dell'ADHD e l'importanza di una diagnosi precoce

Circa un terzo dei bambini con ADHD va incontro a remissione completa del disturbo, che sembra pertanto configurarsi come un "ritardo semplice nello sviluppo delle funzioni attentive ed esecutive". La metà dei bambini con ADHD continua invece a presentare sintomi di inattenzione e di iperattività/impulsività anche da adolescente e, spesso, anche da adulto.

Altri soggetti (15-20%), oltre a continuare a manifestare i sintomi nucleari del disturbo, presentano delle "cicatrici" legate alla patologia, con evoluzione verso quadri più gravi, sia del versante internalizzante che esternalizzante (disturbi d'ansia, disturbi dell'umore di tipo unipolare o bipolare, disturbi dirompenti del comportamento e del controllo degli impulsi, disturbo antisociale di personalità, abuso di sostanze)[2,11-14].

Nel caso di Silvia, il ritardo diagnostico può aver favorito la persistenza dei sintomi nucleari dell'ADHD in adolescenza e l'insorgenza di comorbidità come il disturbo oppositivo-provocatorio (DOP), inoltre la pone a rischio di sviluppare problematiche più gravi.

La presenza di bassa soglia di tolleranza alle frustrazioni, labilità emotiva, emozionalità negativa e comportamenti aggressivi, insieme a una percezione di sé come efficace solo in quanto oppositivo e provocatorio, sembrano essere fattori predisponenti l'evoluzione verso un DOP che è presente in circa il 30-50% dei bambini con ADHD[15]. La presenza di un DOP nell'infanzia, specialmente se associato all'ADHD, è a sua volta predittore di successiva psicopatologia in adolescenza, come il disturbo di condotta (DC) e i disturbi depressivi[2,14,16,17].

Le ripetute esperienze di fallimento, in più contesti di vita, e l'instabilità relazionale e scolastica, hanno favorito, in Silvia, la strutturazione di una percezione soggettiva di incompetenza e inefficacia personale, con sentimenti di demoralizzazione, bassa autostima e ideazione suicidaria; la pongono inoltre a rischio di sviluppare disturbi d'ansia o dell'umore[15].

La demoralizzazione può essere definita come un senso persistente e profondo di fallimento, a cui si accompagnano bassa autostima, arrendevolezza e, talvolta, perdita di significato del vivere. A differenza di quanto accade nella depressione, nella demoralizzazione la perdita di interesse per le attività non è pervasiva e non è consumatoria (non interferisce con la possibilità di godere di attività piacevoli e gratificanti); inoltre l'inibizione all'azione non è tanto legata a una perdita di motivazione e spinta quanto alla percezione soggettiva di essere incapace di agire[18]. La demoralizzazione è in genere correlata all'ideazione suicidaria in maniera indipendente dal disturbo, organico o psichico, a cui si accompagni: secondo alcuni Autori, può preludere all'insorgenza di un disturbo depressivo vero e proprio[19,20].

La presenza di impulsività e di scarsa inibizione, correlate all'ADHD, espongono inoltre Silvia al rischio di sviluppare condotte pericolose (guida ad alta velocità, abuso di sostanze/alcol, coinvolgimento in compagnie potenzialmente devianti) e di mettere in atto comportamenti autolesivi[21,22].

La mancanza di *savoir-faire* sociale ha determinato una profonda sofferenza e può favorire l'insorgenza di disturbi d'ansia e dell'umore[23]. Inoltre, essa può attivare, peraltro in un soggetto che intrinsecamente ha limitate capacità di *problem solving*, strategie disfunzionali, quali il non chiedere aiuto, evitare di affrontare i problemi, utilizzare in modo incongruo i *social network*, lasciarsi coinvolgere in attività criminose o in comportamenti sessuali promiscui, o ricorrere all'abuso di sostanze/alcol[9].

L'insorgenza di comorbidità, in particolare DOP/DC, disturbi affettivi, disturbi d'ansia, sintomi psicotici e, soprattutto nelle femmine, l'abuso di sostanze/alcolici, espone il paziente con ADHD a un aumento del rischio suicidario[21,22] e la progressiva esacerbazione dell'irritabilità nel corso dell'infanzia sembra essere un fattore di rischio diretto di suicidalità in adolescenza[24].

MESSAGGI CHIAVE

- ❏ L'ADHD non è soltanto un disturbo della prima infanzia né tipicamente maschile.
- ❏ Le traiettorie evolutive sono una realtà dinamica in cui si può incidere in modo significativo, attraverso interventi mirati, modificandone il decorso.
- ❏ In un adolescente, la presenza di demoralizzazione, in associazione a impulsività, inattenzione, scarsa tolleranza alle frustrazioni e difficoltà nella regolazione delle emozioni, sono elementi che devono indurre a sospettare un possibile disturbo del neurosviluppo sottostante, come l'ADHD.
- ❏ Grazie al rapporto di fiducia e continuità che instaura con i propri pazienti, il pediatra può individuare i primi campanelli d'allarme e sostenere e incoraggiare la *compliance* agli interventi proposti.
- ❏ Il pediatra può verificare, in occasione delle periodiche visite di monitoraggio e controllo, l'eventuale insorgenza di comorbidità che possono sopraggiungere nel percorso evolutivo, indagando la cosa giusta al momento giusto.

Il trattamento dell'ADHD

È multimodale e comprende opzioni non farmacologiche e farmacologiche. Le prime, tra cui il *parent training*, il *teacher training* e un intervento psicoterapico di tipo cognitivo-comportamentale, dovrebbero essere intraprese il prima possibile una volta formulata la diagnosi.

Il *parent training*, peraltro, potrebbe essere suggerito ai genitori con bambini a rischio di sviluppare ADHD già in età prescolare e prima di una diagnosi formale.

L'opzione farmacologica è indicata, in Italia, a partire dai 6 anni di età per le forme gravi e invalidanti e/o non responsive agli approcci non farmacologici. Le linee guida internazionali ne suggeriscono peraltro l'uso precoce nelle forme più gravi. La terapia di prima scelta è il metilfenidato[25-28].

Esso è efficace nel trattamento dei sintomi nucleari e svolge un ruolo protettivo nei confronti dello sviluppo di comorbidità e di ideazione suicidaria[9,29].

Inoltre, nei casi in cui vi sia un quadro di demoralizzazione secondario al disturbo, il miglioramento dei sintomi nucleari consente una remissione del senso di inefficacia personale con miglioramento del tono dell'umore[9].

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Metilfenidato e ADHD

Le domande a cui bisogna rispondere

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Il metilfenidato è il farmaco di prima scelta per il trattamento dell'ADHD. Si riportano gli elementi chiave che possono aiutare il pediatra, la famiglia (e il neuropsichiatra) a trovare le risposte alle domande più frequenti per un corretto monitoraggio clinico e farmacologico del proprio paziente.

CASO CLINICO 1

Ada, 10 anni, ha ricevuto diagnosi di disturbo da deficit attentivo con iperattività (ADHD) all'età di 7 anni in seguito alle frequenti segnalazioni da parte delle maestre della scuola primaria che evidenziavano una marcata irrequietezza motoria, difficoltà nel rispetto delle regole, inattenzione con tendenza all'evitamento di attività cognitivamente impegnative e conseguente compromissione dell'apprendimento e del funzionamento scolastico.

Dopo sei mesi dall'attivazione di un percorso psicoeducativo riabilitativo globale che includeva anche il *parent training* per la coppia genitoriale nonché il *teacher training* rivolto al personale docente, veniva riferita persistenza di marcati sintomi di inattenzione, facile faticabilità e distraibilità mentre la bambina iniziava a verbalizzare sentimenti di demoralizzazione e autosvalutazione con senso di scarsa efficacia personale.

Previo consenso informato scritto da parte di entrambi i genitori e a seguito della somministrazione di una dose test in ambiente ospedaliero (0,3 mg/kg), Ada ha quindi intrapreso terapia farmacologica con metilfenidato nella formulazione a rilascio immediato *(Ritalin)* alla posologia di 10 mg (ore 8:00).

Tale terapia è stata modulata settimanalmente con l'aggiunta di 10 mg, sino alla posologia finale di 10 mg (ore 8:00) + 10 mg (ore 11:00) + 10 mg (ore 14:00) con significativo beneficio sul funzionamento in tutti i contesti di vita, in assenza di effetti indesiderati a eccezione di una moderata inappetenza per la quale sono stati forniti consigli ai genitori (favorire pasti più calorici la mattina a colazione e la sera a cena, integrare le merende con *snack* graditi, effettuare delle "pause terapeutiche" la domenica e durante le vacanze scolastiche).

Dopo circa un anno di trattamento farmacologico, in seguito alle difficoltà riportate dalle maestre nel garantire una puntuale somministrazione della dose delle 11:00 e della riluttanza della bambina ad allontanarsi dalla classe per assumere la terapia con la dovuta discrezione, è stato ritenuto opportuno suggerire il passaggio alla formulazione a rilascio modificato (*Equasym* 30 mg) con un buon controllo dei sintomi clinici sino alle primissime ore del pomeriggio. Al fine di garantire un adeguato controllo dei sintomi inattentivi per lo svolgimento dei compiti a casa, la terapia è stata poi ulteriormente integrata con l'aggiunta di *Ritalin* 10 mg alle (ore 15:00).

Attualmente frequenta la quinta classe della scuola primaria e assume

METHYLPHENIDATE AND ADHD
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Key words
Methylphenidate, Child and adolescent psychopharmacology, ADHD, Efficacy, Tolerability

Summary
Methylphenidate is the first-choice medication for the treatment of ADHD in children and adolescents. Over the past two decades, several randomised controlled trials re-peatedly showed its efficacy on both the core symptoms and the quality of life besides its tolerability in the short term. The most common adverse effects include sleep disturb-ance, nervousness, reduced appetite, weight loss, headache, elevated blood pressure and heart rate. These effects are generally mild, transient and easily manageable by clinicians. Despite the reassuring data in terms of short-term safety and tolerability, some questions still remain open with respect to the treatment effects in the long term. In the meantime it is however appropriate to continue to refer to the current European clinical practice guidelines. The paper reports treatment indications, information about the mechanism of action, the Italian available formulations and the answers to the most frequent questions for a correct clinical and pharmacological monitoring of young pa-tients.

ancora la terapia con metilfenidato con beneficio. Tale terapia è stata nel tempo rimodulata, sulla base della risposta clinica, sino alla posologia attuale *Equasym* 40 mg (ore 8:00) + *Ritalin* 15 mg (ore 15:00). Durante il passaggio alla scuola secondaria di primo grado sarà rivalutata l'opportunità di proseguire tale trattamento eventualmente con una sospensione graduale guidata durante le vacanze natalizie.

ADHD E METILFENIDATO

L'ADHD è uno tra i più frequenti disturbi del neurosviluppo, con possibile significativo impatto sulle *performance* scolastiche e sul funzionamento familiare e sociale. Se non adeguatamente trattato, in età adolescenziale e adulta può portare a depressione, all'emarginazione sociale e a una crescente difficoltà di adattamento alle norme sociali con conseguenti comportamenti devianti e frequente uso di sostanze di abuso.

Nell'ambito di un auspicabile trattamento multimodale, la terapia farmacologica si è dimostrata altamente efficace nel ridurre i sintomi nucleari dell'ADHD, e gli psicostimolanti rappresentano il trattamento di prima scelta in Europa da più di 60 anni con un tasso di risposta pari ad almeno l'80%.

Il metilfenidato, in particolare, è uno degli psicostimolanti maggiormente utilizzati e, dal 2007, è disponibile anche in Italia con indicazione per l'ADHD nei soggetti di età pari o superiore ai 6 anni. Numerose evidenze supportano l'efficacia del metilfenidato, nel breve termine, nel ridurre rapidamente l'irrequietezza motoria, l'inattenzione e l'impulsività in maniera significativa. Seppur in modo minore, contribuisce inoltre a migliorare la qualità delle interazioni sociali, a diminuire l'aggressività e a prevenire il rischio di depressione, suicidalità e abuso di sostanze.

Il meccanismo attraverso cui gli stimolanti riducono i sintomi dell'ADHD non è stato ancora completamente chiarito. Tuttavia è noto che esercitano la loro azione sui trasportatori sia dopaminergici che noradrenergici aumentando così il rilascio di dopamina e noradrenalina nello spazio extra-sinaptico, sia a livello sottocorticale striatale che nella corteccia prefrontale.

In Italia, il metilfenidato è attualmente disponibile in una formulazione a rilascio immediato *(Ritalin)* e in due formulazioni a rilascio modificato *(Equasym* e *Medikinet).*

La formulazione a rilascio immediato è associata a una rapida insorgenza dell'effetto terapeutico (circa 30 minuti), ed è in genere indicata per i soggetti più giovani e *drug naïve.* Viene somministrato in almeno due dosi giornaliere (es. prima di andare a scuola e dopo pranzo) e fino a tre volte al giorno (ore 8, ore 11, ore 14). Il dosaggio test è di 0,3 mg/kg, che può essere gradualmente titolato sino a un massimo di 0,9 mg/kg/dose.

Le formulazioni a rilascio prolungato sono in realtà delle formulazioni a rilascio "intermedio", con una durata di azione pari a circa 6-8 ore, pertanto possono richiedere l'aggiunta di una seconda dose il pomeriggio o essere combinate con la formulazione a rilascio immediato per ottenere un maggior beneficio.

Nelle capsule di *Equasym*, il 30% della dose è costituita da componenti a rilascio immediato e il 70% da componenti a rilascio prolungato. Il farmaco viene somministrato in un'unica dose al mattino, prima di colazione. Si raccomanda di iniziare con 10 mg/die ed effettuare l'aggiustamento posologico mediante incrementi settimanali di 10 mg, fino a un massimo di 60 mg al giorno. In *Medikinet* il 50% della dose è costituita da componenti a rilascio immediato, l'altro 50% da componenti a rilascio prolungato. Il farmaco viene somministrato in un'unica dose al mattino, dopo colazione. Anche in questo caso si raccomanda di iniziare con una dose di 10 mg/die e di procedere all'aggiustamento posologico mediante incrementi settimanali di 10 mg sino a un massimo di 60 mg/die.

In termini di tollerabilità, il metilfenidato è generalmente sicuro e facilmente gestibile. I più comuni effetti indesiderati includono insonnia, irritabilità, inappetenza, calo ponderale, cefalea, tachicardia e incremento della pressione arteriosa. Tali effetti sono comunque generalmente lievi, transitori, reversibili e facilmente monitorabili dallo specialista.

Nonostante la sua comprovata efficacia, nel 2007 la Commissione Europea ha richiesto alla Commissione per i Prodotti Medicinali per Uso Umano (CHMP) maggiori informazioni sulla sicurezza del metilfenidato nel lungo termine. A gennaio 2009 il CHMP ha concluso che i benefici legati all'assunzione di tale farmaco sono superiori ai rischi, ma sono stati richiesti più dati per definire gli esiti di una terapia a lungo termine (> 1-5 anni) e in conseguenza di ciò, nel 2012, la Commissione Euorpea ha finanziato un grosso progetto di ricerca sulla sicurezza nel lungo termine del metilfenidato: *Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects* (ADDUCE; *http://adhd-adduce.org*). Il progetto è stato attualmente completato e a breve i risultati delle analisi saranno pubblicati. Tali risultati forniranno maggiori evidenze per la gestione clinica e la definizione di un'adeguata durata di terapia, i potenziali effetti avversi e *outcome* più specifici da monitorare.

LE DOMANDE DEI GENITORI E DEI PEDIATRI

1. Il metilfenidato è un sedativo?

Il metilfenidato è uno psicostimolante, per cui tutt'altro che sedativo. Migliorando la neurotrasmissione di dopamina e noradrenalina (i neurotrasmettitori che regolano le nostre capacità attentive), il farmaco aiuta il bambino a essere più concentrato nell'esecuzione dei compiti, trovandoli più piacevoli e meno noiosi. Il bambino avrà conseguentemente meno bisogno di muoversi (l'irrequietezza motoria è infatti frequentemente legata alla necessità di impegnare il tempo in qualche modo).

Se si dovesse notare che il bambino è "eccessivamente sedato" significa che sta sperimentando un effetto indesiderato.

In tal caso sarà necessario ridurre la posologia o sospendere la terapia. L'obiettivo è infatti garantire un miglior funzionamento globale senza interferire con il temperamento del bambino.

2. Il farmaco crea dipendenza?

Il farmaco può essere sospeso in qualsiasi momento (la domenica, nelle vacanze scolastiche ed estive), e questo dimostra che non crea alcuna dipendenza. Inoltre, alcune evidenze scientifiche suggeriscono un possibile effetto protettivo del farmaco rispetto all'uso di sostanze di abuso in età adolescenziale o adulta.

3. Per quanto tempo dovrà assumere la terapia?

In genere vengono formulati dei piani di trattamento annuali (da settembre a giugno in base all'anno scolastico) e, l'anno successivo, si rivaluta l'opportunità di proseguire o interrompere il trattamento, sulla base della risposta clinica e delle necessità del paziente.

4. A quale età è bene iniziare il trattamento?

Il metilfenidato è prescrivibile dai 6 anni di età. Le linee guida europee raccomandano un approccio multimodale, per gradi, che combina interventi psicosociali con terapie mediche. Il farmaco è prescrivibile previo piano terapeutico da parte dello specialista di un Centro di riferimento per l'ADHD, dai 6 sino ai 18 anni, nelle forme di ADHD di entità moderata o severa e laddove gli interventi psicoeducativi da soli siano risultati inefficaci.

5. Quali sono gli effetti avversi più comuni e i relativi protocolli di monitoraggio?

I più comuni effetti collaterali includono sonnolenza, nervosismo, inappetenza, cefalea, dolori addominali, tachicardia, variazioni della pressione arteriosa e della frequenza cardiaca. Effetti avversi meno comuni includono calo ponderale e ritardo della crescita nell'uso prolungato. Raramente sono stati osservati sintomi più severi quali sintomi psicotici o reazioni allergiche tali da richiedere la sospensione della terapia. La maggior parte degli effetti avversi sono comunque transitori, tollerabili e facilmente gestibili. Strategie per gestire gli eventi avversi includono uno stretto monitoraggio, aggiustamenti posologici, modifiche degli orari di somministrazione, cambio di formulazione o di farmaco e, meno frequentemente, l'aggiunta di una terapia specifica per trattare l'effetto collaterale.

Si raccomanda al pediatra il monitoraggio dei parametri auxologici e cardiovascolari, a distanza di una settimana, un mese, tre mesi e poi semestralmente dall'inizio della terapia, attraverso l'uso di curve standardizzate.

6. Quali sono le comorbidità psichiatriche e internistiche per le quali il trattamento con metilfenidato è controindicato?

Gli stimolanti sono controindicati in alcune condizioni cliniche, la maggior parte delle quali raramente osservabili durante l'infanzia: schizofrenia, depressione severa, ipertiroidismo, aritmia cardiaca, ipertensione da moderata a severa, angina, glaucoma, ipersensibilità individuale o concomitante uso di inibitori delle monoamino-ossidasi (IMAO). In accordo con lo specialista, è comunque possibile instaurare la terapia in situazioni cliniche stabilizzate.

7. Per quanto tempo è utile proseguire la terapia? Si può programmare una "terapia al bisogno"?

È utile proseguire la terapia finché il soggetto acquisisca adeguate capacità di gestione e programmazione personale, tali da consentirgli un soddisfacente funzionamento globale nei principali contesti di vita. Si può programmare una "terapia al bisogno" sulla base delle esigenze cliniche, per esempio introducendo le vacanze terapeutiche per la gestione degli effetti indesiderati o nel caso di un adolescente prevalentemente inattento che acconsenta ad assumere la terapia solo per lo svolgimento e l'esecuzione di attività strutturate cognitivamente impegnative.

INTERROGATIVI APERTI PER IL NEUROPSICHIATRA

8. È possibile prescrivere il metilfenidato a tardoadolescenti e giovani adulti?

I Centri di riferimento per l'ADHD possono prescrivere la terapia con metilfenidato in soggetti di qualsiasi età dai 6 anni ed entro i 18. Successivamente, i Centri di riferimento per l'adulto potranno garantire la prosecuzione della terapia ai soggetti che l'abbiano intrapresa prima dei 18 anni o eventualmente prescriverlo *off-label* in soggetti maggiorenni che abbiano ricevuto una diagnosi tardiva o non abbiano potuto usufruire della terapia farmacologica in età adolescenziale.

9. Quali sono i dati di sicurezza ed efficacia dei farmaci per l'ADHD nel lungo termine?

I dati della letteratura attualmente disponibili, inclusi i dati di follow-up a vent'anni dello studio cardine sul trattamento dell'ADHD *The Multimodal Treatment ADHD study* (MTA), confermano che i farmaci per l'ADHD sono sufficientemente sicuri anche nel lungo termine con un minimo impatto clinico sulla crescita (più accentuato nei primi 12 mesi sul peso e nei primi 24-30 mesi sull'altezza) e sul sistema cardiovascolare (lieve incremento della pressione arteriosa e della frequenza cardiaca senza danno d'organo). Non evidenti effetti sulla maturazione puberale. In termini di effetti psichiatrici, il metilfenidato risulterebbe addirittura protettivo rispetto all'uso di sostanze, alla depressione e all'ideazione suicidaria. Suggeribile invece procedere con cautela nel caso di tic, epilessia e disturbi del sonno.

CASO CLINICO 2

Gabriele, 17 anni, ha ricevuto diagnosi di ADHD e disturbo specifico dell'apprendimento all'età di 9 anni. Al tempo effettuò un percorso riabilitativo mirato di circa 18 mesi sulle difficoltà di apprendimento e un intervento comportamentale di *child training* associato a un *parent training* con lie-

MESSAGGI CHIAVE

❏ Il metilfenidato è un farmaco sufficientemente sicuro e gli effetti indesiderati sono in genere temporanei, reversibili e facilmente gestibili. In caso di insorgenza di eventi avversi, nella maggior parte dei casi, non è necessario sospendere la terapia e i pazienti possono continuare a beneficiare del trattamento.

❏ Il trattamento farmacologico deve basarsi su un approccio personalizzato che tenga conto del soggetto nella sua interezza, compresi la qualità di vita e gli aspetti relazionali e familiari.

❏ Il futuro nella ricerca per l'ADHD deve comprendere studi di efficacia e sicurezza nel lungo termine che includano disegni di studio differenti dai classici *trial* clinici randomizzati quali: studi randomizzati con disegni di sospensione del trattamento, studi di popolazione con metodologie di controllo individuale o studi longitudinali di follow-up.

vi benefici. Durante la frequenza della scuola secondaria di primo grado, gli insegnanti riferivano persistenza di marcate difficoltà attentive associate a scarsa motivazione verso le attività scolastiche e lo svolgimento dei compiti a casa con significativo impatto sul suo rendimento nonostante le comprovate abilità cognitive. I genitori, inviati dal pediatra in consulenza presso il Centro di riferimento per l'ADHD, rifiutavano il trattamento farmacologico, preferendo intensificare gli interventi psicoeducativi privatamente attraverso il supporto allo studio quotidiano con un pedagogista e una psicoterapia a indirizzo cognitivo-comportamentale settimanale.

All'età di 17 anni giunge nuovamente in consulenza presso il Centro di riferimento per l'ADHD, su sua richiesta, lamentando marcate difficoltà attentive e l'impossibilità a sostenere i ritmi scolastici del liceo scientifico che ha deciso di frequentare con buona progettualità per il futuro. Nonostante il ragazzo riferisca uso frequente di cannabinoidi (in taluni periodi anche quotidiano), in associazione all'intervento di supporto psicologico, si inizia terapia con metilfenidato a rilascio modificato *(Equasym)* sino a 90 mg/die (60 mg ore 8 + 30 mg ore 14) con discreto beneficio sui sintomi inattentivi. Dopo alcuni mesi, per il persistere dell'uso frequente di sostanze di abuso e una moderata labilità del tono dell'umore, viene associata terapia con acido valproico (*Depakin chrono* 500 mg ore 8 + 500 mg ore 20). Nel giro di pochi mesi viene riportato un sostanziale miglioramento del quadro clinico con buon funzionamento scolastico e familiare del ragazzo.

Al compimento del diciottesimo anno Gabriele viene preso in carico presso il Centro di riferimento per l'ADHD nell'adulto dove tuttora è seguito e prosegue il monitoraggio clinico e farmacologico. Si è diplomato e si è iscritto all'Università.

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
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(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016, N. 1077 del 02/02/2017 N. 1938 del 15/02/2019) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
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