NEWSLETTER

Il prof. Alessandro Zuddas con determinazione, professionalità, dedizione e simpatia ha definito e insegnato percorsi di cura basati su evidenze per una migliore salute mentale di bambini e adolescenti e delle loro famiglie. Il lavoro scientifico, sociale e politico svolto da Alessandro per garantire anche in Italia un'appropriata diagnosi e terapia per l'ADHD da anni guida la pratica di colleghi, in particolare giovani, ed è punto di repere e fiducia di pazienti e famigliari. Formatosi nella scuola cagliaritana di farmacologia, fruttuosa fucina internazionale, Alessandro ha contribuito con costante profitto a determinare l'efficacia e la sicurezza dei trattamenti farmacologici con studi collaborativi nazionali e internazionali. Formatore e cittadino impegnato, un amico per molti... sarà una invisibile presenza

ISTITUTO DI RICERCHE
FARMACOLOGICHE
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INDICE:

BIBLIOGRAFIA ADHD GIUGNO 2022

Acta Paediatr. 2022 Aug;111:1546-55.

ASSOCIATIONS OF PRETERM BIRTH, SMALL-FOR-GESTATIONAL AGE, PREECLAMPSIA AND PLACENTAL ABRUPTION WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE OFFSPRING: NATIONWIDE COHORT AND SIBLING-CONTROLLED STUDIES.

Beer RJ, Cnattingius S, Susser ES, et al.

AIM: The aim of this study was to investigate preterm birth, small-for-gestational age (SGA), preeclampsia and placental abruption in relation to attention-deficit/hyperactivity disorder (ADHD) in offspring.

METHODS: We conducted a population-based cohort study among non-malformed live-born singleton children in Sweden born during 2002-2014. Using national registries with recorded information, we followed 1,212,201 children for an ADHD diagnosis from 3 to 15 years. We compared ADHD rates between exposure categories using adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional hazards models. We also conducted sibling-controlled analyses among 751,464 full siblings.

RESULTS: There were 27,665 ADHD diagnoses in the cohort. Compared with term birth (37 weeks), adjusted HR (95% CI) for ADHD increased with decreasing gestational age: 1.18 (1.11, 1.25), 1.61 (1.37, 1.89) and 2.79 (2.23, 3.49) for 32-36 weeks, 28-31 weeks and 22-27 weeks. Both spontaneous and medically indicated preterm birth were associated with ADHD. SGA was related to 1.62 (1.49, 1.77) times higher ADHD incidence. Preeclampsia, but not placental abruption, was associated with ADHD. Sibling-controlled analyses showed similar results. Preterm birth did not fully explain the associations of SGA or preeclampsia with ADHD.

CONCLUSION: Preterm birth, SGA and preeclampsia are related to ADHD incidence in offspring

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

Acta Paediatr. 2022 Aug;111:1546-55.

ASSOCIATIONS OF PRETERM BIRTH, SMALL-FOR-GESTATIONAL AGE, PREECLAMPSIA AND PLACENTAL ABRUPTION WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE OFFSPRING: NATIONWIDE COHORT AND SIBLING-CONTROLLED STUDIES.

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CONCLUSION: Preterm birth, SGA and preeclampsia are related to ADHD incidence in offspring

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Am J Audiol. 2022 Jun;31:470-86.

A REVIEW OF THE EFFECT OF CLASSROOM SOUND-FIELD AMPLIFICATION ON CHILDREN IN PRIMARY SCHOOL.

Mealings K.

PURPOSE: Being able to hear the teacher clearly is an important factor for children's learning. However, classrooms often have suboptimal listening conditions. Sound-field amplification systems (SFAS) can help improve classroom listening conditions by increasing the level of the teacher's speech compared to the background noise throughout the classroom. The aim of this review article was to review the effect of SFAS on children in primary school.

METHOD: A comprehensive search of four online databases (ERIC, PubMed, Scopus, and Web of Science) was conducted. The search terms were classroom sound-field amplification and classroom amplified distribution system. Twenty-one articles were deemed relevant for the review plus an additional six from their references.

RESULTS: Most articles were published between 1996 and 2015. Only one article was published since 2016. A range of child populations were studied including typically developing children and children with difficulties and disabilities such as hearing loss, developmental language disorders, attention-deficit/hyperactivity disorder, emotional and behavior disorders, Down syndrome, and developmental disabilities. There were several different measures that were used to evaluate the effectiveness of SFAS including speech perception assessments, language assessments, academic and comprehension assessments, classroom observations, interviews, and questionnaires. Improvements with SFAS were found for speech perception, listening comprehension and auditory analysis, language outcomes, academic outcomes, and behavior.

CONCLUSION: SFAS can benefit children's listening and learning; however, the child's background, classroom reverberation time (limit to < 1 s), and layout and type of learning activities, especially in modern classrooms, need to be taken into consideration

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Ann Gen Psychiatry. 2022;21.

FINDING THE SWEET SPOT: SHARING THE DECISION-MAKING IN ADHD TREATMENT SELECTION.

Tan D, King TR.

Background: Stimulants are often prescribed as first-line therapy for attention-deficit/hyperactivity disorder. Currently, there are many therapeutic options available for clinicians and families to consider when making the decision to use a medication. In practice, selection of a stimulant medication for ADHD is highly

personalized and can be narrowed down to two major factors: finding the optimal duration of the medication effect, and then estimating a starting dose and subsequently fine-tuning the medication to the optimal dosage of the medication. With the possibility of titrating to an optimal stimulant dosage within one prescription of a liquid stimulant, prescribers can recruit the parent/caregiver to actively participate in managing the transition to medication, allowing for greater ownership and a sense of shared control over the process.
Case presentation: The short case series offers a communication method by which clinicians can apply the principles of shared decision-making in helping the parent or caregiver of a newly diagnosed patient with ADHD make informed decisions about medication selection, and to obtain a greater sense of comfort with the new medication regimen.
Conclusions: Much has been published on the importance of clinicians and their patients fostering an environment of clear and unrestricted information-sharing. This short case series illustrates the effectiveness of this approach. Once parents are comfortable with the decision to start drug treatment for ADHD, it is incumbent upon the healthcare provider to ensure that an open channel of communication is maintained, and that parent/caregivers are encouraged to raise concerns as soon as possible

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Appl Neuropsychol Child. 2022 Jul;11:280-90.
ADHD SUBTYPES: DO THEY HOLD BEYOND CORE SYMPTOMS? A MULTILEVEL TESTING OF AN ADDITIVE MODEL.
Rostami M, Khosrowabadi R, Albrecht B, et al.
Attention Deficit Hyperactivity Disorder (ADHD) is characterized as a behavioral syndrome with core symptoms of inattention and/or hyperactivity/impulsivity that constitute, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), predominantly Inattentive and Hyperactive-Impulsive and a combined (additive) presentation that fulfills both criteria. The question remains if the pathophysiological background of both factors is also separate at levels of investigation beyond core symptoms. This would allow a clearer understanding and a more focused treatment approach even with tools derived from these levels. Hence, we assumed that an implicit additive diagnostic model also holds at the levels of associated psychopathology, neuropsychological performance and brain oscillations. We investigated this hypothesis using data of 61 boys (7-12years old) with ADHD and 43 typically developing children. There were no significant differences in age and IQ between groups. Children were examined with Child Behavior Checklist (CBCL), the Integrated Visual and Auditory Test (IVA), and brain oscillations during eyes closed resting state. Inattention characteristics were associated with more pronounced internalizing problems, lower attention, and vigilance during IVA performance and at the Electroencephalography level with elevated Theta and diminished Beta power during eyes closed rest. In contrast, hyperactivity/impulsivity characteristics led to general psychopathology problems and showed at the neuropsychological level faster response speed and deficits in cognitive control and performance consistency, but were on the electroencephalography level without any deficits in EEG power. Considering differences in behavioral, neuropsychology, and electroencephalography levels in each subtype, separate clinical approaches should be recommended for them and an additive model for their combination

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Appl Neuropsychol Child. 2022 Jul;11:291-96.
ROLE OF INFLAMMATION IN CHILDHOOD EPILEPSY AND ADHD COMORBIDITY.
Elhady M, Elattar RS, Elaidy AMA, et al.
Epilepsy is a heterogeneous disorder that is not limited to experiencing seizures but also includes multiple neuropsychiatric squeal (i.e. attention-deficit/hyperactivity disorder (ADHD), depression and anxiety) that adversely impact a child quality of life. However, the underlying mechanism linking both disorders is not yet thoroughly explored. Our objective was to assess pro-inflammatory cytokines levels in children with seizure controlled epilepsy and explore the association between pro-inflammatory cytokines and the co-occurrence of ADHD in such children. A cross-sectional study included 50 children with controlled epilepsy for at least one year, in addition to 30 neurotypical children as controls. All children were assessed by the Conner parent scale for ADHD. Serum interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were measured and correlated to clinical data. In the present study, 23 out of 50 children with epilepsy also had ADHD (46%). Children with ADHD have been found to have a significantly lower age of onset, longer duration of epilepsy,

and a higher serum level of IL-6 and TNF-α than those without ADHD. The Conner's parent rating scale overall total score yielded significant negative correlations with the age of onset of epilepsy and a significant positive correlation with the duration of epilepsy and pro-inflammatory cytokine levels. In addition to active seizures, the presence of elevated circulating inflammation markers may be associated with increased frequency of ADHD in children with epilepsy aged 6-14 years

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Appl Neuropsychol Child. 2022 Jul;11:350-63.

PEDIATRIC BIPOLAR DISORDER: EXECUTIVE, LINGUISTIC, MNEMONIC, AND COGNITIVE EFFICIENCY MAPPING.

Viapiana VF, Rodrigues ACRB, Peters R, et al.

Neuropsychological assessment can enrich our understanding of Pediatric Bipolar Disorder (PB). This study aimed to: (1) analyze the occurrence of neuropsychological frequency of deficits and difficulties in children with PB; (2) verify whether there is a performance difference between PB type I (PB-I) and PB type II (PB-II)/unspecified, and between PB with and without ADHD; and (3) verify the cognitive efficiency differences within the PB group and control groups, and among clinical subgroups. Participants in the study were 16 children diagnosed with PB and 40 children with typical development (6-12years old). The results indicated a high frequency of deficits/difficulties in verbal fluency, cognitive efficiency in performing basic abilities, inhibitory control, cognitive flexibility, and working memory, with emphasis on verbal and executive losses. There were indications that type PB-I and comorbidity with ADHD negatively impact a child's neuropsychological development. The clinical group showed more cognitive efficiency losses compared with the control group, and greater losses were observed in PB-I and in PB with ADHD. The role of neuropsychological evaluation in multidomain and nonlinear statistical analysis is critical to gaining an understanding of the clinical and cognitive heterogeneity of PB

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Appl Neuropsychol Child. 2022 Jul;11:383-90.

IMPACT OF PLACEBO-RELATED INSTRUCTION ON HEG BIOFEEDBACK OUTCOMES IN CHILDREN WITH ADHD.

Skalski S.

Studies to date have not revealed any differences between biofeedback (BFB) methods vs. placebo treatment in reducing ADHD symptoms. The purpose of this randomized controlled study was to assess the impact of placebo expectations on gain in hemoencephalographic (HEG) BFB. The final cohort consisted of 33 children with ADHD aged 9-14. Individuals were assigned to one of two groups (with standard active training instruction vs. placebo-related instruction) and were subjected to five HEG BFB sessions. Children with standard instruction exhibited higher growth of regional cerebral blood oxygenation during the HEG BFB session as well as better results in cognitive tests (vigilance and visual search) at the end of the experiment compared to children with placebo-related instruction. The data obtained indicate the difficulty in designing studies assessing BFB efficacy. Placebo expectation may adversely affect HEG BFB outcomes in children with ADHD

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Appl Neuropsychol Child. 2022 Jul;11:561-66.

NEUROPSYCHOLOGICAL PROFILES OF TWO PATIENTS WITH DIFFERING SCN8A-PATHOGENIC VARIANTS.

Medlin LC, Bello-Espinosa L, Macallister WS.

The impact of gene-related early infancy onset epilepsies in cognitive development can be potentially devastating. Here we report two cases of SCN8A-related epilepsy that highlight the neuropsychological heterogeneity seen with differing de-novo pathogenic variants. Case 1 is a 6-year-old right-handed girl who presented with SCN8A-developmental and epileptic encephalopathy (SCN8A-DEE) and a missense pathogenic variant (c.802A>C), not previously documented in the literature. Her history includes speech and motor delay, with focal motor seizures starting at 4-months. Early EEG showed bilateral centroparietal epileptiform discharges. She shows motor and language delays and prominent motor tics. Testing documented Intellectual Disability (ID) (Mild) with widespread neuropsychological deficits (i.e., academics, attention/executive functions, memory, visual-spatial skills, fine motor, language). Case 2 is an 8-year-old right-handed girl who presented with SCN8A-related epilepsy with c.5630A>G pathogenic variant with

seizure onset at 5-months. Her initial EEG showed right occipital spikes. She shows low average intellect and average academics, but evaluation documented attention deficits, fine motor delays, and behavioral issues in addition to tics; she was diagnosed with Attention-Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, Obsessive Compulsive Disorder, and Tourette's. These cases expand limited knowledge regarding neuropsychological functioning of children with SCN8A-related epilepsy with unique de-novo pathogenic variants. While SCN8A-DEE is clearly associated with ID, other pathogenic variants may show better preserved intellect, despite other neuropsychological and behavioral concerns

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Appl Neuropsychol Child. 2022 Jul;11:553-60.

HIPPOTHERAPY IN NEURODEVELOPMENTAL DISORDERS: A NARRATIVE REVIEW FOCUSING ON COGNITIVE AND BEHAVIORAL OUTCOMES.

Maresca G, Portaro S, Naro A, et al.

Hippotherapy (HT) is a rehabilitative tool inducing psychological and motor improvements using human-horse interaction. HT provides sensory stimulation to the rider through the rhythmic and repetitive movements of the horse, facilitating communication between patients and healthcare professionals, favoring the establishment of a therapeutic alliance. The purpose of this review is to evaluate the effects of HT treatment on cognitive-behavioral processes in neurodevelopmental disorders. We screened studies published between 2002 and 2020 on PubMed, Scopus, Cochrane, and Web of Sciences databases. The search combined the following terms: "hippotherapy"; "horseback riding"; "equine-assisted therapy"; "developmental disorder"; "autism spectrum disorder"; "dyspraxia"; "infantile cerebral palsy"; and "attention-deficit/hyperactivity disorder". This review shows that HT can be a valuable tool for the treatment of developmental disorders. The psychological, cognitive and relational areas could benefit from the animal-child interaction to promote child autonomy, self-esteem, self-efficacy and openness to others. Physical, motor and psychosocial benefits were found in adolescents with anxiety and/or depression disorders, in autism spectrum disorders, dyspraxia, as well as in infantile cerebral palsy and attention deficit hyperactivity disorder. HT could be considered an alternative therapeutic tool thanks to the relationship between patient-horse-instructor and to the sensory-motor and cognitive stimulation that enforce learning processes

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Appl Neuropsychol Child. 2022 Jul;11:220-25.

IMPAIRMENTS IN COMMUNICATION AND SOCIAL INTERACTION IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1: CHARACTERISTICS AND ROLE OF ADHD AND LANGUAGE DELAY.

Cohen R, Halevi A, Aharoni S, et al.

BACKGROUND: Neurofibromatosis type 1 (NF1) is a multisystem neurocutaneous disorder with increased risk of tumor formation and higher incidence of autism spectrum disorder (ASD) than the general population. The aim of the study was to assess the presence of ASD symptoms in young children with NF1 and to examine their potential association with attention deficit hyperactivity disorder (ADHD) and speech delay.

METHODS: The cohort included 30 patients with NF1 attending the multidisciplinary NF1 clinic of a tertiary pediatric medical center from September 2015 through September 2016. The parents/caregivers completed the Social Communication Questionnaire (SCQ) and the Vineland Adaptive Behavior Scales (VABS II).

RESULTS: Sixteen patients (53%) had a previous diagnosis of ADHD. There was a positive association between the presence of ADHD and a low score on the VABS II interpersonal relationships subscale of the Socialization domain. Language delay, documented in 12 children (40%), also correlated with a low interpersonal relationships score.

CONCLUSIONS: ADHD appears to be more a marker than an actual independent risk factor of ASD in NF1. The early evaluation of children with NF1 for interpersonal communication problems and ASD, especially those with a speech delay or ADHD, will alert clinicians to initiate appropriate and timely treatment

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Appl Neuropsychol Child. 2022 Jul;11:240-52.

FEASIBILITY AND POTENTIAL BENEFITS OF AN ATTENTION AND EXECUTIVE FUNCTION INTERVENTION ON METACOGNITION IN A MIXED PEDIATRIC SAMPLE.

Macoun SJ, Pyne S, MacSween J, et al.

The term "metacognition" describes thinking about a cognitive phenomenon or, more simply put, thinking about thinking. Metacognition involves using knowledge about one's cognitive processes to change behavior, including monitoring and controlling cognition. Metacognition is vital for learning and is often more difficult for children with neurodevelopmental concerns (e.g. Attention Deficit Hyperactivity Disorder [ADHD], Fetal Alcohol Spectrum Disorder [FASD], Autism Spectrum Disorders [ASD]), possibly due to underlying deficits in attention and executive functioning (EF). The present study evaluated a 6- to 8-week cognitive intervention aimed at improving attention and EF and children's metacognitive abilities. Participants included a mixed sample of 50 children ages 6-12years presenting with attention and/or EF deficits. Children within the active intervention group completed a game-based attention/EF intervention called Caribbean Quest (CQ), which combines process-specific and compensatory approaches to remediate attention and EF. Educational Assistants (EAs) supported children during gameplay by teaching explicit metacognitive strategies. Pre/post assessments included measures of attention and working memory (WM), metacognitive awareness (child, parent, and EA questionnaires), and metacognitive regulation (metacognitive monitoring and control). Results indicated post-intervention gains in WM, metacognitive awareness, and metacognitive regulation (self-monitoring and metacognitive control). These results provide preliminary support for CQ as potentially beneficial in improving aspects of EF and metacognition in children

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Autism Res. 2022 Jul;15:1261-73.

BEYOND GROUP DIFFERENCES: EXPLORING THE PRELIMINARY SIGNALS OF TARGET ENGAGEMENT OF AN EXECUTIVE FUNCTION TRAINING FOR AUTISTIC CHILDREN.

Edmunds SR, MacNaughton GA, Rueda MR, et al.

Understanding both for whom and how interventions work is a crucial next step in providing personalized care to children with autism spectrum disorder (ASD). Autistic children present with heterogeneity both within core ASD criteria and with respect to co-occurring mental health challenges, which may affect their ability to benefit from intervention. In a secondary data analysis of a randomized control trial evaluating an executive function (EF) training with 70 7- to 11-year-old autistic children, we explored: (1) whether co-occurring attention-deficit/hyperactivity disorder (ADHD) features or anxiety features at baseline moderated the extent to which children benefited from the EF training. In other words, we asked, "For whom is training effective?" We also explored: (2) the extent to which changes in a brain-based measure of target engagement predicted the clinical outcomes of the EF training. This is a step towards asking, "How is training effective?" We found that EF training improved behavioral inhibition only for children with clinically significant co-occurring ADHD features. Anxiety features, while prevalent, did not moderate EF training efficacy. Finally, for the EF training group only, there was a significant correlation between pre-to-post change in an EEG-based measure of target engagement, N2 incongruent amplitude during a flanker task, and change in repetitive behaviors, a behavioral outcome that was reported in the parent RCT to have improved with training compared to waitlist control. This study provides preliminary evidence that EF training may differentially affect subgroups of autistic children and that changes at the neural level may precede changes in behavior. LAY SUMMARY: Understanding both for whom and how interventions work will help us provide personalized care to children with autism spectrum disorder (ASD). Autistic children present with many different strengths and challenges. Co-occurring mental health challenges may affect how much autistic children benefit from intervention. We analyzed secondary data from a rigorously designed pilot intervention study, a randomized control trial (RCT), that enrolled

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Behav Sleep Med. 2022 Jul;20:429-41.

THE ASSOCIATION BETWEEN SLEEP PROBLEMS AND NEUROPSYCHOLOGICAL DEFICITS IN MEDICATION-NAÏVE CHILDREN WITH ADHD.

Lambek R, Thomsen PH, Sonuga-Barke EJS, et al.

BACKGROUND: Children with ADHD are reported to have sleep problems and neuropsychological deficits, but studies examining a potential association between the two are scarce and the use of varying methodology can complicate conclusions.

PARTICIPANTS: A clinical sample of 59 medication-naïve children with ADHD between the ages of 6 and 14 years (71% male).

METHODS: Children underwent polysomnography and multiple sleep latency test, and parent rated sleep habits on the Children's Sleep Habits Questionnaire. Children also completed an extensive neuropsychological battery of executive function and delay aversion tasks, and parents and teachers rated executive function behavior on the Behavior Rating Inventory of Executive Function. Linear regression analyses were conducted with each of the neuropsychological outcomes included as the outcome variable and the sleep parameters as the predictor variables.

RESULTS: The correlations between sleep and neuropsychological outcomes were generally modest, but some sleep parameters (primarily sleep stages and sleep latencies) were associated with objectively and subjectively measured executive function and delay aversion.

CONCLUSIONS: Using objective and subjective gold standard assessment procedures this study supports a (modest) association between sleep and neuropsychological function in children with ADHD

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Behav Anal Pract. 2022 Jun;15:454-65.

USING FIDGET SPINNERS TO IMPROVE ON-TASK CLASSROOM BEHAVIOR FOR STUDENTS WITH ADHD.

Aspiranti KB, Hulac DM.

Using fidget toys is one way to allow students with attention-deficit/hyperactivity disorder (ADHD) to move while completing academic assignments in the classroom. This study investigated the effect of fidget spinners on the on-task behavior of three second-grade students with ADHD. Before beginning treatment, the rules of use were briefly explained and demonstrated to students by the researchers; students were then provided with fidget spinners during treatment sessions in language arts class. A multiple-baseline design across students was used to determine whether each student had higher levels of on-task behavior when using the fidget spinner. Momentary time sampling was used to record on-task behavior; visual analysis of time-series graphs showed large immediate and sustained increases in on-task behavior during fidget spinner use. Implications for implementing a fidget spinner intervention and suggestions for future research are discussed

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2022;7:415-23.

LIMBIC AND EXECUTIVE MESO- AND NIGROSTRIATAL TRACTS PREDICT IMPULSIVITY DIFFERENCES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Elliott BL, D'Ardenne K, Mukherjee P, et al.

Background: Impulsivity is a defining characteristic of attention-deficit/hyperactivity disorder (ADHD), which has been associated with substance use disorders, higher accident rates, and lower educational and occupational outcomes. The meso- and nigrostriatal pathways of the dopamine system are hypothesized to be functionally heterogeneous, supporting diverse cognitive functions and impairments, including those associated with ADHD. We tested whether human midbrain pathways (where dopaminergic cell bodies originate) between the substantia nigra (SN) and ventral tegmental area (VTA) and the striatum differed between participants with ADHD and typically developing adolescent and young adult participants. We also assessed whether pathway connectivity predicted impulsivity regardless of diagnosis.

Methods: Diffusion tensor imaging data were used to predict impulsivity (parent and self-report ratings, task-based behavioral measures) from participants with ADHD and typically developing adolescent and young adult participants (n = 155; 86 male, 69 female). Using probabilistic tractography, we mapped these pathways and divided the tracts into limbic, executive, and sensorimotor based on frontostriatal connectivity. ADHD and typically developing participants differed on all behavioral measures of impulsivity. We used correlation

and machine learning analyses to test for a relationship between tract probabilities and impulsivity regardless of diagnosis.
Results: Participants with ADHD had stronger structural connectivity between SN/VTA regions and the limbic striatum, weaker connectivity with the executive striatum, and no significant differences in sensorimotor tracts. Increased tract integrity between the limbic striatal and SN/VTA regions predicted greater impulsivity, while increased integrity between executive striatal and SN/VTA regions predicted reduced impulsivity.
Conclusions: These findings support the theory that functional diversity in the dopamine system is an important consideration for understanding dysfunction in ADHD

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Biomarkers. 2022;27:230-39.

MICRORNA PROFILE AS POTENTIAL MOLECULAR SIGNATURE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Zhu P, Pan J, Cai QQ, et al.

Aims: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder of neurodevelopment in children. The diagnosis of ADHD mainly relies on the symptoms and some may be misdiagnosed due to age-based variation in behaviours. This study aimed to explore biomarkers that are greatly needed for the accurate diagnosis of ADHD.
Methods: Seven hundred and forty-two samples were retrospectively investigated in three independent cohorts, screening, training, and validation, for circulation microRNA measurement using microarray, Taqman polymerase chain reaction, and regression analysis.
Results: A panel of five miRNAs (miR-4516, miR-6090, miR-4763-3p, miR-4281, and miR-4466) were identified as ADHD independent risk factors that provided a high diagnostic accuracy and specificity of ADHD (AUC = 0.940 and 0.927 in the training and validation datasets, respectively). This panel of miRNAs differentiated ADHD well from control groups. After clinical improvement by treatment, the panel of miRNAs in patients and AUC changed significantly and were close to those in healthy controls. Importantly, the targets of the miRNAs identified were commonly enriched in receptor signalling pathways, ion channels, and synapse structures.
Conclusion: Our study identified a useful panel of miRNAs that have considerable clinical value in evaluating ADHD and provide important evidence for aberrant epigenetic regulation in ADHD

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Biomed J. 2022 Apr;45:265-70.

EFFECTS OF PHYSICAL EXERCISE ON CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chan YS, Jang JT, Ho CS.

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly neurodevelopmental disorders with a complex symptomatology in children, and frequently suffer from deficits in executive functions and motor abilities. Although medication-based treatments usually have a positive effect, possible side effects may result in a need for an adjunctive intervention. Present studies show positive effect of physical exercise on cognitive function. Therefore, the purpose of the current study is thoroughly examine the effects of physical exercise in children with ADHD. Preliminary evidence shows both acute and chronic physical exercise are beneficial to ADHD symptoms, executive function, and motor abilities. Benefits of acute exercise may gradually accumulate over time. Such benefits reflect the positive correlation between cognition and physical activity, and these benefits will also lead to changes in executive function after long-term training. Aerobic could induce to increase the neurotransmitter ie. serotonin, dopamine, brain-derived neurotrophic factor (BDNF) and brain blood flow. Perceptual motor and meditation could lead to neuroplasticity in nerve cells and synaptic connections; furthermore, strengthening the sensory-motor base contributes to the improvement of attention. An exercise program for children with ADHD include to moderate to high intensity interval training and cognitive tasks are suitable. The preliminary state of the evidence supports physical exercise as an adjunctive treatment for ADHD at this time

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Biomed J. 2022 Apr;45:240-49.

TOURETTE DISORDER AND SLEEP.

Blaty JL, DelRosso LM.

Healthy sleep is of utmost importance for growth, development, and overall health. Strong evidence shows that sleep is affected negatively in patients and particularly children with Tourette Disorder (TD). There is also a frequent association of TD with Attention Deficit Hyperactivity Disorder (ADHD) which alone has negative effects on sleep and cumulatively worsens the associated sleep findings. The most consistent polysomnographic findings in patients with TD is decreased total sleep time, lower sleep efficiency and an elevated arousal index. Polysomnography studies have confirmed the presence of movements and persistence of tics during both Rapid Eye Movement (REM) and NREM sleep [1]. In general Patients with TD are found to have an increased incidence of sleep onset and sleep maintenance insomnia. Some studies have shown increased incidence of parasomnias (including sleepwalking, sleep talking and night terrors), but this may be confounded by the increased underlying sleep disruptions seen in TD. The hypersomnolence found in patients with TD is also suggested to be secondary to the underlying TD sleep disruption. There is not a significant association with sleep disordered breathing or circadian rhythm disorders and TD. Treatment of underlying TD is important for the improvement of sleep related TD manifestations and is outlined in this review

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BMC Psychiatry. 2022 Jun;22.

COGNITIVE BEHAVIOURAL GROUP THERAPY AS ADDITION TO PSYCHOEDUCATION AND PHARMACOLOGICAL TREATMENT FOR ADOLESCENTS WITH ADHD SYMPTOMS AND RELATED IMPAIRMENTS: A RANDOMISED CONTROLLED TRIAL.

Haugan ALJ, Sund AM, Young S, et al.

Background: Cognitive behavioural therapy (CBT) is recommended for attention-deficit/hyperactivity-disorder (ADHD) in adolescents. However, all CBTs are not created equal, and the guidelines do not specify which CBT interventions are the most effective for this patient group. This study examines the efficacy of a group CBT without parent involvement as follow-up treatment compared to no additional CBT in adolescents with persistent and impairing ADHD symptoms after a short psychoeducational intervention and medical treatment.

Methods: The authors conducted a two-arm parallel randomized controlled trial in two child and adolescent mental health outpatient clinics in Norway. One hundred patients aged 14–18 years with a diagnosis of ADHD (66%) or subthreshold ADHD (34%) were randomized to either a 12-week group CBT program (N = 50) or a non-CBT control condition (N = 50). Assessments were made at admission to the clinic, two weeks before and two weeks after treatment. The primary outcomes were parent-, teacher- and self-ratings of ADHD symptoms (ADHD Rating Scale-IV), and the secondary outcomes were ratings of ADHD symptom severity, executive function, functional impairment, and emotional problems. Evaluators blinded to group allocation rated ADHD symptom severity with the Clinical Global Impression Scale for Severity (CGI-S) at baseline and post-treatment.

Results: Analyses using mixed-effects models showed no difference between the treatment arms from baseline to post treatment in primary and secondary outcomes.

Conclusions: Contrary to our hypothesis, we found no incremental treatment effect on the part of a group CBT as follow-up to psychoeducation and pharmacological treatment on ADHD symptoms and accompanying impairments. Limitations with the CBT was the large number and low dosage of treatment components, causing restricted time for practice. Unlike evidence-based, individualized targeted CBTs with parent involvement, a group CBT directed solely at the adolescents with no parent involvement does not appear effective for treating ADHD

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BMC Psychiatry. 2022 Jun;22:415.

A WEARABLE DIAGNOSTIC ASSESSMENT SYSTEM VS. SNAP-IV FOR THE AUXILIARY DIAGNOSIS OF ADHD: A DIAGNOSTIC TEST.

Luo J, Huang H, Wang S, et al.

OBJECTIVE: We design a diagnostic test to evaluate the effectiveness and accuracy of A non-intrusive Wearable Diagnostic Assessment System versus SNAP-IV for auxiliary diagnosis of children with ADHD.

METHODS: This study included 55 children aged 6-16 years who were clinically diagnosed with ADHD by DSM-5, and 55 healthy children (typically developing). Each subject completes 10 tasks on the WeDA system (Wearable Diagnostic Assessment System) and Parents of each subject complete the SNAP-IV scale. We will calculate the validity indexes, including sensitivity, specificity, Youden's index, likelihood ratio, and other indexes including predictive value, diagnostic odds ratio, diagnostic accuracy and area under the curve [AUC] to assess the effectiveness of the WeDA system as well as the SNAP-IV.

RESULTS: The sensitivity (94.55% vs. 76.36%) and the specificity (98.18% vs. 80.36%) of the WeDA system were significantly higher than the SNAP-IV. The AUC of the WeDA system (0.964) was higher than the SNAP-IV (0.907). There is non-statistically significant difference between groups (p=0.068), and both of them have high diagnostic accuracy. In addition, the diagnostic efficacy of the WeDA system was higher than that of SNAP-IV in terms of the Youden index, diagnostic accuracy, likelihood ratio, diagnostic odds ratio and predictive value.

CONCLUSION: The advantages of the WeDA system in terms of diagnostic objectivity, scientific design and ease of operation make it a promising system for widespread use in clinical practice

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BMC Psychiatry. 2022 Jun;22:401.

QUESTIONNAIRE-BASED COMPUTATIONAL SCREENING OF ADULT ADHD.

Trognon A, Richard M.

BACKGROUND: ADHD is classically seen as a childhood disease, although it persists in one out of two cases in adults. The diagnosis is based on a long and multidisciplinary process, involving different health professionals, leading to an under-diagnosis of adult ADHD individuals. We therefore present a psychometric screening scale for the identification of adult ADHD which could be used both in clinical and experimental settings.

METHOD: We designed the scale from the DSM-5 and administered it to n=110 control individuals and n=110 ADHD individuals. The number of items was reduced using multiple regression procedures. We then performed factorial analyses and a machine learning assessment of the predictive power of the scale in comparison with other clinical scales measuring common ADHD comorbidities.

RESULTS: Internal consistency coefficients were calculated satisfactorily for TRAQ10, with Cronbach's alpha measured at .9. The 2-factor model tested was confirmed, a high correlation between the items and their belonging factor. Finally, a machine-learning analysis showed that classification algorithms could identify subjects' group membership with high accuracy, statistically superior to the performances obtained using comorbidity scales.

CONCLUSIONS: The scale showed sufficient performance for its use in clinical and experimental settings for hypothesis testing or screening purpose, although its generalizability is limited by the age and gender biases present in the data analyzed

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BMJ Open. 2022 Jun;12:e055385.

DIGITAL COGNITIVE TRAINING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A STUDY PROTOCOL OF A RANDOMISED CONTROLLED TRIAL.

Richmond S, Kirk H, Gaunson T, et al.

INTRODUCTION: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders and is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with daily functioning. Children with ADHD are developmentally vulnerable, with the disorder linked to emotional regulation difficulties, behavioural disturbances, as well as academic challenges. Emerging evidence suggests that children with ADHD may benefit from cognitive training interventions, including those

focused on attention. This study aims to assess the immediate and long-term efficacy of an attention training intervention in children with ADHD.
METHODS AND ANALYSIS: This study is a preregistered, parallel, double blind, randomised controlled trial. Participants will comprise 104 children with a diagnosis of ADHD aged 5-8 years 11 months. Participants will be randomly allocated to either an adaptive, digital game-based (1) attention training programme (intervention) or (2) a numeracy programme (control). Both programmes will be delivered on a touchscreen tablet, and children will complete five 20min sessions per week for a 5-week period at home (25 sessions in total). Assessments of the primary outcome (ie, attention and inhibitory control) and secondary outcomes (ie, selective attention, interference control, sustained attention, inhibition, behavioural attention, impairment in everyday functioning, working memory and executive functioning) will occur at preintervention, immediately postintervention and at 3-month follow-up. Multivariate linear regression will be employed to examine primary and secondary outcomes. The data analyst will be blinded to group membership.
ETHICS AND DISSEMINATION: Ethics approval has been obtained from the Monash University HREC (20495). Results will be disseminated through peer-reviewed journals, conference presentations, media outlets, the internet and various community/stakeholder activities.
TRIAL REGISTRATION NUMBER: ACTRN12620000964910, UTN U1111-1250-2620

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Brain Sciences. 2022;12.
THE RELATIONSHIP BETWEEN MOTOR COORDINATION ABILITY, COGNITIVE ABILITY, AND ACADEMIC ACHIEVEMENT IN JAPANESE CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.
Higashionna T, Iwanaga R, Tokunaga A, et al.
Motor coordination abilities are related to cognitive abilities and academic achievement in children with neurodevelopmental disorders. However, the similarities and differences of these relationships in children with autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (AD/HD) have not been explored. The purpose of this study was to investigate the relationship between motor coordination abilities, cognitive abilities, and academic achievement in Japanese children with ASD and AD/HD. Participants included 20 children with ASD, 20 children with AD/HD, and 20 typically developing children, matched for age and gender. Their motor coordination abilities were assessed with the Movement Assessment Battery for Children-2 (MABC-2). Furthermore, cognitive ability and academic achievement were assessed with the Kauffman Assessment Battery for Children-II (K-ABCII). Results demonstrated that the MABC-2 Total score significantly correlated with the K-ABCII Simultaneous processing, Planning, Total cognitive ability, Writing and Arithmetic scores in children with ASD. However, in children with AD/HD, there was no significant correlation between MABC-2 and K-ABCII subscale scores. The results of this study indicated that the relationship between motor coordination ability, cognitive ability, and academic achievement differs between ASD and AD/HD. This difference might indicate the non-similarity of neurological characteristics and encourage consideration for an approach that accommodates the features of neurodevelopmental disorders in children

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Brain Struct Funct. 2022 Jul;227:1963-79.
CORTICO-AMYGDALAR CONNECTIVITY AND EXTERNALIZING/INTERNALIZING BEHAVIOR IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.
Nakua H, Hawco C, Forde NJ, et al.
BACKGROUND: Externalizing and internalizing behaviors contribute to clinical impairment in children with neurodevelopmental disorders (NDDs). Although associations between externalizing or internalizing behaviors and cortico-amygdalar connectivity have been found in clinical and non-clinical pediatric samples, no previous study has examined whether similar shared associations are present across children with different NDDs.
METHODS: Multi-modal neuroimaging and behavioral data from the Province of Ontario Neurodevelopmental Disorders (POND) Network were used. POND participants aged 6-18 years with a primary diagnosis of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD), as well as typically developing children (TDC) with T1-weighted,

resting-state fMRI or diffusion weighted imaging (DWI) and parent-report Child Behavioral Checklist (CBCL) data available, were analyzed (total n=346). Associations between externalizing or internalizing behavior and cortico-amygdalar structural and functional connectivity indices were examined using linear regressions, controlling for age, gender, and image-modality specific covariates. Behavior-by-diagnosis interaction effects were also examined.
RESULTS: No significant linear associations (or diagnosis-by-behavior interaction effects) were found between CBCL-measured externalizing or internalizing behaviors and any of the connectivity indices examined. Post-hoc bootstrapping analyses indicated stability and reliability of these null results.
CONCLUSIONS: The current study provides evidence towards an absence of a shared linear relationship between internalizing or externalizing behaviors and cortico-amygdalar connectivity properties across a transdiagnostic sample of children with different primary NDD diagnoses and TDC. Different methodological approaches, including incorporation of multi-dimensional behavioral data (e.g., task-based fMRI) or clustering approaches may be needed to clarify complex brain-behavior relationships relevant to externalizing/internalizing behaviors in heterogeneous clinical NDD populations

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Br J Clin Pharmacol. 2022.

THE ROLE OF PLACEBO RESPONSE IN THE EFFICACY OUTCOME ASSESSMENT IN VILOXAZINE EXTENDED-RELEASE PIVOTAL TRIALS IN PAEDIATRIC SUBJECTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Nasser A, Gomeni R, Wang Z, et al.

Aims: Four Phase 3 studies evaluated efficacy and safety of viloxazine extended-release in the treatment of attention-deficit/hyperactivity disorder (ADHD). The primary efficacy objective-change from baseline in ADHD Rating Scale-5 (ADHD-RS-5) Total score at end of study (EOS) was not met in one of the studies (812P304). A band-pass analysis was performed to evaluate the impact of placebo response on the results.
Methods: The distribution of placebo response at EOS of each trial was evaluated. The 2.5th and 97.5th percentiles of the distribution of ADHD-RS-5 Total score were used as boundaries for the band-pass analysis. An independent mixed model for repeated measures analysis was conducted for each trial using all eligible data (active and placebo) from the total and band-pass filtered populations.
Results: The 2.5th and 97.5th percentiles at EOS were 3.5 and 53.5, respectively. Application of the band-pass filter (filtering out all subjects [active, n-á= 305 (32.1%) and placebo, n-á= 134 (33.5%)] of clinical sites with placebo scores <3.5 or >53.5) revealed statistically significant improvement at the primary endpoint (600-mg/d viloxazine ER vs. placebo) in Study 812P304 (mean [confidence interval] = 4.9537 [0.5405ΓÇô9.3669]), previously masked by a high placebo response (mean [confidence interval] = 3.5756 [0.3332-7.4844]). The outcome of the analysis indicated that the impact of the band-pass adjustment is greater when placebo response is higher.
Conclusion: This analysis indicated that a higher placebo response in Study 812P304 confounded the assessment of treatment effect. Application of the band-pass methodology confirmed the positive results of the 3 prior studies and the signal detection confounder in the fourth study

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Bulletin of Pharmaceutical Sciences Assiut. 2022;45:281-88.

EFFICACY OF ARIPIPRAZOLE AND RISPERIDONE IN TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A DOUBLE-BLIND CLINICAL TRIAL STUDY.

Dreakhshanpour PF, Deylamsalehi A, Moghaddas SSJ, et al.

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children. Poor academic readiness for school entry, fine motor skills, and social impairment are more common in preschoolers than healthy controls. Since dopaminergic system dysfunction is connected with numerous neuropsychological diseases, including ADHD, antipsychotic drugs are used for the treatment of ADHD. Considering the importance of ADHD treatment in preschoolers and the fact that psychostimulant drugs are less effective in preschoolers and have more adverse effects, this study is conducted to compare the safety and efficacy of risperidone and aripiprazole in the treatment of ADHD. Fifty-five 3-6-year-old children diagnosed with ADHD were randomized to a 12-week trial of treatment with risperidone or aripiprazole1. The assessment was performed by Parent ADHD-RS, Strengths and Difficulties Questionnaire (SDQ), Children's

Global Assessment Scale (CGAS) before treatment, and weeks 2, 4, 6, and 12 of treatment. The study showed that the ADHD-RS score of both groups was significantly reduced after starting the treatment. After the 12th week, the score of aripiprazole's group was significantly less than the score of risperidone's group (p-value = 0.019). In addition, the CGAS scores and the total SDQ score improved for both groups without any statistically significant difference between them. Both risperidone and aripiprazole are effective in the treatment of ADHD among preschool-aged children. Both drugs are well-tolerated, significantly reduce the ADHD-RS score and the total SDQ score and improve the CGAS score

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Child Adolesc Psychiatr Clin N Am. 2022 Jul;31:479-98.

UPDATES IN PHARMACOLOGIC STRATEGIES FOR EMOTIONAL DYSREGULATION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Baweja R, Waxmonsky JG.

Emotional dysregulation (ED) manifesting as irritability or aggression produces appreciable impairment in children with attention deficit hyperactivity disorder and a main reason why they present for treatment. Central nervous system (CNS) stimulants seem to be a safe and tolerable treatment of most youth with these presentations. Optimization of CNS stimulants dose in combination with psychosocial interventions led to reductions in ED. Randomized controlled trials support that addition of risperidone further reduces aggression when these treatments are not sufficient. There is evidence for the efficacy of divalproex, molindone and selective serotonin reuptake inhibitor improve these outcomes when used as adjunct to CNS stimulants

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Child Adolesc Psychiatr Clin N Am. 2022 Jul;31:531-51.

ADDRESSING THE TREATMENT AND SERVICE NEEDS OF YOUNG ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Quintero J, et al.

The transition from adolescence to adulthood is a complex period in which multiple changes take place (education, work, independent living, and social relations). This stage is especially difficult for adolescents suffering from attention deficit hyperactivity disorder (ADHD), who have to move on from child and adolescent mental health services to adult mental health services. This review analyzes developmental and environmental risk and protective factors as well as critical variables such as executive functioning and self-monitoring that influence the course of ADHD in transitional age youth and guide the priorities for an optimal transition of care. The influence of the COVID-19 pandemic is also discussed. We reflect on the unmet needs for an optimal transition of care and propose practice and policy recommendations to achieve this goal

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Child Adolesc Psychiatr Clin N Am. 2022 Jul;31:499-514.

ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATIONS AND SLEEP.

Stein MA, Zulauf-McCurdy C, DelRosso LM.

Sleep problems are common and often increase when initiating pharmacotherapy for ADHD. Stimulants are commonly associated with delayed sleep onset/insomnia although nonstimulants can be associated with daytime sleepiness. There is a wide variability in severity and duration of sleep effects, but most effects are mild and improve over time. Although sleep problems occur in all age groups, preschoolers and adolescents appear to be more vulnerable to adverse effects on sleep than adults and children. Interventions to improve sleep include behavioral therapy, changing dose schedules or formulations, and adding a sleep-promoting agent such as melatonin

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Child Adolesc Psychiatr Clin N Am. 2022 Jul;31:515-30.

ADHD AND SUBSTANCE USE DISORDERS IN YOUNG PEOPLE: CONSIDERATIONS FOR EVALUATION, DIAGNOSIS, AND PHARMACOTHERAPY.

Taubin D, Wilson JC, Wilens TE.

Co-occurring ADHD and substance use disorder (SUD) is a common clinical presentation associated with significant impairment requiring careful evaluation, diagnosis, and treatment. Treatment with medication, along with cognitive behavioral therapy, is generally regarded as effective in addressing symptoms and impairments associated with both disorders. Options for pharmacotherapy include stimulant and nonstimulant therapies administered with careful monitoring of dosage and compliance to optimize efficacy. In high-risk groups such as college students and/or those with SUD, prescribers should address risks of stimulant misuse and diversion through patient and family education, medication monitoring, and other risk-reducing practices

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Child Adolesc Psychiatry Ment Health. 2022;16.

ASSOCIATED PREDICTORS OF FUNCTIONAL IMPAIRMENT AMONG ADOLESCENTS WITH ADHD A CROSS-SECTIONAL STUDY.

Meyer J, Alaie I, Ramklint M, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) in adolescence is associated with functional impairment in several domains of life. To enable development of interventions that more effectively target functional impairment in this age group, the associations between clinical characteristics and impairment need to be clarified. The aim of this study was to investigate the associations between ADHD and functional impairment, if they varied by sex, and the potential impact of comorbid psychiatric symptoms on the associations.

Methods: This was a cross-sectional study including adolescents with ADHD (n = 164) and a reference group of adolescents without ADHD (n = 106). Self-ratings and parental ratings of functional impairment in different life domains were used as outcomes in all analyses. Differences between groups were investigated with comparative analyses. General linear models (GLMs) were used to explore associations between ADHD symptoms and functional impairment in adolescents with ADHD, while adjusting for of comorbid symptoms, sex, and medication.

Results: Adolescents with ADHD displayed higher levels of functional impairment than peers without ADHD, and girls with ADHD rated higher impairment than their male counterparts. The combined ADHD presentation was associated with the highest levels of self-reported impairment, while parental ratings indicated comparable levels of overall impairment across presentations. In the adjusted GLMs, symptoms of inattention were strongly associated with self- and parent-rated impairment in school, but symptoms of hyperactivity/impulsivity were not, whereas symptoms of both inattention and hyperactivity/impulsivity were modestly associated with self-rated impairment with friends. Further, both emotional and conduct problems were associated with impairment in daily life.

Conclusions: Our results suggest that attention difficulties, in particular, seem to impair academic functioning in adolescents with ADHD, and interventions targeting such difficulties are warranted. In addition, comorbid symptoms need to be assessed and treated, and self-reports of functioning should be included in research and clinical practice involving adolescents

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Child Neuropsychol. 2022.

THE PARENT-REPORTED ADHD SYMPTOM INFREQUENCY SCALE (PRASIS): A PARENT REPORT MEASURE OF ADHD SYMPTOM EXAGGERATION.

Lesica S, Skeel R, Fust B.

The present article outlines the development of the parent-reported ADHD symptom infrequency scale (PRASIS), a novel stand-alone questionnaire designed to discriminate between parents exaggerating ratings of ADHD symptoms of their child from parents more accurately reporting symptoms. The PRASIS includes an Infrequency scale (INF) to measure infrequently reported symptoms of ADHD and a clinical scale to measure Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) defined ADHD symptoms

(ADHD Total). An initial list of infrequency and clinical items was revised over the course of three studies, each conducted on a different sample of participants (n_1 = 154, n_2 = 203, n_3 = 167) recruited via CloudResearch and consisting of mothers of children 4–12 years old. Analyses on the final version of the measure demonstrated good to excellent internal consistency (INF α =.87, ADHD Total α =.94) and high convergent validity of the PRASIS ADHD Total scores with ADHD Rating Scale-5 Total scores (r =.87, p <.001). Omnibus ANOVA comparisons demonstrated excellent group discrimination of both the PRASIS Infrequency scale and the PRASIS ADHD scale (Cohen's f = 0.81-0-90). Specificity was above the minimum requirement set a priori (≥.80) and resulting sensitivity was similar or higher than other non-ADHD measures in the symptom validity literature. Specificity and sensitivity are reported for multiple cutoff scores, and positive predictive values (PPV) and negative predictive values (NPV) are presented for several base rates

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Clin EEG Neurosci. 2022.

EFFECTS OF TWENTY HOURS OF NEUROFEEDBACK-BASED NEUROPSYCHOTHERAPY ON THE EXECUTIVE FUNCTIONS AND ACHIEVEMENTS AMONG ADHD CHILDREN.

Liao YC, Guo NW, Su BY, et al.

Objective. Neurofeedback can reduce ADHD symptoms; however, current programs are relatively long, with fewer concerns about executive function (EF). The present study aimed to investigate a 20-hour combined computerized training neurofeedback program.

Methods. Fifty ADHD children were randomly assigned to either the experimental group (EXP) or the wait-list control group (CON), who took training after the post-tests. The EF measures were the Tower of London (ToL), Wisconsin Card Sorting Test (WCST), and Comprehensive Nonverbal Attention Test (CNAT). SNAP-IV and questionnaires reported by parents constituted the behavioral measures. Two-way repeated-measures ANOVA and bootstrapping dependent t-tests were also used.

Results. The F-tests revealed the interaction effects on ADHD symptoms and math scores. The EXP had increased the ToL scores, decreased the error and perseverative error rates on WCST, as well as the dysexecutive index on CNAT in the t-test.

Conclusions. The training effects were related to behavioral symptoms and functions, EFs, and generalized achievement performances. We suggest that future studies could apply to different patients and examine the maintenance of the program

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CNS Spectr. 2022;27:230-31.

D-AMPHETAMINE TRANSDERMAL SYSTEM IN TREATMENT OF CHILDREN AND ADOLESCENTS WITH ADHD: SECONDARY ENDPOINT RESULTS FROM A PHASE 2 TRIAL.

Cutler AJ, Suzuki K, Starling B, et al.

Background. Amphetamines are a first-line treatment for ADHD. The dextroamphetamine transdermal system (d-ATS) was developed as an alternative to oral amphetamine formulations. A randomized controlled trial of d-ATS in children and adolescents with ADHD was conducted, and its primary and key secondary endpoints were met. Here, we report secondary endpoints of the study, further assessing the efficacy and safety of d-ATS.

Methods. This study comprised a 5-week, open-label dose optimization period (DOP) followed by a 2-week, randomized, crossover double-blind treatment period (DBP). All eligible patients received d-ATS 5 mg/9 h and were evaluated weekly for a possible dose increase to 10mg/9 h, 15mg/9 h, and 20mg/9 h. Once reached, the optimal dose was maintained for the DOP and utilized during the DBP. Secondary objectives for this study included assessment of efficacy via Permanent Product Measure of Performance- Attempted and -Correct (PERMP-A, PERMP-C), ADHD-RS-IV, Conners Parent Rating Scale Revised Short Form (CPRS-R:S), and Clinical Global Impression (CGI) scores in a laboratory classroom setting. Efficacy was analyzed using a mixed-model repeated-measures (MMRM) approach. Safety assessments included treatment emergent adverse events (TEAEs) and dermal safety.

Results. In total, 110 patients were enrolled in the DOP, and 106 patients were randomized in the DBP. Patients receiving d-ATS demonstrated significant improvement vs placebo in PERMP-A and -C scores in the DBP consistently from 2 to 12 hours post-dose (P < .001 for all time points). ADHD-RS-IV total scores

improved during the DOP and improved further during the DBP, with a least-squares mean (95% CI) difference for d-ATS vs placebo of -13.1 (-16.2, -10.0; P < .001). Significant differences between placebo and d-ATS in the DBP were also observed for the CPRS-R:S and CGI scales (P < .001). Most TEAEs were mild or moderate, with 3 TEAEs (abdominal pain, irritated mood, and appetite loss) leading to study discontinuation in the DOP and none in the DBP. No patients were discontinued due to dermal reactions in either phase.
Conclusions. d-ATS was effective in the treatment of ADHD in children and adolescents, meeting its primary endpoint (reported elsewhere) and all secondary endpoints. d-ATS was safe and welltolerated, with minimal dermal reactions

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CNS Spectr. 2022;27:242-43.
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED-DOSE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF THE AMPHETAMINE EXTENDED-RELEASE TABLET IN ADULTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.
Cutler AJ, Childress AC, Pardo A, et al.
Background. Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by pervasive impairment in symptoms of inattention, hyperactivity, and impulsivity. Psychopharmacologic treatment is targeted at the management of symptoms of ADHD, and evidence exists thatADHDpersists into adulthood. Clinical practice guidelines recommend a combination of behavior therapy and psychostimulant medication for the treatment of ADHD in children, adolescents, and adults. Psychostimulants are often prescribed for ADHD in adults, and amphetamine long has been considered a mainstay of treatment for this population. As adult patients seek relief from ADHD symptoms early in the workday and into the early evening hours, with fewer required doses, extended-release formulations with an early onset of efficacy and an extended duration of effect are considered very desirable. The amphetamine-extended release tablet (AMPH ER TAB) was developed to provide a portable, easy-to-use amphetamine tablet dosage option that can be chewed or swallowed whole.
Objectives. To evaluate the efficacy and safety of an Amphetamine Extended-Release Tablet (AMPH ER TAB) in adults with ADHD aged 18 to 60 years. Methods: In a 5-week forced dosetitration phase, eligible subjects were randomized to either oral double-blind AMPH ER TAB 5 mg starting dose or matching placebo, once daily in the morning beginning the day after the Baseline Visit. Subjects were titrated up (5 mg increments) each week. Safety and efficacy assessments were done weekly. After Visit 3, subjects received 20 mg for 14 (3) days before Visit 5 (V5). Subjects who could not tolerate study drugs discontinued. A Permanent Product Measure of Performance (PERMP) placement test was done at Screening or Baseline. At V5, efficacy assessments included the administration of serial PERMPs predose, 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours postdose. The primary efficacy endpoint was the mean PERMP-T score across postdose time points during the Visit 5 serial PERMPs. Safety was monitored by AEs assessed at each visit, C-SSRS, vital signs, weight, and assessment of sleep, appetite, mood, and psychotic AEs.
Results. The mean postdose PERMP-T score over all postdose time points at V5 was statistically significantly higher in the AMPH ER TAB group vs placebo (302.8 vs 279.6; P = .0043). Common adverse events were decreased appetite, insomnia, and dry mouth. The majority of TEAEs were mild to moderate in severity, and no SAEs were reported.
Conclusion. The AMPH ER TAB demonstrated efficacy in the treatment of symptoms of ADHD in adults, with an anticipated safety profile

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CNS Spectr. 2022;27:249.
ERROR-RELATED BRAIN ACTIVITY IN ADHD: A SYSTEMATIC REVIEW AND META-ANALYSIS OF ELECTROENCEPHALOGRAPHY MARKERS OF COGNITIVE CONTROL PERFORMANCE.
Awasthi P.
Background. Deviant cognitive control performance is implicated in Attention-Deficit-Hyperactivity-Disorder (ADHD). It is also conjectured to be a potential diagnoser and differentiator between the Inattentive and

Hyperactive-Impulsive ADHD types. Reliable measures have not been established due to the variation in published results.
Methods. We performed a systematic review and meta-analysis of the literature published up to May 2021 with data on electrophysiological correlates, that is, EEG correlates of cognitive control monitoring (error-related negativity, ERN; error positivity, Pe; correct-response negativity, CRN) in ADHD patients and the efficiency of EEG recordings in differentiating between ADHD types. Multiple databases including PubMed, Scopus, Google Scholar, bioRxiv, and medRxiv were searched for eligible literature. Meta-Analyses were performed through statistical tools provided by the open-source metafor package and separately using the Hedge's g standardized mean differences.
Results. Meta-Analyses were performed on a shortlisted set of 125 studies involving 7248 participants. To avoid extraneous variables, the sex ratio was maintained at 50:50, and the age groups of participants were equally varied between early teenagers (12-15 years), late teenagers (15-18 years), young adults (21- 25), and middle-aged adults (29-37). The ADHD-afflicted group showed reduced ERN (Hedge's g = -0.58 [CIs: -0.76, -0.35]) and reduced Pe (Hedge's g = -0.65 [CIs: -0.79, -0.44). The Hyperactive-Impulsive ADHD types (2574/7248 participants) showed an increased CRN (Hedge's g = 0.68 [CIs: 0.71, 0.29]), while the Inattentive ADHD Types (4674/7248 participants) showed a slightly reduced CRN (Hedge's g = -0.25 [CIs: -0.31, -0.28]. The prevalence of counted task errors was higher in the teenagers' group (12-18 years) than the adults' group (21-37 years).
Conclusions. Results suggest that EEG Pattern Markers (especially Pe and CRN) can act as strong differentiators/diagnosers between the Hyperactive-Impulsive and InattentiveADHDtypes. In further development, deep learning classifiers can be built for ADHDtypes using EEG Markers as Features and statistical values as weights

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Cortex. 2022 Aug;153:126-42.

DISSOCIATING EXECUTIVE FUNCTION AND ADHD INFLUENCES ON READING ABILITY IN CHILDREN WITH DYSLEXIA.

Al Dahhan NZ, Halverson K, Peek CP, et al.

Developmental dyslexia (DD) and attention-deficit/hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders among school-age children. These disorders frequently co-occur, with up to 40-50% of children with one diagnosis meeting criteria for the other, and similar percentages of children with either DD or ADHD exhibiting impaired executive functions (EF). Although both ADHD and EF deficits are common in dyslexia, there is little evidence about how ADHD and EF deficits specifically influence the brain basis of reading difficulty in dyslexia, and whether the influences of ADHD and EF on dyslexia can be disentangled. The goal of the current study was to investigate, at both behavioral and brain levels, whether reading performance in individuals with dyslexia is more strongly associated with EF or with diagnostic status of comorbid ADHD. We examined reading abilities and EF in children (8-13 years old) with typical reading ability, DD only, or both DD + ADHD. Across both groups with dyslexia, impaired EF was associated with greater impairment on measures loading onto a reading fluency, but not a reading accuracy, factor. There were no significant differences between the DD and DD + ADHD groups on measures of reading fluency or reading accuracy. During functional magnetic resonance imaging (fMRI) while performing a rhyme-matching reading task requiring phonological awareness, typically developing readers showed greater left-hemisphere reading network activation than children with DD or DD + ADHD. Children with DD and DD + ADHD did not show differential activation, but DD children with unimpaired EF showed greater activation than those with impaired EF in reading-related areas. Thus, ADHD status alone had no measurable influence on reading performance or brain activation. Impaired EF in dyslexia, independent of ADHD status, was associated with greater deficits in reading fluency and greater reductions of activation in response to print in the typical left-hemisphere reading network

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Current Neuropharmacology. 2022;20:1564-78.

TARGETING PI3K BY NATURAL PRODUCTS: A POTENTIAL THERAPEUTIC STRATEGY FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Noori T, Sahebgharani M, Sureda A, et al.

Attention-Deficit Hyperactivity Disorder (ADHD) is a highly prevalent childhood psychiatric disorder. In general, a child with ADHD has significant attention problems with difficulty concentrating on a subject and is generally associated with impulsivity and excessive activity. The etiology of ADHD in most patients is unknown, although it is considered to be a multifactorial disease caused by a combination of genetics and environmental factors. Diverse factors, such as the existence of mental, nutritional, or general health problems during childhood, as well as smoking and alcohol drinking during pregnancy, are related to an increased risk of ADHD. Behavioral and psychological characteristics of ADHD include anxiety, mood disorders, behavioral disorders, language disorders, and learning disabilities. These symptoms affect individuals, families, and communities, negatively altering educational and social results, strained parent-child relationships, and increased use of health services. ADHD may be associated with deficits in inhibitory frontostriatal noradrenergic neurons on lower striatal structures that are predominantly driven by dopaminergic neurons. Phosphoinositide 3-kinases (PI3Ks) are a conserved family of lipid kinases that control a number of cellular processes, including cell proliferation, differentiation, migration, insulin metabolism, and apoptosis. Since PI3K plays an important role in controlling the noradrenergic neuron, it opens up new insights into research on ADHD and other developmental brain diseases. This review presents evidence for the potential usefulness of PI3K and its modulators as a potential treatment for ADHD

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Curr Psychiatry Rep. 2001;3:497-506.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND SUBSTANCE USE DISORDERS.

Wilson JJ, Levin FR.

Attention deficit hyperactivity disorder (ADHD) is a common childhood disorder that often continues to manifest symptoms into adulthood. In children and adults, this condition may contribute to addictive vulnerability. Several factors are common to the developmental psychopathology of these conditions, suggesting an underlying deficit in behavioral regulation as an explanation for this comorbidity. Developmentally, faulty learning processes or attempts to self-medicate dysfunctional behavior may contribute to the pathogenesis of substance use disorders. Substance abuse itself also may contribute to the development of attentional deficits and behavioral dysregulation through direct (eg, prenatal or self-inflicted exposures to neurotoxic substances) and indirect (eg, poverty, neglect, abuse) mechanisms. Because ADHD can be identified prior to the peak onset of substance use, effective treatment of this common disorder may reduce the development of substance use disorders. Adult ADHD may also contribute to the development and maintenance of substance use disorders Substance abuse patients may particularly benefit from treatment of this comorbidity

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Dev Med Child Neurol. 2022 Aug;64:944-49.

WHO BENEFITS FROM DIAGNOSTIC LABELS FOR DEVELOPMENTAL DISORDERS?

Werkhoven S, Anderson JH, Robeyns IAM.

The number of diagnoses of developmental disorders is on the rise and the use of labels for developmental disorders, such as attention-deficit/hyperactivity disorder and autism spectrum disorder, is widening. Diagnostic labels can play an important role in helping those who display atypical behaviour and their caregivers to cope with associated challenges and, possibly, to get treatment. But these labels are increasingly contested and associated with a variety of harmful effects. In this paper, we analyze the role diagnostic labels can play in four different contexts (scientific, therapeutic, social, and administrative) and identify what various stakeholders stand to gain or lose with continued, expanded, or abolished use of those labels. Our analysis reveals labels serve different purposes in each of these contexts, benefitting different stakeholders. Any overall evaluation, critique, or defence of labels needs to consider the interests of all stakeholders in these contexts

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Dev Med Child Neurol. 2022.

PARENTING ROLES FOR YOUNG PEOPLE WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TRANSITIONING TO ADULT SERVICES.

Janssens A, Blake S, Eke H, et al.

AIM: To inform transitions from child to adult health services, we explored the work and roles parents take in the care of young people with attention-deficit/hyperactivity disorder (ADHD) aged 14 to 25 years old.

METHOD: Using framework thematic analysis, we analysed data collected from 28 semi-structured interviews with parents of young people with ADHD to generate a typology and triangulated it against findings from 64 interviews with young people with ADHD. The interviews were carried out as part of a three-strand, interactive mixed-method study.

RESULTS: An entourage typology of three parent roles was identified. Parents moved between manager and roadie roles as their child gradually matured. A superfan role was identified which supported young people's positive self-image but may impede withdrawal from the manager role. Continued parental involvement into adulthood reflected a need to maintain the balance of resources required to maintain quality of life for the whole family.

INTERPRETATION: This is the first study to explore parental roles in the health care of young people with ADHD. Parents will vary in their capacity to fulfil the identified roles and step back their care as their children reach adulthood. The findings can inform intervention development to support families and transition between services

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Early Intervent Psychiatry. 2022.

PREDICTORS OF MENTAL HEALTH SERVICE UTILIZATION AS ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER TRANSITION INTO ADULTHOOD.

Girela-Serrano B, et al.

Background: Attention deficit hyperactivity disorder (ADHD) symptoms may persist into adulthood and are likely to cause great problems in young adults. To date, few studies have explored the characteristics of patients diagnosed with ADHD that might influence the utilization of adult mental health services (AMHS). We aimed to examine and identify predictive symptoms of AMHS.

Methods: We analysed data from 114 participants diagnosed with ADHD from a cohort of adolescents recruited at the age of 12–17 years, who, at the time of data analysis, were over 18 years old.

Results: Among AMHS users, hyperactivity/impulsivity measures were significantly more severe ($t = 2.668$, $df = 112$, $p < .001$), ADHD combined subtype diagnosis ($\chi^2 = 4.66$, $df = 1$, $p = .031$) was more frequent and dysregulation profile in the SDQ-P was also significantly higher ($t = -2.497$, $df = 109$, $p = .014$). However, the dysregulation profile did not remain statistically significant after controlling for type of AMHS contact.

Conclusions: Our findings suggest that adolescents with ADHD are more likely continue their care under AMHS if they present more severe symptoms of hyperactivity/impulsivity and emotional dysregulation. The better characterization of the patient profile will help clinicians to early identify groups at-risk and to tailor interventions and prevention strategies

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eBioMedicine. 2022 Jun;80:104039.

LONGER SCREEN TIME UTILIZATION IS ASSOCIATED WITH THE POLYGENIC RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH MEDIATION BY BRAIN WHITE MATTER MICROSTRUCTURE.

Yang A, Rolls ET, Dong G, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) has been reported to be associated with longer screen time utilization (STU) at the behavioral level. However, whether there are shared neural links between ADHD symptoms and prolonged STU is not clear and has not been explored in a single large-scale dataset.

METHODS: Leveraging the genetics, neuroimaging and behavioral data of 11,000+ children aged 9-11 from the Adolescent Brain Cognitive Development cohort, this study investigates the associations between the polygenic risk and trait for ADHD, STU, and white matter microstructure through cross-sectionally and longitudinal analyses.

FINDINGS: Children with higher polygenic risk scores for ADHD tend to have longer STU and more severe ADHD symptoms. Fractional anisotropy (FA) values in several white matter tracts are negatively correlated with both the ADHD polygenic risk score and STU, including the inferior frontal-striatal tract, inferior frontal-occipital fasciculus, superior longitudinal fasciculus and corpus callosum. Most of these tracts are linked to visual-related functions. Longitudinal analyses indicate a directional effect of white matter microstructure on the ADHD scale, and a bi-directional effect between the ADHD scale and STU. Furthermore, reduction of FA in several white matter tracts mediates the association between the ADHD polygenic risk score and STU.
INTERPRETATION: These findings shed new light on the shared neural overlaps between ADHD symptoms and prolonged STU, and provide evidence that the polygenic risk for ADHD is related, via white matter microstructure and the ADHD trait, to STU.
FUNDING: This study was mainly supported by NSFC and National Key R&D Program of China

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eBioMedicine. 2022 Jun;80:104075.

TOWARDS PATHOPHYSIOLOGY-BASED INTERVENTIONS FOR CHILDREN WITH ADHD AND INCREASED SCREEN TIME UTILISATION.

Cortese S.

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Egypt J Neurol , Psychiatr Neurosurg. 2022;58.

PREVALENCE OF SCHOOL BULLYING AND ITS RELATIONSHIP WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER AND CONDUCT DISORDER: A CROSS-SECTIONAL STUDY.

Ahmed GK, Metwaly NA, Elbeh K, et al.

Background: School bullying is the most widespread form of violence among adolescents. It has been identified as a critical problem for students and has evolved into a public health issue and global crisis. The study aims to assess the prevalence of school bullying among primary school students and its relationship with attention deficit hyperactive disorder (ADHD) and conduct disorders. Among the 280 primary school students those aged 10-12 years were recruited. All participants were assessed by parent interview, the Arabic version of the bullying behavior scale for children and adolescents and the Arabic version of the Conners Teacher Rating Scale-28.
Results: We found that the prevalence rate of bullying behavior was 12.5% among students. In bullying students group, males were higher percentage (15.8%) than females (9%). Also, they had the highest mean scores regarding verbal bullying and social bullying, followed by psychological and physical bullying. Regarding Conners, the higher mean scores of conduct problem, passive-inattentive, and hyperactivity index were associated with bullying students in compared to students without bullying.
Conclusions: The prevalence of school bullying among primary school students was 12.5%. Also, there was significant association between bullying students and having attention deficit hyperactive disorder (ADHD) and/or conduct disorder

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Encephale. 2022.

TRANSITION FROM CHILD AND ADOLESCENT MENTAL HEALTH CARE TO ADULT SERVICES FOR YOUNG PEOPLE WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) OR AUTISM SPECTRUM DISORDER (ASD) IN EUROPE: BARRIERS AND RECOMMENDATIONS.

Maurice V, Russet F, Scocco P, et al.

Transition in mental health care is the process ensuring continuity of care of a young patient arriving at the CAMHS (Child and Adolescent Mental Health Service) age boundary within mental health services. Transition refers to a transfer to an adult mental health service (AMHS), to private care or other mental health community services. A transition plan can also lead to a managed end of specialized care with involvement of a general practitioner or social services. For young people with a diagnosis of ADHD (Attention Deficit Hyperactivity Disorder) or ASD (Autism Spectrum Disorder), two disorders that persist into adulthood, an optimal transition would ensure continuity of care or facilitate access to specialized care in the case of a discharge. Transition typically occurs during adolescence, a known sensitive period when young people may

experience major changes at several levels: physiological, psychological and social. Any barrier in the transition process resulting in discontinuity of care may worsen the symptoms of ADHD or ASD and can ultimately adversely affect the global mental health of young people with such neurodevelopmental disorders. The objectives of this narrative review are: 1/to identify the barriers in the transition process in mental health services often faced by young people with these two disorders; 2/to highlight specific recommendations for strengthening the CAMHS-AMHS interface that have been proposed by various countries in Europe

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Encephale. 2022 Jun;48:232-40.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND EXECUTIVE DYSFUNCTION IN PRESCHOOL CHILDREN. A COMPARISON OF NEPSY AND BRIEF-P ASSESSMENTS.

Ohmann S, Wurzer M, Popow C.

OBJECTIVE: The aim of the study was to explore prevalence, interrelations and accuracy of assessing psychopathology, intelligence, and executive functions (EF) in preschool children with ADHD (age 2.1-6.5 years).

METHOD: We prospectively investigated 115 preschool outpatient children (91 boys, 24 girls, aged 4.3±1.0 years) with the clinical diagnosis of ADHD. Assessment included clinical history, background, psychosocial problems (CBCL, C-TRF), ADHD (DISYPS external ratings), cognitive performance (WPPSI-III, K-ABC), and executive functions (BRIEF-P, NEPSY).

RESULTS: We found a high frequency of dysexecutive problems in up to 64 % in the parental BRIEF-P assessments, up to 62 % in the BRIEF-P teachers' assessments, and 62 % in the NEPSY functional assessments. Parental and teachers' BRIEF-P scores were only correlated in one subscale, inhibition, and NEPSY and BRIEF-P were not correlated at all. It was found that 42.5 % of the children with noticeable findings had agreeing results in all three, and another 45 % in two tests.

CONCLUSIONS: About 2/3 of the ADHD preschool children had detectable EF dysfunctions. In order to assess dysexecutive problems, multi-method testing is mandatory

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Environ Res. 2022 Sep;212:113555.

PRENATAL ORGANOPHOSPHORUS PESTICIDE EXPOSURE AND EXECUTIVE FUNCTION IN PRESCHOOL-AGED CHILDREN IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY (MOBA).

Thistle JE, Ramos A, Roell KR, et al.

Introduction: Prenatal exposure to organophosphorus pesticides (OPPs) has been associated with neurodevelopmental deficits in children, however evidence linking OPPs with specific cognitive mechanisms, such as executive function (EF), is limited.

Objective: This study aims to evaluate the association between prenatal exposure to OPPs with multiple measures of EF in preschool-aged children, while considering the role of variant alleles in OPP metabolism genes.

Methods: We included 262 children with preschool attention-deficit/hyperactivity disorder (ADHD), and 78 typically developing children, from the Preschool ADHD substudy of the Norwegian, Mother, Father, and Child Cohort Study. Participants who gave birth between 2004 and 2008 were invited to participate in an on-site clinical assessment when the child was approximately 3.5 years; measurements of EF included parent and teacher rating on Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P), and three performance-based assessments. We measured OPP metabolites in maternal urines collected at ~17 weeks' gestation to calculate total dimethyl- (ΣDMP) and diethyl phosphate (ΣDEP) metabolite concentrations. We estimated multivariable adjusted β's and 95% confidence intervals (CIs) corresponding to a change in z-score per unit increase in log-ΣDMP/DEP. We further characterized gene-OPP interactions for maternal variants in PON1 (Q192R, M55L), CYP1A2 (1548T > C), CYP1A1 (IntG > A) and CYP2A6 (-47A > C).

Results: Prenatal OPP metabolite concentrations were associated with worse parent and teacher ratings of emotional control, inhibition, and working memory. A one log-∑DMP increase was associated with poorer teacher ratings of EF on the BRIEF-P (e.g. emotional control domain: β = 0.55, 95% CI: 0.35, 0.74), when weighted to account for sampling procedures. We found less consistent associations with performance-

based EF assessments. We found some evidence of modification for PON1 Q192R and CYP2A6 -47A > C. Association with other variants were inconsistent.
Conclusions: Biomarkers of prenatal OPP exposure were associated with more adverse teacher and parent ratings of EF in preschool-aged children

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Ethiop J Health Sci. 2022 Mar;32:321-30.

PREVALENCE AND ASSOCIATED FACTORS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN AGED 6-17 YEARS IN NORTH EASTERN ETHIOPIA.

Mulu GB, Mohammed AY, Kebede WM, et al.

BACKGROUND: Attention-deficit hyperactivity disorder is one of the public neurodevelopmental disorders characterized by impulsivity and restlessness or hyperactivity. This study aimed to assess the prevalence of Attention-deficit hyperactivity disorder and its associated factors among children aged 6 to 17 years in Shewa Robit town, Northeastern Ethiopia, 2020.
METHODS: A community-based cross-sectional study was conducted among 365 children aged 6-17 years from Feb 1-March 30, 2020, at Shewa Robit town. Systematic random sampling was employed to select study participants. Data were collected by interview using structured and pretested questionnaires. Finally, data was entered using Epi-data 4.2 and analyzed using SPSS version 25. Bivariable and multivariable binary logistic regression analysis was conducted to identify associated factors of attention deficit hyperactivity disorder. Odds ratios with 95% CI were calculated, and variables having a p-value < 0.05 were considered statistically significant.
RESULT: The prevalence of ADHD among children aged 6 to 17 years was 13%. Financial crises [AOR 4.76(95% CI 1.51-15.05)], children a previous history of the mental problem [AOR 8.45(95% CI 1.24-57.43)], C/S delivery [AOR 6.38(95% CI 1.26-32.26)] and substance use in life [AOR 2.43(95% CI 1.09-5.43)] were significantly associated with attention deficit hyperactivity disorder.
CONCLUSION: The prevalence of ADHD in children 6 to 17 years old was high (13%). Financial crises, children's history of mental disorders, C/S delivery, and lifetime substance use were significantly associated with attention deficit hyperactivity disorder. Therefore, particular attention should be given to mothers and children with significant factors

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Ethn Health. 2022 Jul;27:1088-102.

ADVERSE CHILDHOOD EXPERIENCES AND MENTAL HEALTH CONDITIONS AMONG MULTIRACIAL ADOLESCENTS.

Weller BE, Conrad JK, Wilburn VG, et al.

Objective: The objective of this study was to verify the factor structure of the household dysfunction type of ACE using data from the National Survey of Children's Health (NSCH), and then examine whether household dysfunction (measured as a latent construct) was associated with mental health conditions among multiracial adolescents.
Design: We used cross-sectional data collected in 2016 from caregivers who completed the NSCH and analyzed data from a subpopulation of adolescents (12-17) who reported more than one race (n = 1,231). Mplus 8.4 was used to conduct confirmatory factor analysis and probit models from a structural equation modeling framework.
Results: Results from this study indicated that the household dysfunction type of ACE, as a latent construct, had good model fit and was significantly associated with depression [standardized coefficient [B] = .50, 95% confidence interval [CI] .36, .65], anxiety [B = .61, 95% CI .48, .73], behavior problems [B = .58, 95% CI .44, .72], and ADHD [B = .54, 95% CI .38, .69] for multiracial adolescents.
Conclusions: Household dysfunction may result in adolescents being separated (physically or emotionally) from their caregivers, which may hinder adolescents' ability to establish or maintain one of the most important relationships needed to promote racial/ethnic identity development and mental health. Implications for advancements in theory and NSCH are presented

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Eur J Clin Pharmacol. 2022 Jul;78:1095-104.

A VIEW OF RESPONSE AND RESISTANCE TO ATOMOXETINE TREATMENT IN CHILDREN WITH ADHD: EFFECTS OF CYP2C19 POLYMORPHISMS AND BDNF LEVELS.

Demirci E, Sener EF, Gul MK, et al.

OBJECTIVE: Although several genes have previously been studied about the treatment of Attention Deficit Hyperactivity Disorder (ADHD), the number of studies investigating the effects of genes on atomoxetine (ATX) treatment is very limited. In this study, we aimed to investigate the effect of CYP2C19 polymorphisms, which have a role in ATX biotransformation, on the treatment response and also to assess whether there is a relationship between BDNF and treatment response in children and adolescents with ADHD.

METHODS: One hundred children with ADHD and 100 healthy controls (HCs) were included in this study. The treatment response was assessed 2 months after the start of the ATX treatment. DNA samples from peripheral venous blood were replicated using PCR and analyzed using the ILLUMINA next-generation sequencing method. The resulting fastqs were analyzed using Basespace's Variant Interpreter Program. Plasma BDNF levels were evaluated with ELISA kits.

RESULTS: Treatment response was found to be lower in both heterozygous and homozygous carriers of the c.681G>A (CYP2C19*2) polymorphism. When the BDNF level was compared, it was found to be significantly higher in the ADHD group compared to HCs. Also, BDNF has a stronger predictive value for assessing resistance to ATX treatment.

CONCLUSIONS: To our knowledge, this is the first study to assess the effects of CYP2C19 polymorphisms and BDNF levels together on ATX treatment in children. Further studies with an extensive population are needed to better understand the effects of CYP2C19 polymorphisms on treatment and side effects, as well as the effects of BDNF levels

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Eur J Epidemiol. 2022 May;37:477-94.

HANDLING UNOBSERVED CONFOUNDING IN THE RELATION BETWEEN PRENATAL RISK FACTORS AND CHILD OUTCOMES: A LATENT VARIABLE STRATEGY.

Gustavson K, Davey SG, Eilertsen EM.

BACKGROUND: Several studies have examined maternal health behavior during pregnancy and child outcomes. Negative control variables have been used to address unobserved confounding in such studies. This approach assumes that confounders affect the exposure and the negative control to the same degree. The current study introduces a novel latent variable approach that relaxes this assumption by accommodating repeated measures of maternal health behavior during pregnancy.

METHODS: Monte Carlo simulations were used to examine the performance of the latent variable approach. A real-life example is also provided, using data from the Norwegian Mother, Father, and Child Study (MoBa).

RESULTS: Simulations: Regular regression analyses without a negative control variable worked poorly in the presence of unobserved confounding. Including a negative control variable improved result substantially. The latent variable approach provided unbiased results in several situations where the other analysis models worked poorly. Real-life data: Maternal alcohol use in the first trimester was associated with increased ADHD symptoms in the child in the standard regression model. This association was not present in the latent variable approach.

CONCLUSION: The current study showed that a latent variable approach with a negative control provided unbiased estimates of causal associations between repeated measures of maternal health behavior during pregnancy and child outcomes, even when the effect of the confounder differed in magnitude between the negative control and the exposures. The real-life example showed that inferences from the latent variable approach were incompatible with those from the standard regression approach. Limitations of the approach are discussed

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Eur J Gen Pract. 2022 Dec;28:150-56.

GENERAL PRACTITIONER-CENTRED PAEDIATRIC PRIMARY CARE REDUCES RISK OF HOSPITALISATION FOR MENTAL DISORDERS IN CHILDREN AND ADOLESCENTS WITH ADHD: FINDINGS FROM A RETROSPECTIVE COHORT STUDY.

Mueller A, Sawicki OA, GÃ¼nther MP, et al.

BACKGROUND: General practitioners (GPs) play an essential role in the sustainable management of attention-deficit/hyperactivity disorder (ADHD). To our knowledge, the healthcare programme described here is the first integrated care programme for paediatric ambulatory care embedded in GP-centred-healthcare in Germany.

OBJECTIVES: To compare the health-service-utilisation of patients with ADHD enrolled in a GP-centred-paediatric-primary-care-programme with usual care in terms of disease-related hospitalisation, pharmacotherapy and psychotherapy.

METHODS: In 2018, we conducted a retrospective cohort study of 3- to 18-year-old patients with ADHD in Baden-Wuerttemberg, southern Germany. The intervention group (IG) comprised patients enrolled in a GP-centred-paediatric-primary-healthcare-programme and consulted a participating GP for ADHD at least once. GP-centred-paediatric-primary-care provides high continuity of care, facilitated access to specialist care, extended routine examinations and enhanced transition to adult healthcare. Patients in the control group (CG) received usual care, meaning they consulted a non-participating GP for ADHD at least once. Main outcomes were disease-related hospitalisation, pharmacotherapy and psychotherapy. Multivariable logistic regression was performed to compare groups.

RESULTS: A total of 2317 patients were included in IG and 4177 patients in CG. Mean age was 8.9±4.4. The risk of mental-disorder-related hospitalisations was lower in IG than CG (odds ratio (OR): 0.666, 95% confidence interval (CI): 0.509-0.871). The prescription rate for stimulants was lower in IG (OR: 0.817; 95% CI: 0.732-0.912). There was no statistically significant difference in the participation rate of patients in cognitive behavioural therapy between groups (OR: 0.752; 95% CI: 0.523-1.080).

CONCLUSION: Children and adolescents with ADHD enrolled in GP-centred-paediatric-primary-care are at lower risk of mental-disorder-related hospitalisation and less likely to receive stimulants

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Eur J Pediatr. 2022 Jul;181:2655-61.

MOTOR DEVELOPMENT PROBLEMS IN INFANCY PREDICT MENTAL DISORDERS IN CHILDHOOD: A LONGITUDINAL COHORT STUDY.

Pant SW, Skovgaard AM, AmmitzbÃ¸ll J, et al.

The purpose of this study is to examine whether motor development problems in infancy predicted mental disorders later in childhood, taking a wide array of potential confounding variables into consideration. This longitudinal study included an unselected study population of 33238 newborn children from the Copenhagen area, Denmark. Data on the predictor variable, motor development problems at 8-10 months of age, were obtained from the community health nurses' systematic evaluation of the child's motor development during a home visit and stored in the Child Health Database. Data on outcome, diagnosed mental disorders before the age of 8 years, were obtained from the Danish National Patient Register. Potential confounding variables were obtained from the Child Health Database, the National Birth Register and the Civil Registration System. The prevalence of motor development problems at 8-10 months of age was 19.3%; the incidence of any diagnosed mental disorder from 11 months of age to the 8th birthday was 4.0%. Motor development problems were associated with an increased risk of being diagnosed with a mental disorder before the 8th birthday, adjusted odds ratio (AOR) 1.47 (1.29-1.67). Motor development problems were associated with later neurodevelopmental disorders, AOR 1.77 (1.52-2.06), in particular autism spectrum disorders, AOR 1.63 (1.31-2.03), hyperactivity/attention deficit disorders, AOR 1.29 (1.03-1.61) and disorders of intellectual disability, AOR 3.28 (2.39-4.49).

Conclusion: Motor development problems as early at 8-10 months of age were predictive of neurodevelopmental disorders before the 8th birthday. The findings call for clinical attention and more research on preventive potentials in the community child health care.

What is known: • Children with ASD, ADHD and ID have high prevalence of early motor development problems.

What is new:

• Motor development problems in infancy predicted neurodevelopmental disorders before the 8th birthday.

• This observation could improve early identification and prevention of mental health problems in childhood

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Eur Arch Psychiatry Clin Neurosci. 2022.

Omega-3/6 supplementation for mild to moderate inattentive ADHD: a randomised, double-blind, placebo-controlled efficacy study in Italian children.

Carucci S, Romaniello R, Demuru G, et al.

Recently there has been a growing interest in non-pharmacological treatments for ADHD. We evaluated the efficacy of a specific Omega-3/6 dietary supplement (two capsules containing 279 mg eicosapentaenoic acid [EPA], 87 mg Docosahexaenoic Acid [DHA], 30 mg gamma linolenic acid [GLA] each) in ameliorating inattentive symptoms in inattentive-ADHD children (6–12 years) with a baseline ADHD-RS-Inattention score ≥ 12. Secondary objectives included changes in global functioning, severity of illness, depression, and anxiety symptoms, learning disorders and in the fatty acids blood levels. The study was a randomised, double-blind, placebo-controlled efficacy and safety trial with a 6-month double-blind evaluation of Omega-3/6 vs placebo (Phase-I) and a further 6-month-open-label treatment with Omega-3/6 on all patients (Phase-II). In total 160 subjects were enrolled. No superiority of Omega-3/6 supplement to placebo was observed on the primary outcome (ADHD-RS-inattention score) after the first 6-months, with 46.3% of responders in the Omega-3/6 group and 45.6% in the placebo group; a slight (not statistically significant) reduction in Omega-6/3 ratio blood levels was measured in the active treatment group. Twelve months after enrolment, percentages of responders were similar between groups. A mild statistical, although not clinically significant, improvement was observed on the ADHD-RS-total score in the Omega-3/6 group but not on the ADHD-RS-Inattention score; a slight (not-statistically significant) reduction in Omega-6/3 ratio was observed in the group taking active treatment only during Phase II. In conclusion, no clinical beneficial effects of Omega-3/6 were detected on inattentive symptoms, suggesting a limited role of Omega-3/6 dietary products in children with mild ADHD-I. Trial registration: At the time of the Ethical submission, according to the clinical trial Italian law, registration was not mandatory for food additive as Omega 3/6 were then classified. The trial was approved by the Ethical Committee of the Cagliari University Hospital (resolution n. 662; September 22nd, 2011)

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Eur Child Adolesc Psychiatry. 2022.

FUNCTIONAL SOMATIC SYMPTOMS IN PRESCHOOL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SECONDARY ANALYSIS OF DATA FROM A RANDOMIZED CONTROLLED TRIAL OF PARENT TRAINING.

Larsen LB, Daley D, Lange AM, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) can be more stress-vulnerable, and thereby, it has been suggested, prone to develop functional somatic symptoms (FSS) compared to their peers. In this paper, using data from 160 children aged 3ΓÇô7-áyears with ADHD from the DΓÇÖSNAPP study, a randomized controlled trial testing a parent training intervention, we addressed a number of questions about the role of FSS in ADHD. First, are FSS levels higher in an ADHD sample than in the children of the general population. Second, do FSS levels predict psychopathology and health-related quality of life (HRQoL) in ADHD samples. Third, does FSS levels moderate the effect of parent training on ADHD symptoms. We found that preschoolers with ADHD experienced more severe FSS than a general population-based sample (18.80% vs. 2.11%). Severe FSS were associated with increased psychopathology and impaired daily function and lower HRQoL. Level of baseline FSS did not moderate the effect of parent training on ADHD. FSS in preschool children with ADHD is associated with impaired daily functioning, but further research is warranted to determine the clinical impact of FSS in children with ADHD

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Eur Child Adolesc Psychiatry. 2022.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FROM PRESCHOOL TO SCHOOL AGE: CHANGE AND STABILITY OF PARENT AND TEACHER REPORTS.

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

Identifying attention-deficit/hyperactivity disorder (ADHD) in pre-schoolers may improve their development if treated, but it is unclear whether ADHD symptoms from this age are stable enough to merit treatment. We

aimed to investigate the stability of parent- and teacher-reported ADHD symptoms and ADHD classified above the diagnostic symptom thresholds, including for hyperactivity-impulsivity (HI), inattention and combined presentations from age 3 to 8-áyears. This study is part of the longitudinal, population-based Norwegian Mother, Father and Child Cohort Study. At child age 3 years, parents were interviewed and teachers rated ADHD symptoms. At age 8-áyears, parents (n = 783) and teachers (n = 335) reported ADHD symptoms by the Child Symptom Inventory-4. We found a significant reduction in the mean number of parent-reported ADHD and HI symptoms from age 3 to 8-áyears, but otherwise similar mean numbers. Parent-reported ADHD symptoms were moderately correlated between ages, while correlations were low for teachers. A total of 77/108 (71%) of the children classified with parent-reported HI presentation at age 3-áyears were no longer classified within any ADHD presentation at age 8 years, the only clear trend across time for either informant. There was a low to moderate parent-teacher-agreement in the number of reported symptoms, and very low informant agreement for the classified ADHD presentations. Overall, clinicians should exercise caution in communicating concern about HI symptoms in preschool children. Age 3 years may be too early to apply the ADHD diagnostic symptom criteria, especially if parents and teachers are required to agree

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Eur Child Adolesc Psychiatry. 2022.

A META-ANALYTIC REVIEW OF THE IMPACT OF ADHD MEDICATIONS ON ANXIETY AND DEPRESSION IN CHILDREN AND ADOLESCENTS.

Bryant A, Schlesinger H, Sideri A, et al.

Anxiety and depression are listed as common side effects for medications licensed for treating ADHD in children and adolescents. This meta-analytic review of randomised controlled trials aimed to explore the effect of medications on symptoms of anxiety and depression in children and adolescents with ADHD. A meta-analytic review of ADHD drug trials in children and adolescents was conducted. Random effects meta-analyses were conducted on anxiety and depression outcomes measured by validated psychological scales or side effect rating scales. Only 11% of eligible trials in this review reported anxiety and/or depression as an outcome or side effect, limiting the conclusions of the meta-analyses. Relative to placebo control, no significant effect of medication was found for symptoms of anxiety or depression in randomised controlled trials of ADHD medication in children and adolescents. This review highlights the systemic lack of mental health outcome reporting in child and adolescent ADHD drug trials. The importance of widespread implementation of standardised measurement of mental health outcomes in future trials is discussed

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Eur Child Adolesc Psychiatry. 2022.

PROBING THE OVERARCHING CONTINUUM THEORY: DATA-DRIVEN PHENOTYPIC CLUSTERING OF CHILDREN WITH ASD OR ADHD.

Deserno MK, Bathelt J, Groenman AP, et al.

The clinical validity of the distinction between ADHD and ASD is a longstanding discussion. Recent advances in the realm of data-driven analytic techniques now enable us to formally investigate theories aiming to explain the frequent co-occurrence of these neurodevelopmental conditions. In this study, we probe different theoretical positions by means of a pre-registered integrative approach of novel classification, subgrouping, and taxometric techniques in a representative sample (N = 434), and replicate the results in an independent sample (N = 219) of children (ADHD, ASD, and typically developing) aged 7ΓÇô14-áyears. First, Random Forest Classification could predict diagnostic groups based on questionnaire data with limited accuracyΓÇösuggesting some remaining overlap in behavioral symptoms between them. Second, community detection identified four distinct groups, but none of them showed a symptom profile clearly related to either ADHD or ASD in neither the original sample nor the replication sample. Third, taxometric analyses showed evidence for a categorical distinction between ASD and typically developing children, a dimensional characterization of the difference between ADHD and typically developing children, and mixed results for the distinction between the diagnostic groups. We present a novel framework of cutting-edge statistical techniques which represent recent advances in both the models and the data used for research in psychiatric nosology. Our results suggest that ASD and ADHD cannot be unambiguously characterized as

either two separate clinical entities or opposite ends of a spectrum, and highlight the need to study ADHD and ASD traits in tandem

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Eur Child Adolesc Psychiatry. 2022.

DEVELOPMENTAL SIGNS OF ADHD AND AUTISM: A PROSPECTIVE INVESTIGATION IN 3623 CHILDREN.

Cervin M.

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are neurodevelopmental disorders with an early onset. Guidelines recommend a careful evaluation of developmental history when assessing the disorders, but it is unclear how children with ADHD and ASD differ from their peers growing up. In this study, physical, family, psychological, social, and educational information were examined in 3623 ethnically diverse children that were prospectively followed from birth to age 15 as part of the Fragile Families and Child Wellbeing Study. Fifteen-thousand variables were screened, and 506 variables included in the final analyses. Accuracy of the most indicative information to predict ADHD and ASD diagnoses in adolescence was evaluated. Adolescents with ADHD (n = 627) and ASD (n = 91) differed from their peers on a plethora of developmental signs, with signs closely related to the core symptoms of the disorders after age 5 being most indicative of the disorders. Predictive models correctly identified 66% of individuals with ADHD and 81% of those with ASD, but 62ΓÇô88% of identified cases were false positives. The mean proportion of developmental deviations was 18.7% in the ADHD group, 20.0% in the ASD group, and 15.6% in peers; youth with both ADHD and ASD (n-á=-á50)-ádeviated on 21.8% of all developmental signs and had more pronounced deviations than those with ADHD or ASD alone. ADHD and ASD are characterized by broad and non-specific developmental deviations. Developmental information alone cannot be used to accurately predict diagnostic status in adolescence and false positives are likely if the diagnostic process relies heavily on such information. Developmental deviations are part of normal development and common in children without ADHD and ASD. Etiological heterogeneity and considerable temporal fluctuation in the core characteristics of ADHD and ASD may explain the lack of distinct developmental patterns

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Europ J Spec Needs Educ. 2022.

TEACHERS GENDERED PERCEPTIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER A LITERATURE REVIEW.

Olsson A.

This study provides a systematic review of previous research about teachers' gendered perceptions of pupils with diagnoses or symptoms of attention deficit hyperactivity disorder (ADHD). This review was conducted using the databases Scopus, Web of Science and ERIC. Nineteen articles were selected after narrowing down a total of 121 articles, in accordance with inclusion criteria. In sum, previous research concludes that teachers' identification, assessment and attitudes related to pupils with ADHD diagnoses or symptoms are associated with the pupils' gender. When pupils exhibit academic, emotional or behavioural difficulties, teachers assess girls' impairments more severe than boys' impairments. Nevertheless, teachers are more likely to recommend treatment, counselling and/or medication to boys than to girls. While teachers' perceptions of pupils' difficulties are gendered, strategies or methods for teaching pupils with ADHD seem not to be. In the articles included in this review, there are hardly any examples given of gender-sensitive teaching methods. Furthermore, it is concluded that regardless of gender aspects, a deficit perspective dominates in research presented in this article, and it appears that children are held responsible for school difficulties while the school setting is not

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European Review for Medical and Pharmacological Sciences. 2022;26:3858-71.

RELATIONSHIP BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND TEMPOROMANDIBULAR DISORDERS IN ADULTS: A QUESTIONNAIRE-BASED REPORT.

Stelcer B, et al.

OBJECTIVE: The symptoms of the attention deficit hyperactivity disorder (ADHD) persist in the adult years of life in most cases. They appear in adults with accompanying psychosocial problems. Temporomandibular disorder (TMD) refers to signs and symptoms associated with pain of non-dental origin in the oro-facial

region, functional and structural disruptions of the masticatory system, especially the temporomandibular joints (TMJs) and masticatory muscles. The aim of the study was to show the relationship between the presence of ADHD symptoms in adulthood, in relation to the intensity of pain experienced in the face and problems connected to the TMD symptomatology, as well as sleep disorders.
PATIENTS AND METHODS: The study group consisted of 252 individuals aged 18-55 years of both sexes, generally healthy. Each participant was asked to fill in several questionnaires, namely: ASRS (the World Health Organization ADHD Adult Self-Report Scale), DIVA (18 questions, 9 for concentration and attention disorders with an option in adulthood and childhood, 9 for hyperactivity and impulsivity with an option in adulthood and childhood), Athens Insomnia Scale, Stanford Sleepiness Scale (SSS), DC/ TMD classification (Diagnostic Criteria for Temporomandibular Disorders - biaxial diagnostic criteria based on the biopsychosocial model).
RESULTS: Results show that when ADHD symptoms observed in childhood persist, personality disorders, social relations disorders and affective disorders are found more often in adults than motor hyperactivity.
CONCLUSIONS: There is a positive association between ADHD and the occurrence of symptoms of TMD in adults. This study confirmed this picture, extending it to include pain and sleep disorders

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Fertility and Sterility. 2018;110:e66.

EXAMINATION OF BEHAVIORAL DIFFICULTIES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN CONCEIVED BY INFERTILITY TREATMENT.

Yeung E, Sundaram R, Lin T, et al.

OBJECTIVE: To evaluate whether children conceived with infertility treatment differ in behavioral difficulties and attention deficit/hyperactivity at 7-8 years of age from children not conceived with infertility treatment. To determine whether there are differences by type of infertility treatment (i.e., assisted reproductive technologies (ART) or ovulation induction (OI)). DESIGN: The Upstate KIDS Study is a matched exposure birth cohort which recruited newborns based on birth certificate indication of infertility treatment use. For every singleton conceived with treatment, three singletons who were not conceived with treatment were recruited (between 2008-2010) frequency matched on region of birth in New York State (excluding New York City).
MATERIALS AND METHODS: Mode of conception was based on maternal report at 4 months postpartum. Linkage of the cohort to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System was conducted to verify ART use. Behavioral difficulties were assessed using the Strengths and Difficulties Questionnaire (SDQ) at 7 years (n=946) and hyperactivity/inattention using the Vanderbilt questionnaire at 8 years of age (n=1041). Maternal questionnaires were scored and clinical cut-points used to define difficulties. Maternal report at 7 or 8 years of age of physician diagnoses or medication use for ADHD was also evaluated (n=1301). Logistic regression estimated adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for having difficulties/hyperactivity adjusting for sociodemographic factors, smoking and parity.
RESULTS: Thirty-three percent of children were conceived by infertility treatment, with 15% by ART and 18% by OI. Children conceived with infertility treatment did not exhibit any more behavioral difficulties than their peers at age 7 (aOR: 1.17; 95% CI: 0.70-1.94). Neither inattention or hyperactivity at age 8 were associated with infertility treatment (aOR: 0.84; 95% CI: 0.43-1.64 and 0.65; 95% CI: 0.30, 1.38, respectively). Their combination based on the Vanderbilt questionnaire (attention deficit hyperactivity disorder, ADHD) did not differ (aOR: 1.06; 95% CI: 0.46, 2.45). Maternal report of a history of ADHD of their children (10%) also did not differ by infertility treatment use (aOR: 1.21; 95% CI: 0.77, 1.90). Results were similar in the ART and OI subgroups.
CONCLUSIONS: Despite concerns that children conceived with infertility treatment are at risk for health issues, our findings show that behavioral difficulties and inattention/hyperactivity did not differ at 7-8 years of age

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Front Behav Neurosci. 2022 May;16.

NEURAL MARKERS OF METHYLPHENIDATE RESPONSE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Arnett AB, Rutter TM, Stein MA.

Background: Despite widespread use of stimulants to treat ADHD, individual responses vary considerably and few predictors of response have been identified. The identification of reliable and clinically feasible biomarkers would facilitate a precision medicine approach to pharmacological treatment of ADHD. We test the hypothesis that two electroencephalography (EEG) based neural signatures of ADHD, resting aperiodic slope exponent and novelty P3 amplitude, are markers of methylphenidate response in children. We hypothesize that positive response to methylphenidate treatment will be associated with greater abnormality of both neural markers.

Methods: Twenty-nine 7-11 year-old children with ADHD and a history of methylphenidate treatment, and 30 controls completed resting EEG and visual oddball event related potential (ERP) paradigms. ADHD participants were characterized as methylphenidate responders (n = 16) or non-responders (n = 13) using the clinical global improvement (CGI-I) scale during blinded retrospective interview. All participants abstained from prescribed medications for at least 48 hours prior to the EEG.

Results: As expected, methylphenidate responders (CGI-I rating < 3) demonstrated attenuated P3 amplitude relative to controls. Unexpectedly, methylphenidate non-responders showed atypically flat aperiodic spectral slope relative to controls, while responders did not differ on this measure.

Conclusion: ADHD symptoms associated with atypical patterns of intrinsic neural activity may be less responsive to methylphenidate. In contrast, ADHD symptoms associated with abnormal frontal-striatal neural network excitation may be correctable with methylphenidate. Altogether, EEG is a feasible and promising candidate methodology for identifying biomarkers of stimulant response

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Frontiers in Neuroscience. 2022;16.

ABNORMAL INSULAR DYNAMIC FUNCTIONAL CONNECTIVITY AND ITS RELATION TO SOCIAL DYSFUNCTIONING IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Fateh AA, Huang W, Mo T, et al.

Anomalies in large-scale cognitive control networks impacting social attention abilities are hypothesized to be the cause of attention deficit hyperactivity disorder (ADHD). The precise nature of abnormal brain functional connectivity (FC) dynamics including other regions, on the other hand, is unknown. The concept that insular dynamic FC (dFC) among distinct brain regions is dysregulated in children with ADHD was evaluated using Insular subregions, and we studied how these dysregulations lead to social dysfunctioning. Data from 30 children with ADHD and 28 healthy controls (HCs) were evaluated using dynamic resting state functional magnetic resonance imaging (rs-fMRI). We evaluated the dFC within six subdivisions, namely both left and right dorsal anterior insula (dAI), ventral anterior insula (vAI), and posterior insula (PI). Using the insular sub-regions as seeds, we performed group comparison between the two groups. To do so, two sample t-tests were used, followed by post-hoc t-tests. Compared to the HCs, patients with ADHD exhibited decreased dFC values between right dAI and the left middle frontal gyrus, left postcentral gyrus and right of cerebellum crus, respectively. Results also showed a decreased dFC between left dAI and thalamus, left vAI and left precuneus and left PI with temporal pole. From the standpoint of the dynamic functional connectivity of insular subregions, our findings add to the growing body of evidence on brain dysfunction in ADHD. This research adds to our understanding of the neurocognitive mechanisms behind social functioning deficits in ADHD. Future ADHD research could benefit from merging the dFC approach with task-related fMRI and non-invasive brain stimulation, which could aid in the diagnosis and treatment of the disorder

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Front Psychiatry. 2022;13.

URINARY METABOLOMIC STUDY IN A HEALTHY CHILDREN POPULATION AND METABOLIC BIOMARKER DISCOVERY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Tian X, Liu X, Wang Y, et al.

Objectives: Knowledge of the urinary metabolomic profiles of healthy children and adolescents plays a promising role in the field of pediatrics. Metabolomics has also been used to diagnose disease, discover novel biomarkers, and elucidate pathophysiological pathways. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood. However, large-sample urinary metabolomic studies in children with ADHD are relatively rare. In this study, we aimed to identify specific biomarkers for ADHD diagnosis in children and adolescents by urinary metabolomic profiling.

Methods: We explored the urine metabolome in 363 healthy children aged 1-18 years and 76 patients with ADHD using high-resolution mass spectrometry.

Results: Metabolic pathways, such as arachidonic acid metabolism, steroid hormone biosynthesis, and catecholamine biosynthesis, were found to be related to sex and age in healthy children. The urinary metabolites displaying the largest differences between patients with ADHD and healthy controls belonged to the tyrosine, leucine, and fatty acid metabolic pathways. A metabolite panel consisting of FAPy-adenine, 3-methylazelaic acid, and phenylacetylglutamine was discovered to have good predictive ability for ADHD, with a receiver operating characteristic area under the curve (ROC-AUC) of 0.918. A panel of FAPy-adenine, N-acetylaspartylglutamic acid, dopamine 4-sulfate, aminocaproic acid, and asparaginyl-leucine was used to establish a robust model for ADHD comorbid tic disorders and controls with an AUC of 0.918

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General Psychiatry. 2021;34.

PSYCHOMETRIC PROPERTIES OF THE CAREGIVER STRAIN QUESTIONNAIRE AMONG CHINESE PARENTS OF CHILDREN WITH ADHD OR ASD.

Yang R, Zhou H, Liu J, et al.

Background There is an urgent need in clinical practice to measure the stress of parenting. The Caregiver Strain Questionnaire (CGSQ) was found to be useful to measure parenting stress, but it has not been validated among the Chinese population.

Aims To assess the reliability and construct validity of the Chinese version of CGSQ among Chinese parents.

Methods From 2016 to 2017, 266 parents (patient group) with a child having DSM-5-defined attention deficit hyperactivity disorder (ADHD) (n=107) or autism spectrum disorder (ASD) (n=159) and 268 parents of healthy children (control group) were recruited to the present study in Kunming, Yunnan province. All the parents were asked to fill out the Chinese version of CGSQ. We conducted exploratory factor analysis and confirmatory factor analysis (CFA) to verify construct validity of CGSQ in both patient and control groups. Cronbach's +¦ coefficient as an index of internal consistency was assessed for each subscale. Fourteen days later, 23 subjects filled out the scale again. Intra-class correlation coefficient was calculated to evaluate the test-retest reliability.

Results (1) Cronbach's alpha of the global scale was 0.901 for the control group and 0.952 for the patient group. The test-retest reliability for the whole scale was 0.890; (2) CFA indicated that the three-factor model had better fitting indices compared with the two-factor model in both groups. Besides, the fitting indices in the patient group were more favourable than those of the control group, with 2/df=1.564, Goodness-of-Fit Index=0.841, Comparative Fit Index=0.954, and root mean square error of approximation=0.065 for the patient group at three-factor model; (3) The caregiver strain of ASD parents was statistically higher than that of ADHD parents, and caregiver strain of ADHD parents was higher than that of control group.

Conclusion These findings provide initial evidence to support the construct validity and reliability of CGSQ as a parenting stress measurement tool for Chinese parents, especially for parents of children with ADHD or ASD

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Global Advances in Health and Medicine. 2022;11:24.

EVIDENCE OF SAFETY IN A RCT OF A MULTI-NUTRIENT TREATMENT FOR CHILDREN WITH ADHD AND EMOTIONAL DYSREGULATION: THE MADDY STUDY.

Leung B, Srikanth P, Gracious B, et al.

Methods: This study analyzed the change in AEs in the PAERS which consisted of 43 symptom questions and measured at baseline, week 4, and week 8. Frequency (proportions) were calculated for all treatment-emergent AEs and principal component analysis was conducted to determine grouping of 16 psychiatric-specific AEs. A combined score ranged from 0 to 5 was created based on symptom presence, functional impairment, and severity of the psychiatric AEs. Mean score change was calculated from baseline to week 8 and between groups with intention-to-treat and perprotocol samples.

Results: Data from 126 children were analyzed. Their mean age was 9.8 (SD=1.7), with majority (73%) male, White (88%), and 72% diagnosed with ADHD prior to the study initial evaluation. Baseline presence of PAERS symptoms was similar between treatment groups, and no betweengroup differences for treatment-emergent adverse events (AEs) were detected. Analysis of psychiatric AEs showed the micronutrient group showed a greater decrease than the placebo group with a between-group difference in change of -0.36 (95% CI: -0.67, -0.04; p=0.03) with ITT data and -0.48 (95% CI: -0.81, -0.15; p=0.005) with per-protocol data.

Background: Purpose: There is a paucity of safety data on nutritional supplementation use in the pediatric population. The Pediatric Adverse Event Rating Scale (PAERS) measured adverse events (AEs) of children aged 6 to 12 years enrolled in the Micronutrients for ADHD in Youth (MADDY) study. The MADDY study was an eight-week multi-site fully blinded randomized placebo-controlled trial. The purpose of this study was to determine the safety of a broad-spectrum multi-nutrients intervention using the PAERS.

Conclusion: The PAERS results demonstrated that the multi-nutrient supplement did not result in more adverse events with respect to psychiatric symptoms than placebo, suggesting it is a safe intervention

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Health Technol Assess. 2022 Jun;26:1-140.

SENSORY INTEGRATION THERAPY FOR CHILDREN WITH AUTISM AND SENSORY PROCESSING DIFFICULTIES: THE SENITA RCT.

Randell E, Wright M, Milosevic S, et al.

Background: Carers report unmet need for occupational therapy services addressing sensory difficulties in autism, yet insufficient evidence exists to recommend a therapeutic approach.

Objectives: Our aim was to determine the clinical effectiveness and cost-effectiveness of sensory integration therapy for children with autism and sensory difficulties across behavioural, functional and quality-of-life outcomes.

Design: We carried out a parallel-group randomised controlled trial, incorporating an internal pilot and a process evaluation. Randomisation utilised random permuted blocks.

Setting and participants: Children were recruited via services and self-referral in Wales and England. Inclusion criteria were having an autism diagnosis, being in mainstream primary education and having definite/probable sensory processing difficulties. Exclusion criteria were having current/previous sensory integration therapy and current applied behaviour analysis therapy.

Intervention: The intervention was manualised sensory integration therapy delivered over 26 weeks and the comparator was usual care.

Outcomes: The primary outcome was problem behaviours (determined using the Aberrant Behavior Checklist), including irritability/agitation, at 6 months. Secondary outcomes were adaptive behaviour, functioning and socialisation (using the Vineland Adaptive Behavior Scales); carer stress (measured using the Autism Parenting Stress Index); quality of life (measured using the EuroQol-5 Dimensions and Carer Quality of Life); functional change (according to the Canadian Occupational Performance Measure); sensory processing (determined using the Sensory Processing Measure™ at screening and at 6 months to examine mediation effects); and cost-effectiveness (assessed using the Client Service Receipt Inventory). Every effort was made to ensure that outcome assessors were blind to allocation.

Results: A total of 138 participants were randomised (n = 69 per group). Usual care was significantly different from the intervention, which was delivered with good fidelity and adherence and minimal contamination, and was associated with no adverse effects. Trial procedures and outcome measures were acceptable. Carers and therapists reported improvement in daily functioning. The primary analysis included 106 participants.

There were no significant main effects of the intervention at 6 or 12 months. The adjusted mean difference between groups on the Aberrant Behavior Checklist - irritability at 6 months post randomisation was 0.40 (95% confidence interval -2.33 to 3.14; p = 0.77). Subgroup differences in irritability/agitation at 6 months were observed for sex of child (intervention × female = 6.42, 95% confidence interval 0.00 to 12.85; p = 0.050) and attention deficit hyperactivity disorder (intervention × attention deficit hyperactivity disorder = -6.77, 95% confidence interval -13.55 to -0.01; p = 0.050). There was an effect on carer stress at 6 months by region (intervention × South England = 7.01, 95% confidence interval 0.45 to 13.56; p = 0.04) and other neurodevelopmental/genetic conditions (intervention × neurodevelopmental/genetic condition = -9.53, 95% confidence interval -18.08 to -0.98; p = 0.030). Carer-rated goal performance and satisfaction increased across sessions (p < 0.001), with a mean change of 2.75 (95% confidence interval 2.14 to 3.37) for performance and a mean change of 3.34 (95% confidence interval 2.63 to 4.40) for satisfaction. Health economic evaluation suggests that sensory integration therapy is not cost-effective compared with usual care alone.

Limitations: Limitations included variability of the intervention setting (i.e. NHS vs. private), delay for some receiving therapy, an error in administration of Vineland Adaptive Behavior Scales and no measurement of comparator arm goal performance.

Conclusions: The intervention did not demonstrate clinical benefit above standard care. Subgroup effects are hypothesis-generating only. The intervention is likely to be effective for individualised performance goals, although it is unclear whether effects were in addition to standard care or were maintained.

Future work: Further investigation of subgroup effects is needed.

Trial registration: This trial is registered as ISRCTN14716440.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 26, No. 29. See the NIHR Journals Library website for further project information

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Infant Behav Dev. 2022;68.

THE INTERACTION BETWEEN INFANT NEGATIVE EMOTIONALITY AND COGNITION PREDICTS ADHD-RELATED BEHAVIORS IN TODDLERHOOD.

Joseph HM, Lorenzo NE, Wang FL, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder commonly identified in childhood. Affective and cognitive characteristics that are identifiable as early as infancy could be signals of risk for developing ADHD. Specifically, the interplay between emotionality and cognition may be important in predicting early symptoms of ADHD. This study examined the independent and interactive effects of infant negative emotionality and cognition on the development of inattention and hyperactivity/impulsivity in toddlerhood among infants at high and low familial likelihood for ADHD. Participants were 64 infants (M = 8.7, SD = 1.8) at high (n = 32) and low (n = 32) familial likelihood for ADHD, defined as at least one parent with ADHD or two parents without ADHD, respectively. Negative emotionality and cognition in infancy were assessed using the Infant Behavior Questionnaire and the Bayley's Scales of Infant and Toddler Development, and ADHD symptoms were assessed at toddler follow-up (M= 20.0, SD= 3.2) using the Child Behavior Checklist. Accounting for the quality of parent-child interaction, infantsΓÇÖ negative emotionality (+¦ =.033, p =.938) and cognition (+¦ =.006, p =.884) did not independently predict toddlersΓÇÖ ADHD-related behaviors, but their interaction did (+¦ =.110, p =.019). For infants with higher levels of cognition (>95th percentile), higher negative emotionality predicted more ADHD-related behaviorss. For infants with lower levels of cognition (<11th percentile), higher negative emotionality predicted fewer ADHD-related behaviors. There may be two affective-cognitive pathways to inattention and hyperactivity/impulsivity in toddlerhood. The combination of higher levels of negative emotionality and cognition may result in greater frustration when goals are blocked, resulting in the expression of dysregulated behaviors (i.e., ADHD symptoms). Alternatively, low levels of negative emotionality and cognition combined may lead to dysregulation that is primarily cognitive in nature (such as the inattention symptoms of ADHD). Investigating affective and cognitive processes simultaneously may be important for increasing understanding of the early signals of ADHD risk

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Int J Clin Pract. 2022;2022:4836731.

EFFECT OF VITAMIN D ON PARAXONASE-1, TOTAL ANTIOXIDANT CAPACITY, AND 8-ISOPROSTAN IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mohammadzadeh HN, Samadi M, Seyedi CM, et al.

METHOD: In this double-blind, randomized, placebo-controlled trial, 75 children (aged 6-12) diagnosed with ADHD were randomly assigned into two groups. The supplementation group received vitamin D3 (2000IU), and the control group received a placebo for 3 months. Blood samples were collected at baseline and after intervention to analyze the 25(OH)D, paraxonase-1 activity (PON-1), Total Antioxidant Capacity (TAC), and 8-isoprostan levels.

RESULTS: A significant rise in circulating 25(OH)D was observed in the vitamin D group versus the placebo group at the end of the study. There was no reduction in 8-isoprostan levels in the vitamin D group compared to the placebo group. Serum paraxonase-1 and TAC concentration decreased in both groups, but these alterations were not statistically significant in the treatment group versus the placebo group at the end of the intervention.

CONCLUSION: Vitamin D supplementation for 3 months did not have beneficial effects on biomarkers of oxidative stress status. To confirm these findings, further studies on children are suggested

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

LISTENING TO WHITE NOISE IMPROVED VERBAL WORKING MEMORY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PILOT STUDY.

Chen IC, Chan HY, Lin KC, et al.

Existing research demonstrates that children with attention-deficit/hyperactivity disorder (ADHD) underperform in cognitive tasks involving working memory (WM) due to hypo-arousal, which has led to the development of arousal regulation models to determine proper levels of arousal and optimal cognitive outcomes. The present study focuses on investigating the effects of external auditory stimuli on verbal WM in children with ADHD. Thirteen children with ADHD (aged 6-10 years old) and thirteen age- and gender-matched children with typical development (TD) completed the verbal WM task when listening to no sound, white noise, or pleasant music. A two-way repeated-measures analysis of variance was used to compare the verbal WM performance between groups in the three auditory conditions. Children with ADHD showed the best verbal WM performance when listening to white noise and the worst performance when listening to no sound. Yet, children with TD performed the best in the no-sound condition and the worst in the white noise condition. Our findings suggest auditory white noise is beneficial for ideal arousal regulation and cognitive performance involving verbal WM for children with ADHD and support the moderate brain arousal model. Providing external white noise is a non-invasive and cost-effective approach to improving verbal WM in children with ADHD in real-world contexts

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

MENTAL HEALTH CONDITIONS ACCORDING TO STRESS AND SLEEP DISORDERS.

Merrill RM.

The purpose of this study was to compare associations between stress and sleep disorders (insomnia, hypersomnia, and sleep apnea), identify potential modifying effects, and compare associations between stress and types of sleep disorders with selected mental health conditions. Analyses were based on 21,027 employees aged 18-64 years in 2020 who were insured by the Deseret Mutual Benefit Administrators (DMBA). The risk of stress (2.3%) was significantly greater in women, singles, and those with dependent children. The risk of a sleep disorder was 12.1% (2.1% for insomnia, 1.0% for hypersomnia, and 10.1% for sleep apnea). The risk of stress was significantly greater for those with a sleep disorder (136% overall, 179% for insomnia, and 102% for sleep apnea after adjusting for age, sex, marital status, dependent children, and sleep disorders). The risk of stress among those with sleep apnea was significantly greater for singles than for married individuals. Approximately 9.5% had anxiety, 8.5% had depression, 2.0% had ADHD, 0.6% had bipolar disorder, 0.4% had OCD, and 0.1% had schizophrenia. Each of these mental health conditions was significantly positively associated with stress and sleep disorders. Bipolar disorder and schizophrenia were

more strongly associated with stress and sleep disorders than were the other mental health conditions. Insomnia was more strongly associated with anxiety, bipolar disorder, OCD, and schizophrenia than was sleep apnea

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

PRENATAL EXPOSURE TO ORGANOPHOSPHORUS PESTICIDES AND PRESCHOOL ADHD IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY.

Manley CK, Villanger GD, Thomsen C, et al.

Prenatal organophosphorus pesticide (OPP) exposure has been associated with child attention-deficit/hyperactivity disorder (ADHD) in agricultural communities and those that are exposed to residentially applied insecticides. To examine this association in populations that are exposed primarily through diet, we estimate the associations between prenatal OPP exposure and preschool ADHD in the Norwegian Mother, Father and Child Cohort Study (MoBa), and describe modification by paraoxonase 1 (PON1) gene variants. We used participants from the MoBa Preschool ADHD Sub-study (n = 259 cases) and a random sample of MoBa sub-cohort participants (n = 547) with birth years from 2004 to 2008. Prenatal urinary dialkylphosphate (DAP) metabolites (total diethylphosphate [DEP] and total dimethylphosphate [DMP]) were measured by an ultra-performance liquid chromatography-time-of-flight system and summed by molar concentration. Maternal DNA was genotyped for coding variants of PON1 (Q192R and L55M). We used a multivariable logistic regression to calculate the odds ratios (OR) and 95% confidence intervals, adjusted for maternal education, parity, income dependency, age, marital status, ADHD-like symptoms, pesticide use, produce consumption, and season. We found no associations between DAP metabolite concentrations and preschool ADHD. The adjusted ORs for exposure quartiles 2-4 relative to 1 were slightly inverse. No monotonic trends were observed, and the estimates lacked precision, likely due to the small sample size and variation in the population. We found no evidence of modification by PON1 SNP variation or child sex. Maternal urinary DAP concentrations were not associated with preschool ADHD

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

THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE AS A VALUABLE SCREENING TOOL FOR IDENTIFYING CORE SYMPTOMS AND BEHAVIOURAL AND EMOTIONAL PROBLEMS IN CHILDREN WITH NEUROPSYCHIATRIC DISORDERS.

Grasso M, Lazzaro G, Demaria F, et al.

The Strengths and Difficulties Questionnaire (SDQ) is a worldwide questionnaire used for the early identification of behavioural/emotional symptoms in children and adolescents with neuropsychiatric disorders. Although its prognostic power has been studied, it has not yet been tested whether SDQ: (i) can identify pathognomonic symptoms across a variety of neurodevelopmental and neuropsychiatric disorders, (ii) can capture emotional and behavioural problems associated with the main diagnosis, as well as shared transdiagnostic dimensions, and (iii) can detect changes in symptomatology with age. The present study evaluated nearly 1000 children and adolescents overall with Global Developmental Delay (GDD), Intellectual Disability (ID), Language Disorder (LD), Specific Learning Disorder (SLD), Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), Mood Disorder (MD), Anxiety Disorder (AD), and Eating Disorders (ED). We found that SDQ: (i) can identify the core symptoms in children with ASD, ADHD, MD, and AD via specific subscales; (ii) can capture the associated emotional and behavioural symptoms in children with LD, GDD, ID, SLD, and ED; and (iii) can detect changes in the symptomatology, especially for GDD, LD, ASD, ADHD, and AD. SDQ is also able to recognise the transdiagnostic dimensions across disorders. Our results underscore the potential of SDQ to specifically differentiate and identify behavioural/emotional profiles associated with clinical diagnosis

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

SLEEP DISTURBANCES IN CHILDREN WITH ATTENTIONAL DEFICIT HYPERACTIVITY DISORDER AND SPECIFIC LEARNING DISORDERS.

Saccani MS, Ursumando L, Di Vera S, et al.

Sleep disturbances may be a significant source of distress for children with neurodevelopmental disorders, and consequently also for their families. Crucially, sleep disturbances might be influenced by comorbidity. Attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD) often co-occur, and consequently, investigating sleep disturbances in children with comorbidity of ADHD and SLD is essential. Our study aimed at detecting sleep difficulties in a group of 74 children with ADHD, 78 children with SLD, and 76 children with ADHD and SLD by using the Sleep Disturbances Scale for Children. The results showed that sleep difficulties emerge more clearly in children with comorbid ADHD and SLD compared to children with only ADHD or SLD. These sleep difficulties were not due to differences in ages and behavioral/emotional problems. In conclusion, evaluating sleep disturbances is important when assessing and managing children with ADHD, SLD, and particularly with the two comorbid conditions, to better understand their difficulties and develop tailored interventions

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Int J Epidemiol. 2022 Jun;51:910-18.

CIRCULATING LEVELS OF MATERNAL VITAMIN D AND RISK OF ADHD IN OFFSPRING: RESULTS FROM THE VITAMIN D ANTENATAL ASTHMA REDUCTION TRIAL.

Chu SH, Huang M, Kelly RS, et al.

Background: Low levels of circulating 25-hydroxy-vitamin D [25(OH)D] have been shown to associate with prevalent attention-deficit/hyperactivity disorder (ADHD), but few studies have examined the association between 25(OH)D during fetal development and risk of childhood ADHD.

Methods: Maternal plasma 25(OH)D was measured at 10-18 and 32-38 weeks of gestation, with sufficiency defined as 25(OH)D ≥ 30 ng/ml. Offspring ADHD status between ages 6-9 years was measured by parent report of clinical ADHD diagnosis among 680 mother-child pairs from the Vitamin D Antenatal Asthma Reduction Trial. Association between maternal 25(OH)D and child ADHD was assessed using logistic regression, adjusting for maternal age, race and ethnicity. Effect modification by offspring sex was also assessed.

Results: No associations between maternal 25(OH)D at 10-18 weeks of gestation and offspring ADHD were observed. In the third trimester, we observed associations between maternal vitamin D sufficiency and offspring ADHD [odds ratio (OR) 0.47, 95% confidence interval (CI) 0.26-0.84], in addition to maternal 25(OH)D sufficiency category, comparing the deficient (OR 0.34, 95% CI 0.12-0.94), insufficient (OR 0.41, 95% CI 0.15-1.10) and sufficient (OR 0.20, 95% CI 0.08-0.54) categories against highly deficient 25(OH)D, respectively. Stratified analyses revealed a protective association for sufficient maternal 25(OH)D and child ADHD among males (OR 0.47, 95% CI 0.23-0.94); the synergy index for additive effect modification of risk was 1.78 (95% CI 0.62-5.08).

Conclusions: Higher levels of maternal vitamin D in the third trimester are associated with lower risk of ADHD in offspring, with modest evidence for a stronger effect among male offspring. However, larger studies will be necessary to confirm these findings

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Int J Epidemiol. 2022 Jun;51:919-30.

DECLINE IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER TRAITS OVER THE LIFE COURSE IN THE GENERAL POPULATION: TRAJECTORIES ACROSS FIVE POPULATION BIRTH COHORTS SPANNING AGES 3 TO 45 YEARS.

Wootton RE, Riglin L, Blakey R, et al.

Background: Trajectories of attention-deficit hyperactivity disorder (ADHD) traits spanning early childhood to mid-life have not been described in general populations across different geographical contexts. Population trajectories are crucial to better understanding typical developmental patterns.

Methods: We combined repeated assessments of ADHD traits from five population-based cohorts, spanning ages 3 to 45 years. We used two measures: (i) the Strengths and Difficulties Questionnaire (SDQ) hyperactive-inattentive subscale (175 831 observations, 29 519 individuals); and (ii) scores from DSM-

referenced scales (118 144 observations, 28 685 individuals). Multilevel linear spline models allowed for non-linear change over time and differences between cohorts and raters (parent/teacher/self).
Results: Patterns of age-related change differed by measure, cohort and country: overall, SDQ scores decreased with age, most rapidly declining before age 8 years (-0.157, 95% CI: -0.170, -0.144 per year). The pattern was generally consistent using DSM scores, although with greater between-cohort variation. DSM scores decreased most rapidly between ages 14 and 17 years (-1.32%, 95% CI: -1.471, -1.170 per year). Average scores were consistently lower for females than males (SDQ: -0.818, 95% CI: -0.856, -0.780; DSM: -4.934%, 95% CI: -5.378, -4.489). This sex difference decreased over age for both measures, due to an overall steeper decrease for males.
Conclusions: ADHD trait scores declined from childhood to mid-life, with marked variation between cohorts. Our results highlight the importance of taking a developmental perspective when considering typical population traits. When interpreting changes in clinical cohorts, it is important to consider the pattern of expected change within the general population, which is influenced by cultural context and measurement

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Int J Psychophysiol. 2022 Jul;177:43-60.

A COMPARATIVE REVIEW OF THE PSYCHOPHYSIOLOGY OF ATTENTION IN CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Karakay S.

The present review focuses on the development of attention as indexed in the electrical activity of the brain under a systematic framework of attention-related paradigms and experimental tasks in typically developing children (TDC). The framework is organized according to the filter and selective-set paradigms of attention research and experimental tasks that these models commonly use. The first part of the review discusses age-variant changes in the event-related potentials (ERPs) of TDC. Age affects the parameters of the various attention-related components (latencies and amplitudes) independently and differentially. The changes are mainly in the form of decreasing latencies, showing that aging increases the speed and efficiency of attentional processing. High task difficulty and cognitive load produce a shift in TDC from early selection, which involves a perceptual analysis, to late selection, which involves target detection. The second part of the review discusses attentional processing in children with attention deficit hyperactivity disorder (ADHD). Relative to TDC, ERP differences in ADHD are mainly represented in component amplitudes, which normally vary according to task difficulty and cognitive load. The literature permits a review of the differences between children with ADHD and age-matched TDC in not only ERPs but also in resting electroencephalogram (EEG) and event-related oscillations (EROs). Some of the differences between children with ADHD and TDC are quantitative and in the form of maturational lag, while others are qualitative and in the form of maturational deviance. The early gamma-band response (GBR) appears to be a significant biomarker of ADHD. The match-and-utilization model, which delineates the pervasive role that early GBR plays in the bottom-up and top-down processes of attention, applies to ADHD. The integrative approach of the present review reveals the gaps in the relevant literature and suggests directions for future studies by way of which a comprehensive understanding of ADHD may be possible

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Int J Qual Stud Health Well -being. 2022 Dec;17:2088456.

AMBIVALENT BONDS, POSITIVE AND NEGATIVE EMOTIONS, AND EXPECTATIONS IN TEACHERS' PERCEPTIONS OF RELATIONSHIP WITH THEIR STUDENTS WITH ADHD.

Krtek A, Malinakova K, Rudnicka RK, et al.

A growing body of research has been focusing recently on the life and well-being of students with attention-deficit/hyperactivity disorder (ADHD) and also on the well-being of their teachers. However, there is a need for in-depth, qualitative insights into ADHD issues from the teachers' perspectives. Therefore, the main aim of this qualitative study was to use thematic analysis to explore how teachers perceive the relationship with students with ADHD and the factors that influence the quality of this relationship. Sixteen teachers working with adolescent ADHD students were interviewed for this purpose. The results indicate that the quality of the teacher-ADHD student relationship is associated with the ADHD students related behaviours, ambivalent emotions of the teacher, the teacher's beliefs about ADHD and the beliefs about the determinants of the

behaviour of the students with ADHD and the teacher's approaches and methods of work in the classroom. Furthermore, the results suggest that increasing the quality of the teachers' well-being is associated with knowledge of ADHD determinants, regulation of ambivalent emotions, empathy, teachers' ability to perceive positive qualities and the potentials of the students with ADHD and their motivation to teach ADHD students

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Int J Environ Res Public Health. 2022;19.

STRUCTURAL EQUATION MODELING (SEM): GAMING DISORDER LEADING UNTREATED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TO DISRUPTIVE MOOD DYSREGULATION.

Tzang RF, Chang CH, Chang YC.

Background: Internet gaming disorder (IGD) in youths likely leads to disruptive mood dysregulation, especially among those with attention-deficit/hyperactivity disorder (ADHD). Whether IGD mediates the pathways leading ADHD to disruptive emotional dysfunction remains unclear. This study aims to elucidate the direct or indirect influence of IGD on ADHD;

Method: The Swanson, Nolan, and Pelham Version IV questionnaire was used to evaluate symptoms of ADHD and oppositional defiant disorder, and the Chen gaming disorder scale was used to measure IGD. A psychiatrist diagnosed ADHD, IGD, and disruptive mood dysregulation disorder (DMDD)-like symptoms. Structural equation modeling was applied to evaluate the role of IGD in mediating ADHD progression to disruptive mood dysregulation;

Results: Among a total of 102 ADHD youths, 53 (52%) of them with IGD were significantly more likely to have poor interpersonal relationships ($p < 0.01$) and DMDD-like symptoms ($p < 0.01$) than ADHD youths without IGD. IGD played a mediating role in increasing the risk of disruptive mood dysregulation in ADHD youths;

Conclusions: The findings suggest that IGD mediates ADHD's progression to disruptive mood dysregulation. Intensive biopsychosocial interventions are warranted for ADHD youths with IGD. More children and adolescents became mood-dysregulated after excessive gaming during the COVID-19 pandemic; this study's results suggest that child mental health experts develop earlier detection and prevention strategies for children and adolescents hidden behind internet addiction

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Int J Environ Res Public Health. 2022;19.

NEUROLOGICAL MECHANISMS OF DIAGNOSIS AND THERAPY IN SCHOOL CHILDREN WITH ADHD IN POLAND.

Nermend M, Flaga-Gieruszy+äska K, Kroplewski Z, et al.

The paper aims to present a holistic view of attention deficit hyperactivity disorder (ADHD) in pedagogical, psychological, legal, and social dimensions in Polish schools. The authors present the benefits of neurofeedback therapy for elementary school pupils. In order to verify the validity, the paper compares the concordance of a medical diagnosis confirming ADHD syndrome with the occurrence of abnormal electrical brain function recording and abnormalities therein as well as the effectiveness of the neurofeedback therapy. The study confirms that the reported problems faced by pupils and affecting their emotional functioning are reflected in their EEG records. Conclusions from the study lead to the proposal that the neurofeedback assessment should be performed at schools, which should result in the implementation of effective therapy. Moreover, the neurofeedback method should be promoted in Polish schools as an alternative to pharmacological therapy, which, as the research proves, is not always effective. Neurofeedback therapy, similarly to behavioral therapy, is very much needed and useful because it provides optimal conditions for the child's development and shapes their relations with the environment effectively and harmlessly

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J Am Acad Child Adolesc Psychiatry. 2022 Jul;61:892-904.

PSYCHIATRIC OUTCOMES, FUNCTIONING, AND PARTICIPATION IN EXTREMELY LOW GESTATIONAL AGE NEWBORNS AT AGE 15 YEARS.

Frazier JA, Cochran D, Kim S, et al.

OBJECTIVE: To evaluate the prevalence, co-occurrence, sex differences, and functional correlates of DSM-5 psychiatric disorders in 15-year-old adolescents born extremely preterm.

METHOD: The Extremely Low Gestational Age Newborns (ELGAN) Study is a longitudinal study of children born <28 weeks gestation. At age 15, 670 adolescents completed the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), the Youth Self-Report, a disability scale of participation in social roles, and cognitive testing. Parents completed a family psychiatric history questionnaire.
RESULTS: The most prevalent psychiatric disorders were anxiety, attention-deficit/hyperactivity disorder, and major depression. More girls met criteria for anxiety than boys. Though 66% of participants did not meet criteria for a psychiatric disorder, 15% met criteria for 1, 9% for 2, and 8% for 3 psychiatric disorders. Participants with 2 psychiatric disorders were more likely to have repeated a grade, to have an individualized educational program, and to have a lower nonverbal IQ than those with no psychiatric disorders. Participants with any psychiatric disorder were more likely to use psychotropic medications; to have greater cognitive and functional impairment; and to have mothers who were single, were on public health insurance, and had less than a high school education. Finally, a positive family psychiatric history was identified more frequently among adolescents with 3 psychiatric disorders.
CONCLUSION: Among adolescents born extremely preterm, anxiety, major depression, and attention-deficit/hyperactivity disorder were the most prevalent psychiatric disorders at age 15. Adolescents with >1 psychiatric disorder were at increased risk for multiple functional and participatory challenges

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J Am Acad Child Adolesc Psychiatry. 2022 Jul;61:934-45.
GENOME-WIDE ASSOCIATION META-ANALYSIS OF CHILDHOOD AND ADOLESCENT INTERNALIZING SYMPTOMS.
Jami ES, Hammerschlag AR, Ip HF, et al.
OBJECTIVE: To investigate the genetic architecture of internalizing symptoms in childhood and adolescence.
METHOD: In 22 cohorts, multiple univariate genome-wide association studies (GWASs) were performed using repeated assessments of internalizing symptoms, in a total of 64,561 children and adolescents between 3 and 18 years of age. Results were aggregated in meta-analyses that accounted for sample overlap, first using all available data, and then using subsets of measurements grouped by rater, age, and instrument.
RESULTS: The meta-analysis of overall internalizing symptoms (INT(overall)) detected no genome-wide significant hits and showed low single nucleotide polymorphism (SNP) heritability (1.66%, 95% CI = 0.84-2.48%, n(effective) = 132,260). Stratified analyses indicated rater-based heterogeneity in genetic effects, with self-reported internalizing symptoms showing the highest heritability (5.63%, 95% CI = 3.08%-8.18%). The contribution of additive genetic effects on internalizing symptoms appeared to be stable over age, with overlapping estimates of SNP heritability from early childhood to adolescence. Genetic correlations were observed with adult anxiety, depression, and the well-being spectrum ($|r(g)| > 0.70$), as well as with insomnia, loneliness, attention-deficit/hyperactivity disorder, autism, and childhood aggression (range $|r(g)| = 0.42$-0.60), whereas there were no robust associations with schizophrenia, bipolar disorder, obsessive-compulsive disorder, or anorexia nervosa.
CONCLUSION: Genetic correlations indicate that childhood and adolescent internalizing symptoms share substantial genetic vulnerabilities with adult internalizing disorders and other childhood psychiatric traits, which could partially explain both the persistence of internalizing symptoms over time and the high comorbidity among childhood psychiatric traits. Reducing phenotypic heterogeneity in childhood samples will be key in paving the way to future GWAS success

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J Atten Disord. 2022 Aug;26:1357-68.
A RANDOMIZED, PLACEBO-CONTROLLED LABORATORY CLASSROOM STUDY OF THE EFFICACY AND SAFETY OF DASOTRALINE IN CHILDREN WITH ADHD.
Wigal S, Tsai J, Bates JA, et al.
OBJECTIVE: To evaluate the efficacy of dasotraline 2 mg/day for treatment of ADHD in children weighing 30kg.
METHOD: Children (ages 6-12) with ADHD were randomized to 14 days of once-daily evening doses of dasotraline 2 mg (n = 47) or placebo (n = 48). Efficacy was assessed at Baseline and day-15 in seven, 30-

minutes classroom sessions on each day (8:00 a.m. to 8:00 p.m.; 12-24 hours post-dose). The primary endpoint was change from Baseline at Day-15 in the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score averaged over the seven, serial timepoints.
RESULTS: Treatment with dasotraline was associated with significant improvement versus placebo in the primary SKAMP-combined score (least squares mean [SE] change from Baseline at Day-15: -3.67 [0.775] vs. +1.57 [0.773]; p < .001; effect size, 1.04).
CONCLUSION: Dasotraline 2 mg/day was found to be efficacious and generally well tolerated in this placebo-controlled, laboratory classroom study of children ages 6 to 12 years with ADHD.
CLINICALTRIALS.GOV IDENTIFIER: NCT03231800

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J Atten Disord. 2022 Aug;26:1293-303.
INCREMENTAL VALIDITY OF MULTI-METHOD AND MULTI-INFORMANT EVALUATIONS IN THE CLINICAL DIAGNOSIS OF PRESCHOOL ADHD.
Chen IC, Lee PW, Wang LJ, et al.
OBJECTIVES: This study investigated the discriminative validity of various single or combined measurements of electroencephalogram (EEG) data, Conners' Kiddie Continuous Performance Test (K-CPT), and Disruptive Behavior Disorder Rating Scale (DBDRS) to differentiate preschool children with ADHD from those with typical development (TD).
METHOD: We recruited 70 preschoolers, of whom 38 were diagnosed with ADHD and 32 exhibited TD; all participants underwent the K-CPT and wireless EEG recording in different conditions (rest, slow-rate, and fast-rate task).
RESULTS: Slow-rate task-related central parietal delta (1-4Hz) and central alpha (8-13Hz) and beta (13-30Hz) powers between groups with ADHD and TD were significantly distinct (p<.05). A combination of DBDRS, K-CPT, and specific EEG data provided the best probability scores (area under curve=0.926, p<.001) and discriminative validity to identify preschool children with ADHD (overall correct classification rate=85.71%).
CONCLUSIONS: Multi-method and multi-informant evaluations should be emphasized in clinical diagnosis of preschool ADHD

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J Atten Disord. 2022 Aug;26:1335-46.
EARLY DEVELOPMENT OF ADHD AND ODD SYMPTOMS FROM THE TODDLER TO PRESCHOOL YEARS.
Brown HR, Laws HB, Harvey EA.
OBJECTIVE: ADHD and ODD are commonly co-occurring, but often studied individually. This study evaluated common trajectories of these disorders and explored how they co-develop in early childhood.
METHOD: Community parents (N=273) completed online surveys about their 2-year-old. Children's inattention, hyperactivity/impulsivity, and oppositional defiant disorder symptoms over 2 years were examined using latent class, dual trajectory, and cross-lagged analyses.
RESULTS: Most children followed low symptom trajectories. A small portion showed high, moderate, or increasing trajectories. The hyperactive/impulsive domain of ADHD showed a declining symptoms group. Children in high ODD groups were likely to be in high ADHD symptom groups; the converse was true but probabilities were lower. Hyperactive/impulsive symptoms predicted ODD symptoms across time, more than vice versa.
CONCLUSION: The study extends the small body of literature assessing early development of ADHD and ODD. Findings suggest that earlier intervention for symptoms of ADHD may mitigate risk of developing ODD

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J Atten Disord. 2022 Aug;26:1369-78.
ASSOCIATIONS BETWEEN VIDEO GAME ENGAGEMENT AND ADHD SYMPTOMS IN EARLY ADOLESCENCE.
Tiraboschi GA, West GL, Boers E, et al.

OBJECTIVE: We aim to investigate the direction of causality of the association between adolescent video game playing and later development of ADHD symptoms using a population-based sample of Canadian Youth.
METHOD: The present study is based on longitudinal cohort data (N = 1,467). Youth self-reported weekly hours of video game playing as well as ADHD symptoms at both 12 and 13 years of age.
RESULTS: Cross-lagged panel model were estimated to examine how adolescent video game playing prospectively contributes to ADHD symptoms while simultaneously considering how adolescent ADHD symptoms may prospectively contribute to videogame playing. Analyses revealed a significant positive association between adolescent video games playing at age 12 and ADHD symptoms at age 13. Youth ADHD symptoms at age 12 did not predict video game use at age 13.
CONCLUSION: Our results help clarify the direction of causality of the association between video game playing and ADHD symptoms and provide evidence that video game playing can represent a risk factor for the development of attention problems in early adolescence

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J Atten Disord. 2022 Aug;26:1283-92.
HOSPITAL-BASED MODIFIED COGMED WORKING MEMORY TRAINING FOR YOUTH WITH ADHD.
Sol SS, McAuley T.
OBJECTIVE: This study evaluated a modified working memory training program, Cogmed, for ADHD youth.
METHOD: Forty youth were randomized to modified Cogmed training (MCT) or treatment as usual (CON). MCT was delivered in an outpatient mental health clinic in 3 weekly 35-minute sessions with a dedicated coach for 10 weeks. Participants completed assessments at baseline, after the intervention, and again 3 months later.
RESULTS: After controlling for baseline, groups were comparable on working memory, academics, and ADHD symptoms. The MCT group was rated by parents and teachers as having fewer executive function challenges and youth endorsed better self-concept compared with the CON group.
CONCLUSIONS: MCT was associated with some improvement, which could not be attributed to increased working memory capacity and may reflect other facets of the program. Results question the usefulness of Cogmed but highlight considerations for optimizing adherence, engagement, and the therapeutic alliance in interventions for ADHD youth

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J Atten Disord. 2022 Aug;26:1271-82.
"LATE-ONSET" ADHD SYMPTOMS IN YOUNG ADULTHOOD: IS THIS ADHD?
Riglin L, Wootton RE, Livingston LA, et al.
Objective: We investigated whether "late-onset" ADHD that emerges in adolescence/adulthood is similar in risk factor profile to: (1) child-onset ADHD, but emerges later because of scaffolding/compensation from childhood resources; and (2) depression, because it typically onsets in adolescence/adulthood and shows symptom and genetic overlaps with ADHD.
Methods: We examined associations between late-onset ADHD and ADHD risk factors, cognitive tasks, childhood resources and depression risk factors in a population-based cohort followed-up to age 25 years (N=4224-9764).
Results: Parent-rated late-onset ADHD was like child-onset persistent ADHD in associations with ADHD polygenic risk scores and cognitive task performance, although self-rated late-onset ADHD was not. Late-onset ADHD was associated with higher levels of childhood resources than child-onset ADHD and did not show strong evidence of association with depression risk factors.
Conclusions: Late-onset ADHD shares characteristics with child-onset ADHD when parent-rated, but differences for self-reports require investigation. Childhood resources may delay the onset of ADHD

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J Child Adolesc Psychopharmacol. 2022 Jun;32:250-77.

CAN NEUROCOGNITIVE OUTCOMES ASSIST MEASUREMENT-BASED CARE FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? A SYSTEMATIC REVIEW AND META-ANALYSES OF THE RELATIONSHIPS AMONG THE CHANGES IN NEUROCOGNITIVE FUNCTIONS AND CLINICAL OUTCOMES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PHARMACOLOGICAL AND COGNITIVE TRAINING INTERVENTIONS.

Lee S, Hill TR, Johnson B, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental conditions among school-age children. Early intervention and ongoing evaluation of treatment effectiveness are essential to minimize the life-long negative impact of ADHD. Neurocognitive functions have been reported to improve with pharmacological and cognitive training interventions for children with ADHD. We evaluated the value of measuring change in neurocognitive functions following ADHD interventions as a treatment outcome. We systematically reviewed randomized control trials of two distinctive types of ADHD interventions-pharmacological treatments and cognitive training-and summarized the changes in neurocognitive and clinical outcomes using a series of meta-analyses. Both pharmacological and cognitive training interventions showed positive effects on some aspects of neurocognitive functions. However, there were no significant correlations between changes in neurocognitive function (e.g., inhibition) and changes in ADHD behavioral symptoms (e.g., impulsive behavior). Although the associations between changes in neurocognitive function and clinical outcomes are not well studied, based on current findings, it is not suitable to use change in neurocognitive outcomes as a proxy for change in ADHD clinical symptom-based outcomes. There is, however, notable value in monitoring changes in neurocognitive function associated with ADHD interventions to achieve the following aims: (1) understanding full treatment effect on children with ADHD, (2) identifying ancillary indicators of subclinical changes, and (3) provision of objective and less biased measures of treatment effects. These findings are important evidence that changes in neurocognitive function could be a co-occurring objective indication that parallels the clinical effects of ADHD treatments

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J Clin Child Adolesc Psychol. 2022 Jul;51:543-55.

CO-OCCURRING PSYCHOPATHOLOGY MODERATES SOCIAL SKILLS IMPROVEMENT IN A RANDOMIZED CONTROLLED TRIAL OF A COLLABORATIVE SCHOOL-HOME INTERVENTION FOR CHILDREN WITH ADHD.

Morgan JE, Dvorsky MR, Meza JI, et al.

OBJECTIVE: Children with ADHD often exhibit marked impairment in their social skills, but evidence-based psychosocial interventions for ADHD have shown limited efficacy in remediating these deficits. Co-occurring psychopathology exacerbates social deficits in children with ADHD and is a plausible moderator of treatment response. To identify factors contributing to variable social skills treatment response, we examined co-occurring externalizing, depression, and anxiety symptoms as moderators of social skills outcomes in a randomized controlled trial of the Collaborative Life Skills (CLS) program, an evidence-based collaborative school-home ADHD intervention.

METHOD: Participants were 159 children with ADHD (M age = 8.35 years, 28.3% female) at 27 schools in an urban public school district. Twenty-three schools were randomly assigned to CLS or usual services, with an additional four schools assigned to Spanish-adapted CLS or usual services. Multi-informant measures of co-occurring psychopathology and social skills were collected at baseline and post-treatment.

RESULTS: Parent-rated externalizing and depression symptoms moderated treatment effects on social skills, whereby higher symptomatology in each domain was unrelated to social skills improvement in the CLS group but predicted worsening social skills in response to usual services. In contrast, teacher-rated anxiety moderated treatment effects on social skills, whereby higher anxiety predicted greater social skills improvement in response to CLS but was unrelated to social skills outcomes following usual services.

CONCLUSIONS: Findings reflect novel evidence that child psychopathology domains exhibit unique moderating effects on social skills treatment response in children with ADHD. We discuss implications for optimizing evidence-based interventions to target social impairment in this population

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J Clin Child Adolesc Psychol. 2022 Jul;51:443-52.

PSYCHOMETRIC AND NORMATIVE INFORMATION ON THE CHILD AND ADOLESCENT BEHAVIOR INVENTORY IN A NATIONALLY REPRESENTATIVE SAMPLE OF UNITED STATES CHILDREN.

Burns GL, Preszler J, Becker SP.

OBJECTIVE: Psychometric and normative information is provided for the Sluggish Cognitive Tempo, Attention Deficit/Hyperactivity Disorder (ADHD) Inattention, ADHD Hyperactivity/Impulsivity, Oppositional Defiant Disorder, Callous-Unemotional Behaviors (Limited Prosocial Emotions specifier), Anxiety, Depression, Social Impairment, Friendship Difficulties, and Academic Impairment Scales of the Child and Adolescent Behavior Inventory (CABI) with a nationally representative sample of U.S. children.
METHOD: Mothers of 2,056 kindergarten to sixth-grade children (M ± SD(age) = 8.49 ± 2.15 years; 49% girls) completed the CABI, and 307 randomly selected mothers completed the CABI again 4 weeks later.
RESULTS: The 10-factor model (one factor for each CABI scale) provided a close fit for the total sample as well as for boys and girls separately. Each scale showed invariance of like-item loadings and thresholds for boys and girls across a 4-week interval with excellent test-retest factor correlations and no significant factor mean changes. Normative information (T-scores) is provided for the 10 scales separately for boys and girls, with test information functions supporting the use of the scales for screening purposes.
CONCLUSION: The normative information on the CABI provides support for the use of the 10 scales to inform the clinical care of individual children, with the positive psychometric properties of the scores providing additional support for the use of the scales for research. Copies of the scale and norms are available for free to clinicians and researchers

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J Clin Endocrinol Metab. 2022 Jun;107:2047-56.

GROWTH HORMONE AND THYROID FUNCTION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER UNDERGOING DRUG THERAPY.

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

CONTEXT: The trends in hormone indices of children with attention deficit hyperactivity disorder (ADHD) who received long-term medication treatment remains controversial.
OBJECTIVE: This prospective study aimed to examine the changes in the growth hormone and thyroid hormone systems among children with ADHD undergoing various medication treatments.
METHODS: In total, 118 children who were diagnosed with ADHD and were drug-naive were observed naturalistically over 12 months. Of them, 22 did not receive any medication, while 39, 40, and 17 were treated with low doses of short-acting methylphenidate (MPH) (14±6.7 mg/day), osmotic-release oral system (OROS) long-acting MPH (32±9.6 mg/day), and atomoxetine (29.2±9.7 mg/day), respectively. Blood samples were obtained at both the baseline and the endpoint (month 12) to measure serum levels of insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3), prolactin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and free T4.
RESULTS: Trends for IGF-1, IGFBP-3, prolactin, TSH, T3, T4, and free T4 levels were similar among the 4 groups. Changes in serum levels of IGF-1 were positively correlated with changes in height and weight of all the children with ADHD. However, patients who received MPH treatment had less body weight gain than the nonmedicated group. The ratio of MPH doses to body weight was inversely correlated with the increment in height.
CONCLUSION: There were no changes in thyroid or growth hormones associated with the low doses of ADHD medications used in this study within 1 year's duration. Nonetheless, patients' growth and the appropriateness of drug dosage should be closely monitored

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J Dev Behav Pediatr. 2022 Jun;43:273-82.

PERSPECTIVES OF RURAL PRIMARY CARE CLINICIANS ON PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CARE.

O'Dell SM, Gormley MJ, Schlieder V, et al.

OBJECTIVE: Despite efficacious treatments, evidence-based guidelines, and increased availability of integrated behavioral health care, youth coping with attention-deficit/hyperactivity disorder (ADHD) receive

suboptimal care. More research is needed to understand and address care gaps, particularly within rural health systems that face unique challenges. We conducted a qualitative study within a predominantly rural health system with a pediatric-integrated behavioral health care program to address research gaps and prepare for quality improvement initiatives, including primary care clinician (PCC) trainings and clinical decision support tools in the electronic health record (EHR).
METHOD: Semistructured interviews were conducted with 26 PCCs representing clinics within the health system. Interview guides were based on the Practical Robust Implementation and Sustainability Model to elicit PCC views regarding determinants of current practices and suggestions to guide quality improvement efforts. We used thematic analysis to identify patterns of responding that were common across participants.
RESULTS: PCCs identified several internal and external contextual factors as determinants of current practices. Of note, PCCs recommended increased access to continuing education trainings held in clinic over lunch and delivered in less than 30 minutes. Suggested improvements to the EHR included incorporating parent and teacher versions of the Vanderbilt Rating Scale into the EHR, documentation templates aligned with evidence-based guidelines, and alerts and suggestions to aid medication management during appointments.
CONCLUSION: Future research to identify implementation strategies to help rural PCCs adopt innovations are needed given the increased responsibility for managing ADHD care and intractable gaps in access to behavioral health care in rural regions

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J Dev Behav Pediatr. 2022 Jun;43:e296-e303.
MENTAL HEALTH AND DEVELOPMENTAL DISORDER DIAGNOSES OF FOSTER AND NONFOSTER CHILDREN ENROLLED IN MEDICAID.
Keefe RJ, Cummings ADL, Greeley CS, et al.
OBJECTIVE: This study used Medicaid claims to compare the prevalence of mental health disorders (MHDs) and developmental disorders (DDs) between foster and nonfoster youth.
METHODS: Medicaid claims data were used to identify MHDs and DDs. Diagnosis codes were categorized into 16 MHD and 8 DD groups. Children were enrolled in their respective Medicaid plan for at least 30 days and had at least 1 health care encounter generating a claim. Prevalence was compared between children in foster care and children not in foster care overall and by age group. Logistic regression was used to compare the odds of having an MHD or DD diagnosis.
RESULTS: Of the 8706 children in foster care, 20.1% had an MHD compared with 9.7% of the 392,815 nonfoster children. Overall, the 5 most prevalent MHD and DD conditions among foster youth were attention-deficit/hyperactivity disorder (ADHD) (11.0%), miscellaneous (9.3%), bipolar disorders (5.6%), communication disorders (5.4%), and depressive disorders (5.1%). The 5 most prevalent conditions among children not in foster care were ADHD (6.1%); communication disorders (3.0%); disruptive, impulse control, and conduct disorders (2.7%); specific learning disorders (2.5%); and trauma and stressor-related disorders (2.4%). Anxiety was significantly higher among nonfoster children. The prevalence of the most common conditions by age group is reported. Overall, children in foster care had 2.5 and 2.3 times higher odds of having an MHD or DD diagnosis, respectively.
CONCLUSION: Children in foster care had significantly higher rates of mental health and DD diagnoses compared with children not in foster care

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J Dev Behav Pediatr. 2022 Jun;43:252-61.
PSYCHOTROPIC MEDICATION USE BY CHILDREN WITH AUTISM SERVED IN PUBLICLY FUNDED MENTAL HEALTH SETTINGS.
Caplan B, Chlebowski C, May G, et al.
OBJECTIVE: The aim of this study was to characterize patterns of and factors associated with psychotropic medication use in children with autism spectrum disorder (ASD) receiving publicly funded mental health services.
METHOD: Data were extracted from 202 children with ASD participating in a cluster randomized trial of An Individualized Mental Health Intervention for ASD conducted in 29 publicly funded mental health programs.

Children with ASD were aged 5 to 13 years (M = 9.1 years, SD = 2.4), and were 84.2% male and 59.9% Latinx. Child ASD and cognitive functioning were determined by standardized assessment. Caregivers reported child psychotropic medication use, behavior problems, ASD symptom severity, mental health symptoms, family demographics, and caregiver strain at the baseline.
RESULTS: Nearly half (49.5%) of participants used psychotropic medication(s) within the past 6 months, with stimulants being most commonly reported. Child co-occurring attention-deficit/hyperactivity disorder (ADHD) (B = 1.55, p < 0.01; 95% confidence interval [CI]: 0.53-2.57), lower cognitive functioning (B = -0.03, p = 0.02; 95% CI: -0.05 to <0.00), and non-Hispanic White ethnicity (vs Hispanic/Latinx; B = 1.02, p = 02; 95% CI: -1.89 to -0.14) were associated with a greater likelihood of using any type of medication. Factors associated with medication use varied by class: stimulants-ADHD, lower ASD symptom severity, and more intensive behavior problems; SSRIs-higher ASD symptom severity; alpha-2 agonists-ADHD, higher ASD symptom severity, lower cognitive functioning, and higher caregiver strain; and antipsychotics-none.
CONCLUSION: The findings highlight factors associated with psychotropic medication use for a clinically complex population, which may inform community care improvement efforts

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J Head Trauma Rehabil. 2022 May;37:134-43.
USAGE PATTERNS OF AN MHEALTH SYMPTOM MONITORING APP AMONG ADOLESCENTS WITH ACUTE MILD TRAUMATIC BRAIN INJURIES.
Schmidt M, Babcock L, Kurowski BG, et al.
OBJECTIVE: To understand usage patterns of SMART (Self-Monitoring Activity Regulation and Relaxation Treatment) mHealth app among adolescents with acute mild traumatic brain injuries (mTBIs) and to identify individual characteristics that influenced app usage.
SETTING: Emergency departments of tertiary care children's medical center.
PARTICIPANTS: Children aged 11 to 18 years with mTBI in the past 2 weeks, English-speaking, no evidence of severe TBI, and no preexisting neurological impairment.
DESIGN: Nested cohort of the intervention arm of a randomized clinical trial (n = 34).
MHEALTH APP INTERVENTION: SMART was a month-long educational program on mTBI designed to promote self-monitoring and management of recovery. SMART included digital symptom and activity self-monitoring surveys, feedback on symptom changes, and 8 modules providing psychoeducation, strategies for symptom management, and training in active problem solving.
MAIN MEASURES: App usage time, navigation, and interaction data were automatically collected. Usage involved inputting symptom ratings/activities and reviewing modules. Patterns of symptom/activity reporting and completion of learning modules data were analyzed. Predictors of app utilization, including individual characteristics, resilience (Connor-Davidson Resilience Scale), and coping (Coping Strategies Inventory-Short Form), were analyzed using Spearman correlations.
RESULTS: Participants completed symptom monitoring an average of 9 days over the month. Participants completed an average of 1.87 learning modules out of 7. Parent income and education, comorbid attention-deficit/hyperactivity disorder (ADHD), and emotional engagement coping style predicted symptom monitoring. Parental income, comorbid ADHD, and greater reliance on emotional engagement coping predicted module completion.
SIGNIFICANT ADVERSE EVENTS: None.
CONCLUSION: Adolescents of higher socioeconomic status and those who manage their emotions using active engagement spent more time on both components of the SMART program

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J Learn Disabil. 2022 Jul;55:272-91.
PREDICTING AND EVALUATING TREATMENT RESPONSE: EVIDENCE TOWARD PROTRACTED RESPONSE PATTERNS FOR SEVERELY IMPACTED STUDENTS WITH DYSLEXIA.
Middleton AE, Farris EA, Ring JJ, et al.
Great strides have been made in the development of effective methods of instruction for children with dyslexia. However, individual response to treatment varies, and weaknesses persist for some students with dyslexia despite otherwise effective instruction. Continued efforts are needed to support the prospective

identification of poor response, particularly in routine intervention settings. The current study addressed whether indicators of dyslexia risk as outlined by hybrid diagnostic models predict response in children who received Tier 3 dyslexia intervention in their schools. The program's efficacy has been previously documented in remediating reading abilities in children with dyslexia. Data were examined from 115 elementary-age children who received routine Tier 3 dyslexia intervention in their schools. Logistic regression revealed powerful effects of preintervention fluency and gender in predicting response, with weaker effects of decoding and rapid naming. Attention-deficit/hyperactivity disorder status also played a role in predicting response. Phonological awareness and listening-reading comprehension discrepancy did not predict response. Profile analyses indicated near- and far-transfer of skill for the adequate response group, whereas growth in the poor response group was limited to near-transfer. Findings support a continuum of severity that may be associated with less robust growth and generalization over the course of the intervention

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J Pediatr Psychol. 2022 Jun;47:652-61.

NATIONAL NORMS FOR THE VANDERBILT ADHD DIAGNOSTIC PARENT RATING SCALE IN CHILDREN.

Anderson NP, Feldman JA, Kolko DJ, et al.

OBJECTIVE: To provide national norms and percentiles for both research and clinical scoring modalities of the Vanderbilt Attention Deficit/Hyperactivity Disorder (ADHD) Diagnostic Parent Rating Scale (VADPRS) for a representative sample of children ages 5-12 in the United States.

METHOD: The five clinical subscales of the VADPRS were completed by 1,570 caregivers of children ages 5-12 in the United States, with children representative of the national population on key demographic variables including race, sex, ethnicity, family income, and family educational level. Descriptive statistics and measures of internal consistency of both dimensional and symptom count scoring were provided for each of the five clinical subscales of the inventory, as well as percentiles and group comparisons for select dimensional scoring subscales based on age and child sex.

RESULTS: Measures of internal consistency for each subscale using both scoring modalities of the VADPRS ranged from high to acceptable. There were statistically significant differences among the different subscales for both age (ADHD hyperactivity, anxiety/depression) and sex [both presentations of ADHD, oppositional defiant disorder (ODD)] for the total sample. These differences, however, were modest in magnitude and unlikely to be clinically meaningful.

CONCLUSIONS: This study enhances the research and clinical utility of the VADPRS by providing national norms and percentiles for each of its subscales. Differences between age and sex across the sample were statistically significant for two of the subscales (Hyperactivity and Anxiety/Depression) with additional subscales significant for sex alone (Inattentive and ODD), but these differences were not substantial enough to indicate a need for separate cut-offs for screening purposes

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J Psychiatr Res. 2022 Jul;151:122-30.

ASSOCIATION BETWEEN PARENTAL MENTAL ILLNESS AND AUTOIMMUNE DISEASES IN THE OFFSPRING - A NATIONWIDE REGISTER-BASED COHORT STUDY IN SWEDEN.

Nevriana A, Pierce M, Abel KM, et al.

Mental illness has been previously linked with autoimmune diseases, yet the associations between parental mental illness and offspring's risk of autoimmune diseases is largely unknown. We conducted a population-based cohort study of 2,192,490 Swedish children born between 1991 and 2011 and their parents to determine the associations between parental mental illness and risk of autoimmune diseases among the offspring. Time-dependent diagnoses of parental mental illness (psychosis, alcohol/drug misuse, depression, anxiety, eating disorders, personality disorders, attention deficit hyperactivity disorder, autism spectrum disorder) and offspring autoimmune diseases (type 1 diabetes (T1D), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, psoriasis, multiple sclerosis, inflammatory bowel disease (IBD), coeliac disease) were identified from inpatient/outpatient healthcare visits. Associations were measured by hazard ratios (HRs) adjusted for potential confounders. Overall, parental mental illness was associated with a small increase in risk of offspring's autoimmune diseases (HR 1.05, 95% CI 1.02-1.08). However, parental common mental disorder (anxiety/depression) was associated with higher risk of JIA, psoriasis, and T1D (HR T1D

1.11, 95% CI 1.01-1.22), while maternal psychosis with reduced risk of coeliac disease (HR 0.68, 95% CI 0.49-0.95) and paternal alcohol/drug misuse with reduced risk of IBD (HR 0.80, 95% CI 0.64-0.99). Maternal eating disorders were associated with a markedly increased risk for T1D (HR 1.41, 95% CI 1.05-1.89). Further studies are needed to confirm these findings and to understand underlying mechanisms. There is a need for greater clinical awareness about potential risk of JIA, psoriasis, and T1D among children of parents with common psychiatric morbidity

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JAMA Netw Open. 2022 Jun;5:e2215333.

ASSOCIATION OF MATERNAL USE OF TRIPTANS DURING PREGNANCY WITH RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OFFSPRING.

Harris GM, Wood M, Ystrom E, et al.

IMPORTANCE: Triptans are commonly used in the treatment of migraine. Prenatal exposure to triptans may be associated with adverse fetal neurodevelopment; however, there is limited information about the long-term safety of triptan use during pregnancy.

OBJECTIVE: To examine the association between maternal use of triptans during pregnancy and diagnosis and symptoms of attention-deficit/hyperactivity disorder (ADHD) among offspring.

DESIGN, SETTING, AND PARTICIPANTS: This study used data from the Norwegian Mother, Father and Child Cohort Study (recruitment 1999-2008), linked to national health registries. Live-born singleton children born to women with migraine before or during pregnancy were included. Two analytic samples were defined: one to assess ADHD diagnosis and one to assess ADHD symptoms. Data were analyzed from May 1 to November 30, 2021.

EXPOSURE: Maternal self-report of triptan use during pregnancy. Exposed children were compared with 2 groups of unexposed children whose mothers reported migraine (1) during pregnancy and (2) before pregnancy only.

MAIN OUTCOMES AND MEASURES: An ADHD diagnosis was defined as diagnosis of hyperkinetic disorder or receipt of dispensed ADHD medication. Symptoms of ADHD at 5 years were measured by the Conners' Parent Rating Scale, where a higher score indicates more symptoms of ADHD. Cox proportional hazards regression models and generalized linear models with inverse probability weights were used to estimate weighted hazard ratios (HRs) and standardized mean differences, respectively, with 95% CIs.

RESULTS: The ADHD diagnosis sample comprised 10 167 children (mean [SD] maternal age, 30.2 [4.6] years; 5231 boys [51.5%]), and the ADHD symptoms sample comprised 4367 children (mean [SD] maternal age, 30.6 [4.4] years; 2191 boys [50.2%]). Children were followed up for a mean (SD) of 10.6 (2.2) years. Children with prenatal triptan exposure had no increased risk of ADHD diagnosis compared with unexposed children whose mothers had migraine during pregnancy (weighted HR, 1.16; 95% CI, 0.78-1.74) and compared with unexposed children whose mothers had migraine only before pregnancy (weighted HR, 1.28; 95% CI, 0.84-1.94). There were no differences in ADHD symptom scores between exposed and unexposed children.

CONCLUSIONS AND RELEVANCE: The findings of this study suggest that there is no increased risk of ADHD among offspring associated with prenatal exposure to triptans

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JAMA Pediatr. 2022;176:E216401.

MORTALITY IN PERSONS WITH AUTISM SPECTRUM DISORDER OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Catalí-Lopez F, Hutton B, Page MJ, et al.

Importance: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are childhood-onset disorders that may persist into adulthood. Several studies have suggested that they may be associated with an increased risk of mortality; however, the results are inconsistent.

Objective: To assess the risk of mortality among persons with ASD or ADHD and their first-degree relatives.

Data Sources: A search of MEDLINE, Embase, Scopus, Web of Science, and PsycINFO (published from inception to April 1, 2021) was supplemented by searching reference lists of the retrieved articles. Study Selection: Cohort and case-control studies that reported mortality rate ratios (RRs) in persons with ASD or

ADHD and/or their first-degree relatives compared with the general population or those without ASD/ADHD were included.
Data Extraction and Synthesis: Screening, data extraction, and quality assessment were performed by at least 2 researchers independently. A random-effects model was used to meta-analyze individual studies and assessed heterogeneity (I2).
Main Outcomes and Measures: All-cause mortality in association with ASD or ADHD. Secondary outcome was cause-specific mortality. Results: Twenty-seven studies were included, with a total of 642260 individuals. All-cause mortality was found to be higher for persons with ASD (154238 participants; 12 studies; RR, 2.37; 95% CI, 1.97-2.85; I2, 89%; moderate confidence) and persons with ADHD (396488 participants; 8 studies; RR, 2.13; 95% CI, 1.13-4.02; I2, 98%; low confidence) than for the general population. Among persons with ASD, deaths from natural causes (4 studies; RR, 3.80; 95% CI, 2.06-7.01; I2, 96%; low confidence) and deaths from unnatural causes were increased (6 studies; RR, 2.50; 95% CI, 1.49-4.18; I2, 95%; low confidence). Among persons with ADHD, deaths from natural causes were not significantly increased (4 studies; RR, 1.62; 95% CI, 0.89-2.96; I2, 88%; low confidence), but deaths from unnatural causes were higher than expected (10 studies; RR, 2.81; 95% CI, 1.73-4.55; I2, 92%; low confidence).
Conclusions and Relevance: This systematic review and meta-analysis found that ASD and ADHD are associated with a significantly increased risk of mortality. Understanding the mechanisms of these associations may lead to targeted strategies to prevent avoidable deaths in high-risk groups. The substantial heterogeneity between studies should be explored further.

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JAMA Psychiatry. 2022 Jul;79:718-26.

PREVALENCE AND CORRELATES OF SUICIDE AND NONSUICIDAL SELF-INJURY IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Liu RT, Walsh RFL, Sheehan AE, et al.

IMPORTANCE: Considerably less is known about self-injurious thoughts and behaviors (SITBs) in preadolescence than older age groups, owing partly to the common view that young children are incapable of suicidal thoughts. Yet, preadolescent suicide has increased in recent years and is now the fifth leading cause of death in this age group, leading the National Institute of Mental Health to identify it as a priority for research and intervention.
OBJECTIVE: To assess prevalence estimates of preadolescent SITBs, identify correlates of these outcomes, and conduct head-to-head comparisons of preadolescent and adolescent SITBs in terms of associated characteristics.
DATA SOURCES: MEDLINE, PsycINFO, and Embase were systematically searched from inception through December 23, 2021, for studies on the prevalence and correlates of preadolescent SITBs. The search was restricted to English language publications and peer-reviewed journals.
STUDY SELECTION: Two reviewers independently identified studies providing data on prevalence and correlates of preadolescent SITBs. DATA
EXTRACTION AND SYNTHESIS: Two reviewers independently extracted data from each study, and the Joanna Briggs Institute Checklist for Prevalence Studies was used to assess study quality. Pooled prevalence and Cohen d were derived from random-effects meta-analyses. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed.
MAIN OUTCOMES AND MEASURES: Prevalence and correlates of suicidal ideation, suicide attempts, suicide deaths, and nonsuicidal self-injury among preadolescents.
RESULTS: Fifty-eight studies with 626 486 590 individuals were included. Lifetime prevalence of suicide in the general population was 0.79 per 1 million children. Prevalence for lifetime suicidal thoughts, suicide attempts, and nonsuicidal self-injury among preadolescents were 15.1%, 2.6%, and 6.2%, respectively, in community samples. These data suggest that approximately 17.0% of preadolescents with suicidal ideation transition to attempting suicide. Across several analyses, male individuals appear more likely to have SITBs in preadolescence than adolescence. Correlate data were modest for SITBs other than suicidal ideation, but among specific disorders, attention-deficit/hyperactivity disorder (suicidal ideation: d=0.54 [95% CI,0.34-0.75]) and depression (suicidal ideation: d=0.90 [95% CI,0.71-1.09]; suicide attempts: d=0.47 [95% CI,0.26-0.68]) emerged as the strongest correlates. Among interpersonal factors, child maltreatment (suicidal

ideation: d=2.62 [95% CI,1.56-3.67]) and parental support (suicidal ideation: d=-0.34 [95% CI,-0.46 to -0.22]) yielded the largest effect sizes.
CONCLUSIONS AND RELEVANCE: In this systematic review anda meta-analysis, although preadolescent suicide deaths were rare, other SITB types occur with concerning frequency. Male individuals were at greater risk for SITBs in preadolescence relative to adolescence. Attention-deficit/hyperactivity disorder, child maltreatment, and parental support were especially relevant to suicidal ideation, as well as depression for suicidal thoughts and behaviors, in this age group. Further study, especially of SITBs other than suicidal ideation, is needed

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J Adolesc Health. 2022.
OBESITY IN ADOLESCENTS: UNDERSTANDING THE COMBINED ROLE OF FOOD SECURITY AND EMOTIONAL AND BEHAVIORAL DISORDERS.
Vish NL, Braun J, King M, et al.
Purpose: To examine the associations and interactions between levels of food security and emotional and behavioral disorders with obesity in adolescents.
Methods: Multiple logistic regression modeling was used to analyze the association of adolescent obesity with levels of food security and emotional and behavior disorders in children aged 12-17 years using data from National Health Interview Survey 2016-2018 combined years. Presence of emotional and behavioral disorders within food security categories was added to logistic regression modeling to examine interactions.
Results: When added individually to multiple logistic regression models, marginal and low food security, Attention Deficit Hyperactivity Disorder (ADHD) and anxiety were associated with increased odds of obesity, but very low food security and depression were not. Within the group of adolescents with very low food security, those with anxiety, depression, or ADHD had a nearly two to three-fold increase in odds of obesity compared to adolescents with very low food security and no emotional and behavioral disorders. A similar increase in the odds of obesity with the presence of anxiety, depression, or ADHD was not seen in the adolescents with high food security.
Discussion: This study finds a significant interaction between food security level and emotional and behavioral disorders. The distinction that very low food security in adolescents is only associated with obesity when either anxiety, depression or ADHD are present, but not independently, is an important contribution to understanding complex interactions contributing to obesity

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J Autism Dev Disord. 2022.
TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH MEDICATION IN CHILDREN WITH AUTISM SPECTRUM DISORDER WITH AND WITHOUT INTELLECTUAL DISABILITY: A DBPNET STUDY.
Grater JE, Muniz EI, Silver EJ, et al.
Children with autism spectrum disorder (ASD) and intellectual disability (ID)/global delay (GD) frequently have symptoms of attention-deficit/hyperactivity disorder (ADHD). We describe the practice patterns of developmental behavioral pediatricians (DBPs) in the treatment of children with ASD and coexisting ADHD and compare medication classes for children with and without intellectual disability. In bivariate analyses, we compared demographic characteristics, co-occurring conditions, and medication classes for children with and without intellectual disability. Significantly more patients with ID/GD were prescribed +¦-agonists than patients without ID/GD, but the difference was no longer significant when controlling for age in logistic regression children with ID/GD had more comorbidities and were more likely to be prescribed more than on psychotropic medication. In conclusion, age rather than ID/GD was associated with medication choice

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J Autism Dev Disord. 2022.

EFFECTS OF INTERSECTIONALITY ALONG THE PATHWAY TO DIAGNOSIS FOR AUTISTIC-CHILDREN WITH AND WITHOUT CO-OCCURRING ATTENTION DEFICIT HYPERACTIVITY DISORDER IN A NATIONALLY-REPRESENTATIVE SAMPLE.

Miller HL, Thomi M, Patterson RM, et al.

Children with complex behavioral profiles (e.g., ASD + ADHD) may experience delays in obtaining a final diagnosis. Low-resource or underrepresented groups may be at even greater risk for delayed diagnosis. We assessed the effect of sociodemographic factors, symptom complexity and co-occurring conditions, and identifier of first symptoms on diagnostic trajectories among children aged 3ΓÇô17-áyears diagnosed-áwith ASD (n = 52) or ASD + ADHD (n = 352) from a nationally-representative sample. Race/ethnicity and gender disparities were evident in both groups. Race, symptom complexity, and co-occuring conditions predicted age of final diagnosis and wait time between first concern and final diagnosis, both of which were staggeringly high. Results suggest a complex influence of sociodemographic factors on the diagnostic pathway, and risk of health disparities as a function of intersectionality

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J Child Adolesc Ment Health. 2022.

PRIMARY CAREGIVERS PERSPECTIVES OF THE DISRUPTIVE BEHAVIOUR OF THEIR CHILDREN ATTENDING WESKOPPIES PSYCHIATRIC HOSPITAL, SOUTH AFRICA.

Maro L, van Staden W, Hassim J.

While practitioners might engage caregivers on their understandings of the disruptive behavioural disorders of their children, their perspectives are yet to be examined in a qualitative study. This study explored perspectives of primary caregivers on the disruptive behaviour of children who attended the child unit of Weskoppies Psychiatric Hospital, in South Africa. Qualitative methods were used in a case study design. Nineteen participants were purposively sampled. The participants were interviewed using individual in-depth, semi-structured interviews. Data were analysed using typological and bracketed grounded theory methods. Both methods revealed these themes: confusion, emotional build-up towards a meltdown; loss of others; spiritual and cultural (dis)connectedness; behaviour of others towards the children; something being wrong medically; behavioural difficulties when ΓÇ£I want my wayΓÇØ; emotional turmoil of caregivers; and corrective responses. Differences yielded by the analytic methods were a yearning for a better future, and the perspective that trauma had impacted the childΓÇÖs behaviour. These findings suggest that practitioners may anticipate and support caregivers in their experiences of emotional turmoil, uncertainty and confusion. Caregivers may be informed regarding emotional dysregulation and that a therapeutic resource may be found in the knowledge that the caregivers have a yearning for a better future for their children

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J Clin Psychol. 2022 May;78:913-25.

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY-ADOLESCENT-RESTRUCTURED FORM (MMPI-A-RF) CHARACTERISTICS OF ADHD IN A KOREAN PSYCHIATRIC SAMPLE.

Chakranarayan C, Weed NC, Han K, et al.

Global rates of attention-deficit/hyperactivity disorder (ADHD) have risen. In Korea, ADHD is associated with functional impairments and comorbidity with other psychological disorders. This study examined the correlates of ADHD in a psychiatric sample of Korean adolescents on the Minnesota Multiphasic Personality Inventory-Adolescent-Restructured Form (MMPI-A-RF). In a clinical sample of 247 adolescents, MMPI-A-RF scores from 46 patients diagnosed with ADHD were compared to the remainder of the clinical sample and to the Korean MMPI-A-RF norms. Results demonstrated significantly different scores for the ADHD group on scales indicating externalizing concerns and behavior dysfunction compared with the clinical group with other disorders and to a normative sample. Notable differences were also observed between clinical groups on scales reflecting interpersonal functioning. Relative risk ratio analyses demonstrated that an MMPI-A-RF T-score of 55 was generally most effective for predicting risk for an ADHD diagnosis in the clinical sample

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Journal of Managed Care and Specialty Pharmacy. 2021;27:S62.

HIGHER PERSISTENCE WITH JORNAY PM® (DELAYED-RELEASE/EXTENDEDRELEASE METHYLPHENIDATE) OVER OTHER EXTENDEDRELEASE STIMULANT FOR THE MANAGEMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: REAL-WORLD EVIDENCE A LARGE US CLAIMS DATABASE ANALYSIS.

Lloyd D, Morgan D.

BACKGROUND: Stimulant medications are effective treatments for attention-deficit/hyperactivity disorder (ADHD). Yet, a lack of persistence with the prescribed treatment is frequently observed, which leads to less-than-desired improvements in patients' symptoms and functional impairment. Jornay PM® (formerly HLD200) is an evening-dosed, delayed-release and extended-release methylphenidate (DR/ER-MPH) that is released in the colon and provides a dose-dependent duration of effect for individuals with ADHD. Persistence to DR/ER-MPH treatment is unknown.

OBJECTIVE: To report treatment persistence rates among individuals newly initiated on DR/ER-MPH and other stimulant options in a real-world setting over a 9-month period.

METHODS: Treatment persistence, defined as the time between index prescription and treatment discontinuation (ie, interruption of treatment for 2x the length of the last prescription) was analyzed in 1,365,003 individuals who started stimulant treatment from June 2020-February 2021 using a large US prescription claims database (Formulary Impact Analyzer, IQVIA). Results were stratified by sex, age (6-12y, 13-17y, 18y), and out-of-pocket cost per 30 days (< $5, $5-$49, $50). Persistence rates for DR/ER-MPH were compared to those of extended-release methylphenidates (ER MPH) and ER amphetamines (AMP) using a two-proportion hypothesis test with +¦ = 0.01.

RESULTS: All treatment classes showed the highest discontinuation rate between the 1st and 2nd fills and then relative stabilization to the 8th fill. The persistence rate over the 9-month period was highest with DR/ER-MPH at 33% (n = 10,371), compared to 26% for lisdexamfetamine dimesylate (n = 384,144), 22% for generic ER AMP (n = 463,429), 20% for branded ER MPH or ER AMP analogs (n = 79,663), and 17% for generic ER MPH (n = 427,396; P < 0.01 for all). In subgroup analyses, the persistence rate of DR/ER-MPH remained higher than other ER stimulants regardless of sex, age, or out-of-pocket costs (P < 0.01), with the exception of patients aged 18y who were treated with lisdexamfetamine or ER AMP and/or paid < $5 out-of-pocket.

CONCLUSIONS: Overall, individuals showed higher persistence over 9 months with DR/ER-MPH compared to other ER stimulants: this finding was consistent across the majority of age, sex, and copay categories. Similarly enhanced persistence metrics were not demonstrated with other recently launched ER stimulants. Higher persistence may translate into improved patient outcomes for ADHD patients

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J Mental Health Policy Econ. 2022;25:S22-S23.

NON-ADULT ADHD COST OF ILLNESS: POPULATION STUDY IN CATALONIA (SPAIN).

Mora T, Puig-Junoy J, Jacobs R, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common mental health disorder amongst young children. The natural history of ADHD showed that an important proportion on patients, around 65% of patients continue to meet full criteria or partial remission of symptoms by adulthood (Thapar and Cooper, 2016).

Aims of the Study: Studies of healthcare cost are important to help to plan mental health services and treatment. We contribute calculating the health cost of an ADHD population cohort from Catalonia. Methods: We use a large administrative dataset that includes infor- mation from several providers for the whole population of Catalan children that were born between 1998 and 2012, including those diagnosed with ADHD and those not. We focused on cohorts of children greater than six years old (1,101,215 individuals). This database contains information on: primary care, hospitalizations, emergency care, mental health hospitalization and community mental health care over the period 2013-2017. Via unique personal identifiers, the information is linked between all providers datasets but also to some demographic information. Our identification strategy is based on instrumenting ADHD diagnosis by the probability of being diagnosed by the most visited health care provider based on individual monthly visits to the provider in which this visit was related to ADHD. We estimated by two-part models but using matched individuals as control group and the FMM estimation that only accounts for positive costs.

Results: Our results indicate that ADHD children and adolescents showed 610 higher annual health direct costs compared to not diagnosed counterparts. Also, after being diagnosed and compared to the initial period

and adjusting for the characteristics of the individuals, the costs were higher in: 413 after 1-2 years but stabilized around 370 after 3-5 years.
Discussion and Limitations: It is relevant to study cost of illness for population cohorts using administrative datasets. We lack all expenditures related to private health care use. Implications for Health Care Provision and Use: It is important for the Spanish public administration to know where resources are allocated since coverage in the NHS in Catalonia is universal. Implications for Health Policies & Implications for Further Research: This study constitutes the first from a list regarding complex mental health diseases that will be studied at population level

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J Neurodevelopmental Disord. 2022 Jun;14.

AN ELECTRONIC HEALTH RECORD (EHR) PHENOTYPE ALGORITHM TO IDENTIFY PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDERS (ADHD) AND PSYCHIATRIC COMORBIDITIES.

Slaby I, Hain HS, Abrams D, et al.

Background: In over half of pediatric cases, ADHD presents with comorbidities, and often, it is unclear whether the symptoms causing impairment are due to the comorbidity or the underlying ADHD. Comorbid conditions increase the likelihood for a more severe and persistent course and complicate treatment decisions. Therefore, it is highly important to establish an algorithm that identifies ADHD and comorbidities in order to improve research on ADHD using biorepository and other electronic record data.
Methods: It is feasible to accurately distinguish between ADHD in isolation from ADHD with comorbidities using an electronic algorithm designed to include other psychiatric disorders. We sought to develop an EHR phenotype algorithm to discriminate cases with ADHD in isolation from cases with ADHD with comorbidities more effectively for efficient future searches in large biorepositories. We developed a multi-source algorithm allowing for a more complete view of the patient's EHR, leveraging the biobank of the Center for Applied Genomics (CAG) at Children's Hospital of Philadelphia (CHOP). We mined EHRs from 2009 to 2016 using International Statistical Classification of Diseases and Related Health Problems (ICD) codes, medication history and keywords specific to ADHD, and comorbid psychiatric disorders to facilitate genotype-phenotype correlation efforts. Chart abstractions and behavioral surveys added evidence in support of the psychiatric diagnoses. Most notably, the algorithm did not exclude other psychiatric disorders, as is the case in many previous algorithms. Controls lacked psychiatric and other neurological disorders. Participants enrolled in various CAG studies at CHOP and completed a broad informed consent, including consent for prospective analyses of EHRs. We created and validated an EHR-based algorithm to classify ADHD and comorbid psychiatric status in a pediatric healthcare network to be used in future genetic analyses and discovery-based studies.
Results: In this retrospective case-control study that included data from 51,293 subjects, 5840 ADHD cases were discovered of which 46.1% had ADHD alone and 53.9% had ADHD with psychiatric comorbidities. Our primary study outcome was to examine whether the algorithm could identify and distinguish ADHD exclusive cases from ADHD comorbid cases. The results indicate ICD codes coupled with medication searches revealed the most cases. We discovered ADHD-related keywords did not increase yield. However, we found including ADHD-specific medications increased our number of cases by 21%. Positive predictive values (PPVs) were 95% for ADHD cases and 93% for controls.
Conclusion: We established a new algorithm and demonstrated the feasibility of the electronic algorithm approach to accurately diagnose ADHD and comorbid conditions, verifying the efficiency of our large biorepository for further genetic discovery-based analyses

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Journal of Pediatric Research. 2022;9:116-25.

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

Maden EA, Gaml I.

Aim: Oral diseases can affect various aspects of life in children with attention deficit hyperactivity disorder (ADHD). The aim of this study was to evaluate the oral health conditions, oral health behaviors, and the oral health-related quality of life (OHRQoL) of children with ADHD.

Materials and Methods: A sample of 76 children with ADHD who were treatment naive was compared to 71 healthy children, with ages ranging from 6 to 13 years. Through an intraoral clinical examination, the numbers of decayed, missing, and filled teeth (DMFT, dmft index), the plaque index, the gingival index, occlusion status, overjet, overbite and parafunctional oral habits were determined. The children's parents completed the Turkish version of early childhood oral health impact scale (T-ECOHIS) and questionnaires regarding oral health behaviors and dental care.
Results: The child impact score (CIS) of the T-ECOHIS were significantly higher among those children with ADHD compared to the control group patients (16 versus 12), consistent with poorer OHRQoL. The children with ADHD also had more dental trauma in both dentitions and more frequent nail-biting habits compared to the participants in the control group.
Conclusion: In our study, T ECOHIS-CIS scores showed that those children with ADHD were affected more when compared to those children without ADHD in terms of oral health problems

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Journal of Personalized Medicine. 2022;12.

TASK-RATE-RELATED NEURAL DYNAMICS USING WIRELESS EEG TO ASSIST DIAGNOSIS AND INTERVENTION PLANNING FOR PRESCHOOLERS WITH ADHD EXHIBITING HETEROGENEOUS COGNITIVE PROFICIENCY.

Chen IC, Chen CL, Chang CH, et al.

This study used a wireless EEG system to investigate neural dynamics in preschoolers with ADHD who exhibited varying cognitive proficiency pertaining to working memory and processing speed abilities. Preschoolers with ADHD exhibiting high cognitive proficiency (ADHD-H, n = 24), those with ADHD exhibiting low cognitive proficiency (ADHD-L, n = 18), and preschoolers with typical development (TD, n = 31) underwent the Conners Kiddie Continuous Performance Test and wireless EEG recording under different conditions (rest, slow-rate, and fast-rate task). In the slow-rate task condition, compared with the TD group, the ADHD-H group manifested higher delta and lower beta power in the central region, while the ADHD-L group manifested higher parietal delta power. In the fast-rate task condition, in the parietal region, ADHD-L manifested higher delta power than those in the other two groups (ADHD-H and TD); additionally, ADHD-L manifested higher theta as well as lower alpha and beta power than those with ADHD-H. Unlike those in the TD group, the delta power of both ADHD groups was enhanced in shifting from rest to task conditions. These findings suggest that task-rate-related neural dynamics contain specific neural biomarkers to assist clinical planning for ADHD in preschoolers with heterogeneous cognitive proficiency. The novel wireless EEG system used was convenient and highly suitable for clinical application

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J Psychiatr Res. 2022;152:187-93.

ASSOCIATIONS OF POLYGENIC RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH GENERAL AND SPECIFIC DIMENSIONS OF CHILDHOOD PSYCHOLOGICAL PROBLEMS AND FACETS OF IMPULSIVITY.

Lahey BB, Tong L, Pierce B, et al.

A polygenic risk score (PRS) for attention-deficit/hyperactivity disorder (ADHD) has been found to be associated with ADHD in multiple studies, but also with many other dimensions of problems. Little is known, however, about the processes underlying these transdiagnostic associations. Using data from the baseline and 1-year follow-up assessments of 9- to 10-year-old children in the Adolescent Brain Cognitive DevelopmentΓäó (ABCD-®) Study, associations were assessed between an ADHD PRS and both general and specific factors of psychological problems defined in bifactor modeling. Additionally, prospective mediated paths were tested from the ADHD PRS to dimensions of problems in the follow-up assessment through baseline measures of executive functioning (EF) and two facets of impulsivity: lower perseverance and greater impulsiveness in the presence of surgent positive emotions. Previous findings of modest but significant direct associations of the ADHD PRS with the general factor of psychological problems were replicated in both assessments in 4,483 children of European ancestry. In addition, significant statistical mediation was found from the ADHD PRS to the general factor, specific ADHD, and conduct problems in the follow-up assessment through each of the two facets of impulsivity. In contrast, EF did not statistically mediate associations between the ADHD PRS and psychological problems. These results suggest that

polygenic risk transdiagnostically influences both psychological problems and facets of impulsivity, perhaps partly through indirect pathways via facets of impulsivity

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J Psychiatr Res. 2022;152:25-30.

ADOLESCENTS WITH ADHD ARE AT INCREASED RISK FOR COVID-19 VACCINE HESITANCY.

Dvorsky MR, Breaux R, Langberg JM, et al.

Identifying factors that influence adolescent intentions for COVID-19 vaccination is essential for developing strategic interventions to increase uptake, particularly in subgroups of at-risk adolescents. Attention-deficit/hyperactivity disorder (ADHD) in adolescence is characterized by difficulties regulating attention and behavior, social impairment, and impulsive risk-taking behaviors, which may impact vaccine hesitancy and vaccine uptake. This study examined hesitancy toward COVID-19 vaccines among adolescents with and without ADHD, and explored how ADHD status interacted with malleable social mechanisms and other social determinants of health in predicting vaccine hesitancy. Participants were 196 U.S. adolescents (44.4% male), 45.6% diagnosed with ADHD. Adolescents reported their confidence and willingness toward COVID-19 vaccines from March to May 2021. Adolescents with ADHD reported greater hesitancy and less confidence in COVID-19 vaccine safety compared to adolescents without ADHD ($p < .01$). Only 61.8% of adolescents with ADHD reported vaccine acceptance, compared to 81.3% of adolescents without ADHD. For all adolescents, those who identified as Black or Latinx and with lower family income had greater hesitancy and reduced confidence, whereas greater COVID-19 concerns, media use, and perceived negative impact on relationships was associated with greater vaccination willingness. Social contextual processes significantly interacted with ADHD status such that for adolescents without ADHD, concerns about COVID-19 were associated with increased confidence in vaccine safety. Being noncompliant with social distancing guidelines was associated with greater vaccine hesitancy, only for adolescents with ADHD. A concerted effort is needed to increase trust, confidence, and social relevance among adolescents, especially those with ADHD and from lower socio-economic backgrounds

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J Am Acad Child Adolesc Psychiatry. 2022.

CEREBRO-CEREBELLAR DYSCONNECTIVITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang P, Wang J, Jiang Y, et al.

Objective: Abnormal cerebellar development has been implicated in attention-deficit/hyperactivity disorder (ADHD), although cerebro-cerebellar functional connectivity (FC) has yet to be examined in ADHD. Our objective is to investigate the disturbed cerebro-cerebellar FC in children and adolescents with ADHD.

Method: We analyzed a dataset of 106 individuals with ADHD (68 children, 38 adolescents) and 62 healthy comparison individuals (34 children, 28 adolescents) from the publicly available ADHD-200 dataset. We identified 7 cerebellar subregions based on cerebro-cerebellar FC and subsequently obtained the FC maps of cerebro-cerebellar networks. The main effects of ADHD and age and their interaction were examined using 2-way analysis of variance.

Results: Compared to comparisons, ADHD showed higher cerebro-cerebellar FC in the superior temporal gyrus within the somatomotor network. Interactions of diagnosis and age were identified in the supplementary motor area and postcentral gyrus within the somatomotor network and middle temporal gyrus within the ventral attention network. Follow-up Pearson correlation analysis revealed decreased cerebro-cerebellar FC in these regions with increasing age in comparisons, whereas the opposite pattern of increased cerebro-cerebellar FC occurred in ADHD.

Conclusion: Increased cerebro-cerebellar FC in the superior temporal gyrus within the somatomotor network could underlie impairments in cognitive control and somatic motor function in ADHD. In addition, increasing cerebro-cerebellar FC in older participants with ADHD suggests that enhanced cerebellar involvement may compensate for dysfunctions of the cerebral cortex in ADHD

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Kaohsiung J Med Sci. 2022 Jul;38:719-20.
SMARTPHONE AND INTERNET OVERUSE AND WORSENED PSYCHOPATHOLOGIES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING THE COVID-19 PANDEMIC.
Huang BY, Chen YM, Hsiao RC, et al.

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Mayo Clin Proc. 2022 Jul;97:1339-44.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER OVERDIAGNOSIS AND OVERPRESCRIPTIONS: MEDICALIZATION OF DISTRACTIONS.
Moustafa Y, Chauhan M, Rummans TA.
The use and misuse of prescription stimulants has escalated during the past decade, with concerns of being "the next epidemic." The diagnosis of attention-deficit/hyperactivity disorder and the use of prescription stimulants have rapidly increased in children and adults in the past decade. Amphetamine use more than doubled from 2006 to 2016. In 2018, among illicit substance users in the past year (53.2 million), more than 5 million 12 years or older had misused prescription stimulants. The most commonly reported motivations for misuse were to help with alertness and concentration, in approximately 60% of respondents. Most persons who misused prescription stimulants received the medication from a friend or relative, who got it through a health care provider. It is important to reexamine the pattern of prescription stimulant use after the loosening of Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for attention-deficit/hyperactivity disorder diagnosis. Caveats to the this report could be the understudied specific populations (such as medical students), the exclusion of the military and institutionalized populations from the study, and the variations among individual states in stimulant prescribing patterns

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Medicine. 2019;98.
THE EFFECTS OF PHYSICAL ACTIVITY ON EXECUTIVE FUNCTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Zhang MQ, Liu Z, Ma HT, et al.
Background: The effects of physical activity on executive function are well documented, but whether physical activity contributes to the executive function of attention deficit hyperactivity disorder (ADHD) children are still inconclusive.
Methods: The study is guided by the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). We will search the following databases PubMed, EMBASES, the Cochrane Library, CNKI, and Wanfang-Data to identify the Randomized Controlled Trials evaluating the effects of physical activity on executive function among ADHD children. The language of literature restricted in Chinese and English, which published from inception to January 2019. Two reviewers will screen the studies independently, while risk of bias assessment, data extraction, and inconsistent results will be discussed by the third reviewer. Revman 5.3 and Stata 12 software will be used to complete data analysis and synthesis.
Conclusion: This study will be based on findings of previous studies, thus the ethics approval is not required. The final results will be presented at an international conference and submitted to a peer-reviewed journal of relative field for consideration of publication

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Minerva Pediatr (Torino). 2022 Jun;74:287-93.
DISABILITY AND INCLUSIVE EDUCATION IN AN ITALIAN REGION: ANALYSIS OF THE DATA FOR THE SCHOOL YEAR 2012-2013.
Lanzarini E, Parmeggiani A.
BACKGROUND: In Italy, pupils with disabilities enroll in mainstream schools and attend the ordinary classes at all educational levels. For the past twelve years, the Region Emilia Romagna has witnessed an increase in the number of children who need special support. The aim of the study was to identify the causes of disability in children attending public schools during the school year 2012-2013.
METHODS: The study was designed as a cross-sectional survey. Data were obtained from the Regional Education Department and divided into categories based on clinical diagnoses. Statistical analyses were

performed to analyze the distribution of the diagnostic categories among Provinces and school grades. The most recurrent combinations of illnesses were identified.
RESULTS: Intellectual disability was the most common cause of impairment (38.5%), often associated with epilepsy and autism. Hyperkinetic disorder associated with specific disorders of scholastic skills was the most recurrent combination of diagnoses. Rare diseases were diagnosed in 4.1%, whereas 5.0% of cases were affected by psychopathological disorders.
CONCLUSIONS: Our study is the first in Italy for its focus on the causes of children's disabilities in an Italian region. Being familiar with the causes of disability affecting the children of a territory is important to allocate the available resources efficiently, and to ensure all children's effective social integration

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Minerva Pediatr (Torino). 2022 Jun;74:373-74.
SLEEP PARALYSIS IN TWO CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Donfrancesco R, Melegari MG, Di TM, et al.

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NeuroImage. 2022 Aug;257:119332.
METHYLPHENIDATE REMEDIATES ABERRANT BRAIN NETWORK DYNAMICS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CONTROLLED TRIAL.
Mizuno Y, Cai W, Supekar K, et al.
Methylphenidate is a widely used first-line treatment for attention deficit/hyperactivity disorder (ADHD), but the underlying circuit mechanisms are poorly understood. Here we investigate whether a single dose of osmotic release oral system methylphenidate can remediate attention deficits and aberrancies in functional circuit dynamics in cognitive control networks, which have been implicated in ADHD. In a randomized placebo-controlled double-blind crossover design, 27 children with ADHD were scanned twice with resting-state functional MRI and sustained attention was examined using a continuous performance task under methylphenidate and placebo conditions; 49 matched typically-developing (TD) children were scanned once for comparison. Dynamic time-varying cross-network interactions between the salience (SN), frontoparietal (FPN), and default mode (DMN) networks were examined in children with ADHD under both administration conditions and compared with TD children. Methylphenidate improved sustained attention on a continuous performance task in children with ADHD, when compared to the placebo condition. Children with ADHD under placebo showed aberrancies in dynamic time-varying cross-network interactions between the SN, FPN and DMN, which were remediated by methylphenidate. Multivariate classification analysis confirmed that methylphenidate remediates aberrant dynamic brain network interactions. Furthermore, dynamic time-varying network interactions under placebo conditions predicted individual differences in methylphenidate-induced improvements in sustained attention in children with ADHD. These findings suggest that a single dose of methylphenidate can remediate deficits in sustained attention and aberrant brain circuit dynamics in cognitive control circuits in children with ADHD. Findings identify a novel brain circuit mechanism underlying a first-line pharmacological treatment for ADHD, and may inform clinically useful biomarkers for evaluating treatment outcomes

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NeuroImage Clin. 2022;35.
LONGITUDINAL CHANGES OF ADHD SYMPTOMS IN ASSOCIATION WITH WHITE MATTER MICROSTRUCTURE: A TRACT-SPECIFIC FIXEL-BASED ANALYSIS.
Damatac CG, Soheili-Nezhad S, Blazquez Freches G, et al.
Background: Variation in the longitudinal course of childhood attention deficit/hyperactivity disorder (ADHD) coincides with neurodevelopmental maturation of brain structure and function. Prior work has attempted to determine how alterations in white matter (WM) relate to changes in symptom severity, but much of that work has been done in smaller cross-sectional samples using voxel-based analyses. Using standard diffusion-weighted imaging (DWI) methods, we previously showed WM alterations were associated with ADHD symptom remission over time in a longitudinal sample of probands, siblings, and unaffected individuals. Here, we extend this work by further assessing the nature of these changes in WM microstructure by including an

additional follow-up measurement (aged 18 - 34 years), and using the more physiologically informative fixel-based analysis (FBA).
Methods: Data were obtained from 139 participants over 3 clinical and 2 follow-up DWI waves, and analyzed using FBA in regions-of-interest based on prior findings. We replicated previously reported significant models and extended them by adding another time-point, testing whether changes in combined ADHD and hyperactivity-impulsivity (HI) continuous symptom scores are associated with fixel metrics at follow-up.
Results: Clinical improvement in HI symptoms over time was associated with more fiber density at follow-up in the left corticospinal tract (lCST) (tmax = 1.092, standardized effect[SE] = 0.044, pFWE = 0.016). Improvement in combined ADHD symptoms over time was associated with more fiber cross-section at follow-up in the lCST (tmax = 3.775, SE = 0.051, pFWE = 0.019).
Conclusions: Aberrant white matter development involves both lCST micro- and macrostructural alterations, and its path may be moderated by preceding symptom trajectory

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Neuropsychiatr Enfance Adolesc. 2022.

ADHD AND OBESITY: A NARRATIVE REVIEW FROM THE PERSPECTIVE OF A CHILD PSYCHIATRIST.

Rossi L, Isnard P.

Purpose: This narrative review is aimed at presenting recent evidence on the association between two widespread, chronic, and growing diseases in childhood: attention-deficit/hyperactivity disorder (ADHD) and obesity. Several hypotheses have been put forward about the correlations between the two conditions, concerning prenatal, perinatal and postnatal factors.
Method: We approached this topic through a search of recent literature on this subject, from the perspective of a child psychiatrist, a specialist in child development with an integrative view of the various factors involved in the onset, development and maintenance of a pathological condition, as well as a clinical approach, directed at addressing these factors in a combined manner.
Conclusion: The most important point that emerged from our research and to be considered, as a child mental health specialist, seems to maintain an integrated view of the etiology and the management of mental disorders, through an integrative approach

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Nord J Psychiatry. 2022 Jul;76:365-71.

WHAT CAN A NATIONAL PATIENT REGISTRY TELL US ABOUT PSYCHIATRIC DISORDERS AND REASONS FOR REFERRAL TO OUTPATIENT SERVICES IN YOUTH WITH HEARING LOSS?

Oerbeck B, Ohre B, Zeiner P, et al.

BACKGROUND: Studies of reasons for referral to the Child and Adolescent Mental Health Services (CAMHS) and subsequent psychiatric disorders are missing in youth with Hearing loss (HL). AIMS: To examine the referral reasons to CAMHS and the clinically diagnosed psychiatric disorders in youth with HL among the nationally representative population.
METHODS: The study population was a youth with HL referred to CAMHS and registered in the national Norwegian Patient Registry (NPR) during the years 2011-2016. The results were also compared with some data published from CAMHS for the General Youth Population (GenPop).
RESULTS: Among youth with HL, 18.1% had also been referred to CAMHS compared to about 5% in GenPop, at mean age 9.1years, >70% before age 13years vs. 46% in the GenPop. Boys with HL comprised 57% and were referred about two years earlier than girls with HL. Compared to the GenPop, youth with HL were referred more frequently for suspected neurodevelopmental- and disruptive disorders, and less frequently for suspected emotional disorders. Girls with HL were referred for suspected Attention-Deficit/Hyperactivity Disorder (ADHD) at about the same rate as boys with HL in the 7-12year age group. The most frequently registered psychiatric disorders were ADHD: 29.8%, anxiety disorders: 20.4%, and autism spectrum disorders: 11.0%, while disruptive disorders constituted about 5.0%.
CONCLUSIONS: Youth with HL were referred to CAMHS more often, but earlier than the GenPop, mostly due to ADHD disorders. Although more rarely referred for suspected anxiety disorders, these were frequently diagnosed, suggesting that anxiety was not recognized at referral in youth with HL

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Open Bioinformatics Journal. 2020;13:15-24.

NETWORK BIOLOGY APPROACHES TO IDENTIFY THE DRUG LEAD MOLECULE FOR NEURODEVELOPMENTAL DISORDERS IN HUMAN.

Verma A, Chauhan SS, Pankaj V, et al.

Aims: To identify most novel drug target and lead molecule for neurodevelopmental disorder Autism, Intellectual Disability (ID) and Attention Deficit Hyperactivity Disorder (ADHD) diseases through system biology approaches

Background: Neurodevelopmental disorders (NNDs) are disabilities associated chiefly with the functioning of the neurological system and brain. Children with neurodevelopmental disorders have difficulties with speech, behaviour, learning and other neurological functions. Systems biology is a holistic approach to enciphering the complexity of biological systems and their interactions. It opens the way to a more successful discovery of novel therapeutics.

Objective: To identify most novel drug target and lead molecule for neurodevelopmental disorder Autism, Intellectual Disability (ID) and Attention Deficit Hyperactivity Disorder (ADHD) diseases through system biology approaches.

Methods: A list of genes was collected from NCBI database for Autism, Intellectual Disability (ID) and Attention Deficit Hyperactivity Disorder (ADHD) diseases. STRING database and Cytoscape software was used for construction and interpreting molecular interaction in the network. 3D structure of target protein, was build and validated. The phytochemicals were identified through various research articles and filtered out by virtual screening through Molinspiration. Molecular docking analyses of known phytochemical with target proteins were performed usingAutoDock tool.

Result: AKT1 for Autism, SNAP25 for Intellectual Disability (ID) and DRD4 for Attention Deficit Hyperactivity Disorder (ADHD) were identified as most potential drug target through network study. further the modelled structure of obtained target were undergo molecular docking study with kown phytochemicals. Based on lowest binding energy, Huperzine A for Autism and ID, Valerenic acid for ADHD found to be the most potential therapeutic molecules.

Conclusion: Huperzine A against Autism and ID, Valerenic acid against ADHD found to be the most potential therapeutic molecules and expected to be effective in the treatment of NNDs. Phytochemicals do not have side effects so extract of these can be taken in preventive form too as these disorders occur during developmental stages of the child. Further the obtained molecule if experimentally validated would play promising role for the treatment of NDDs in human

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Pediatr Res. 2022 May;91:1459-68.

BRAIN FUNCTIONAL CONNECTIVITY IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER FOLLOWING REHABILITATION INTERVENTION.

Izadi-Najafabadi S, Rinat S, Zwicker JG.

BACKGROUND: Children with developmental coordination disorder (DCD) show improved motor function after Cognitive Orientation to Occupational Performance (CO-OP) intervention; however, the neural basis for these improvements is unknown.

METHODS: In this randomized waitlist-controlled trial, 78 children with DCD (with/without ADHD) were randomly assigned to either a treatment or waitlist group and underwent three resting-state MRI scans over six months. The treatment group received intervention between the first and second scan; the waitlist group received intervention between the second and third scan.

RESULTS: After CO-OP intervention, children with DCD [13 male, 8 female; mean (SD) age: 10.0 (1.7) years] showed increased functional connectivity between the default mode network and right anterior cingulate gyrus ($p<0.01$). Additional gains were noted at follow-up three months after the intervention, with greater functional connectivity between the dorsal attention network and precentral gyrus ($p<0.02$). However, children with DCD+ADHD [18 male, 1 female; mean (SD) age: 10.0 (1.14) years] did not show brain changes following CO-OP.

CONCLUSION: For children with DCD, increased functional connectivity in networks associated with self-, emotion-, and attention-regulation may underlie motor skill improvements observed after CO-OP intervention. Modifications to the CO-OP protocol may be required to induce similar brain changes in children with DCD+ADHD.

IMPACT: This study provides neuroscientific evidence for the Cognitive Orientation to Occupational Performance (CO-OP) approach as an effective rehabilitation intervention to induce brain and behavioral changes in children with DCD. While children with DCD±ADHD showed improved motor function after CO-OP, only children with DCD showed brain changes after intervention. Children with DCD showed increased functional connectivity in networks associated with self-, emotion-, and attention-regulation after the intervention. Treatment modifications may be required to induce similar brain changes in children with DCD+ADHD. Pediatricians are encouraged to refer children with DCD with and without ADHD for CO-OP intervention to improve their motor skills

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Pediatr Allergy Immunol. 2022;33.

EARLY CHILDHOOD ALLERGY LINKED WITH DEVELOPMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

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

Background: Previous studies reported controversial results regarding the association between allergic disorders and attention deficit hyperactivity disorder (ADHD)/autism spectrum disorder (ASD). The aim of this article was to investigate whether allergic disorders are associated with ADHD/ASD in a large cohort of pediatric patients.

Methods: A retrospective study using the pediatric (0–18 year) database (ICD-9-CM codes) of Clalit Health Services during the years (2000–2018). Diagnosis of all disorders was made by specialist physicians.

Results: A total of 117 022 consecutive non-selective allergic children diagnosed with one or more allergic disorder (asthma, rhinitis, conjunctivitis, skin, food, or drug allergy) and 116 968 non-allergic children were enrolled to our study. The mean follow-up period was 11 ± 6 years. The presence of allergic disorders in early childhood (mean age of allergic diagnosis 4.5 ± 4.3 years) in boys as well as in girls significantly increased the risk to develop ADHD (O.R 2.45, CI 2.39–2.51; p <.0001), ASD (O.R 1.17, CI 1.08–1.27; p <.0001), or both ADHD + ASD (O.R 1.5, CI 1.35–1.79; p <.0001). Children with more than one allergic comorbidity revealed a much higher risk. In a multivariable analysis (adjusted for age at study entry, number of yearly visits, and gender), the risk of allergic children to develop ADHD and ADHD + ASD, but not ASD alone, remained significantly higher.

Conclusion: Allergic disorder in early childhood significantly increased the risk to develop ADHD, and to a less extend ASD, in later life

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Pediatr Obes. 2022.

CHILD ADHD AND AUTISTIC TRAITS, EATING BEHAVIOURS AND WEIGHT: A POPULATION-BASED STUDY.

Harris HA, Bowling A, Santos S, et al.

Background: Children with Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) have an increased obesity risk. Although these conditions commonly co-occur, shared factors relating to obesity risk are unknown.

Objectives: To examine the shared and unique associations of ADHD and autistic traits with eating behaviours and BMI.

Methods: Children (N=4134) from the population-based Generation R Study were categorized into subgroups based on parent-reported ADHD and autistic traits scores at 6 years: ADHDHigh, ASDHigh, ADHD+ASDHigh and REF (reference group: ADHD+ASDLow). Multiple linear regressions examined the associations between subgroups and eating behaviours (at 10 years) and BMIz (at 14 years), relative to REF. Mediation analyses tested the indirect effect of subgroup and BMIz through eating behaviours.

Results: ADHD + ASDHigh children expressed both food approach (increased food responsiveness and emotional overeating) and avoidant eating behaviours (increased emotional undereating, satiety responsiveness/ slowness in eating and picky eating, and decreased enjoyment in food). ASDHigh children were more food avoidant, while ADHDHigh children had more food approach behaviours and greater BMIz. ADHDHigh and BMIz were indirectly associated with food responsiveness and emotional overeating.

Conclusions: ADHD and autistic trait phenotypes show distinct associations with potential obesity risk factors, and further research is needed to improve targeted early intervention

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Pediatr Res. 2022.

IS HOMEOPATHY EFFECTIVE FOR ATTENTION DEFICIT AND HYPERACTIVITY DISORDER? A META-ANALYSIS.

Gaertner K, Teut M, Walach H.

Background: Attention deficit and hyperactivity disorder (ADHD) prevalence is increasing, compliance to treatment is often poor, and additional treatment options are warranted. We aim to investigate whether individualized homeopathic treatment is effective in children with ADHD when compared to placebo or usual care alone.

Methods: Thirty-seven online sources were searched with a last update in March 2021. Studies investigating the effects of individualized homeopathy against any control in ADHD (ICD-10 category F90.0) were eligible. Data were extracted to a predefined excel sheet independently by two reviewers.

Results: Six studies were analyzed. All but one were randomized and showed low-to-moderate risk of bias; two were controlled against standard treatment and four were placebo-controlled and double-blinded. The meta-analysis revealed a significant effect size across studies of Hedges g = 0.542 (95% CI 0.311-0.772; z = 4,61; p < 0.001) against any control and of g = 0.605 (95% CI 0.05-1.16; z = 2.16, p = 0.03) against placebo (n = 4). The effect estimations are based on studies with an average sample size of 52 participants.

Conclusions: Individualized homeopathy showed a clinically relevant and statistically robust effect in the treatment of ADHD. Impact: This paper summarizes the current evidence of individualized homeopathy in attention deficit and hyperactivity disorder (ADHD), and the results show a clinical improvement for patients receiving this additional treatment. Individualized homeopathy has shown evidence of effectiveness in the treatment of ADHD in several small trials, this is the first systematic review and meta-analysis.This data may encourage caregivers to consider co-treatment or referral to individualized homeopathy when treating childhood ADHD

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Pharmacoepidemiol Drug Saf. 2022 Jul;31:810-14.

TRENDS IN ANTIPSYCHOTIC USE FOR YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DISRUPTIVE BEHAVIOR DISORDERS.

DosReis S, Saini J, Hong K, et al.

PURPOSE: To examine trends in off-label antipsychotic use for youth with attention-deficit/hyperactivity disorder with and without a comorbid disruptive behavior disorder.

METHOD: This cross-sectional study of annual trends from 2007 through 2015 used the IQVIA PharMetrics® Plus for Academics data. We identified 165 794 commercially-insured youth 3-18-year-old who had a diagnosis of attention-deficit/hyperactivity disorder and classified them into subgroups with and without disruptive behavior disorders comorbidities. Antipsychotic use, with or without a stimulant, was the primary dependent outcome. Logistic regression estimated the odds of antipsychotic use associated with comorbid attention-deficit/hyperactivity disorder and disruptive behavior disorders, adjusting for age, sex, study year, and other psychotropic use.

RESULTS: Over 70% of the 165 794 youth with attention-deficit/hyperactivity disorder were 5-14-year-old and male, and 12% had disruptive behavior disorders. Antipsychotic prevalence, with or without a stimulant, was 4.4% in 2007 and 3.4% in 2015. Stimulants with antipsychotics increased significantly from 2007 to 2015 for females (19.5%-28.7%) and youth 15-18-year-old (25.9%-32.7%). Adjusting for age, sex, study year, and other psychotropic use, youth with a comorbid disruptive behavior had a 2.5 (95% CI: 2.3, 2.7) higher likelihood of receiving an antipsychotic than youth with attention-deficit/hyperactivity disorder and no comorbidities.

CONCLUSIONS: Antipsychotic use was associated with comorbid disruptive behaviors in youth with attention-deficit/hyperactivity disorder. Off-label antipsychotic use has increased for females and older adolescents

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Phytomedicine. 2022 Jul;102:154191.

PARENT-ADMINISTERED PEDIATRIC TUINA FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN PRESCHOOL CHILDREN: A PILOT RANDOMIZED CONTROLLED TRIAL EMBEDDED WITH A PROCESS EVALUATION.

Chen SC, Yu J, Wang HS, et al.

BACKGROUND: Beneficial effects of parent-administered pediatric tuina on ADHD in children have been reported in previous studies, but no rigorously designed randomized controlled trials (RCTs) have been conducted on it.

OBJECTIVE: To assess the feasibility and preliminary effects of parent-administered pediatric tuina for ADHD symptoms in preschoolers.

METHODS: This project was a two-arm, parallel, open-label, pilot RCT. Sixty-four participants were randomized into two groups at a 1:1 ratio. Parents in the parent-administered tuina group (n = 32) attended an online training program on pediatric tuina for ADHD and conduct this intervention on their children at home. Parents in the parent-child interaction group (n = 32) attended an online training about progressive muscle relaxation exercise and carried out parent-child interactive physical activities with their children at home. Both interventions were carried out every other day during a two-month intervention period, with each manipulation for at least 20 min. Feasibility outcomes included recruitment rate, consent rate, participants' adherence, retention rate, and adverse event. Outcomes were assessed at baseline, week 4, and week 8. The primary outcome measure was the Swanson, Nolan, and Pelham parent scale (SNAP); the secondary outcomes included preschool anxiety scale, children's sleep habits questionnaire, and parental stress scale. A mixed-method process evaluation embedded within the outcome evaluation was performed.

RESULTS: The recruitment rate was 12.8 per month. The consent rate was 98.5%. Good adherence was shown from the parent logbook. Four participants withdraw from the study. No severe adverse event was reported. For the SNAP total score, both groups showed improvement with moderate within-group effect size (Cohen's $d > 0.5$, all $p < 0.001$) and the between-group effect size was minimal ($d(ppc2) < 0.2$, $p > 0.05$). Perceived improvements on children's appetite and sleep quality, and parent-child relationship was observed from the qualitative data.

CONCLUSIONS: The study design and the parent-administered pediatric tuina intervention were feasible. Parent-administered pediatric tuina provided beneficial effects on improving core hyperactivity/impulsivity symptoms in preschool children. Parents perceived improvements on children's appetite and sleep quality. Further large-scale are warranted

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PLoS ONE. 2022;17:e0269495.

PSYCHOSOCIAL FUNCTIONING OF ADOLESCENTS WITH ADHD IN THE FAMILY, SCHOOL AND PEER GROUP: A SCOPING REVIEW PROTOCOL.

Karteczka-Świętek K, Opozda-Suder S, Strojny A.

OBJECTIVE: The objective of this scoping review is to investigate what is known about the psychosocial functioning of adolescents with ADHD. All basic life environments (family, school and peer group) will be considered.

INTRODUCTION: Adolescence is especially critical for people with ADHD-natural maturation may be accompanied by changing symptoms of ADHD. A number of childhood difficulties transform during adolescence and contribute to problems in various areas that comprise psychosocial functioning. The available studies focus on selected domains of psychosocial functioning of adolescents with ADHD, however, to the authors' best knowledge, there is no comprehensive description of this issue. The lack of such a description is the main rationale for conducting this scoping review.

INCLUSION CRITERIA: Pointing to the PCC elements (population, concept, context), the scoping review will include primary studies on the concept of psychosocial functioning (including functioning in the family, school and peer group). In the included studies, the term "psychosocial functioning" (or related) had to be used explicitly. The population will be adolescents (10 to 19 years old) with a formal diagnosis of ADHD (DSM classification) or Hyperkinetic Syndrome (ICD-9) or Hyperkinetic Disorders (ICD-10). There will be no restrictions on the research context.

METHODS: The methodology of scoping reviews will be applied in accordance with the guidelines of the Joanna Briggs Institute (JBI). The following databases: Academic Search Ultimate, ERIC, MEDLINE, ProQuest Central, PsycInfo, Scopus, and databases under the Web of Science will be searched for primary

studies in peer-reviewed journals, written in English and published since 1987. The analyses will be based mainly on frequency counts of the components of psychosocial functioning and population characteristics. The results will be presented in tabular form and supplemented with a descriptive summary. The protocol has been registered on the Open Science Framework: https://doi.org/10.17605/OSF.IO/MS82H [registration DOI]

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Prog Neuropsychopharmacol Biol Psychiatry. 2022 Aug;118:110581.

PERIPHERAL BLOOD INFLAMMATORY MARKERS IN PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): A SYSTEMATIC REVIEW AND META-ANALYSIS.

Misiak B, et al.

It has been observed that subclinical inflammation might be involved in the pathophysiology of attention deficit/hyperactivity disorder (ADHD). However, studies investigating peripheral blood levels of immune-inflammatory markers have provided mixed findings. We performed a systematic review and meta-analysis of studies comparing unstimulated serum or plasma levels of C-reactive protein (CRP) and cytokines in subjects with ADHD and healthy controls (the PROSPERO registration number: CRD 42021276869). Online searches covered the publication period until 30th Sep 2021 and random-effects meta-analyses were carried out. Out of 1844 publication records identified, 10 studies were included. The levels of interleukin (IL)-6 were significantly higher in studies of participants up to the age of 18 years (k = 10, g = 0.70, 95%CI: 0.10-1.30, p = 0.023) and after including those above the age of 18 years (k = 10, g = 0.71, 95%CI: 0.12-1.31, p = 0.019). In turn, the levels of tumor necrosis factor-± (TNF-±) were significantly lower in subjects with ADHD compared to healthy controls (k = 7, g = -0.16, 95%CI: -0.30 - -0.03, p = 0.020). Individual studies had a high contribution to the overall effect, since the overall effect was no longer significant after removing single studies. No significant differences were found with respect to the levels of CRP, IL-1Î², IL-10 and interferon-Î³. The present findings indicate that individuals with ADHD tend to show elevated levels of IL-6 and reduced levels of TNF-Î±. Larger and longitudinal studies recording potential confounding factors and comorbid psychopathology are needed to confirm our findings

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Psychiatr Danub. 2022;34:288-95.

EFFECTS OF MUSICOTHERAPY COMBINED WITH COGNITIVE BEHAVIORAL INTERVENTION ON THE COGNITIVE ABILITY OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Zhu C.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) mainly manifests as learning difficulties, emotional impulsiveness, excessive activities, and attention deficit disorder. Given that it can influence social communication abilities, as well as physical and psychological health and viability, ADHD rehabilitation has attracted close attention. This study aims to discuss the influences of musicotherapy combined with cognitive behavioral intervention on the cognitive ability of children with ADHD and provide some references for ADHD rehabilitation.

SUBJECTS AND METHODS: A total of 120 children with ADHD in the Cooperative Hospital of Guangzhou University from June 2018 to May 2021 were chosen as the research objects. They were divided randomly into the control and observation groups with 60 cases in each group via the observing random digital method. The control group was the blank control and did not receive any intervention. The observation group received 16 weeks of musicotherapy combined with cognitive behavioral intervention. Symptoms and the results of the numerical cross-attention test, the Wisconsin card sorting test, the combined Raven's test (CRT), the Wechsler intelligence scale for children test, and Conner's child behavioral scale for parents of the two groups before and after the intervention were compared.

RESULTS: The relevant indexes of the control group did not show any significant changes after the intervention (P>0.05). In the intervention group, the accurately crossed number and net scores increased significantly, whereas the wrongly crossed number and missed crossed number scores and error; attention deficit; hyperactivity-impulsiveness; and ADHD-RS- total scores declined dramatically after intervention relative to those before the intervention. Moreover, the above indexes of the observation group showed more significant improvements than those of the control group (P<0.05). In the observation group, the conceptual

level percentage and the number of completed classes had significantly increased and the number of discontinuous errors and number of continuous errors after the intervention had dropped sharply compared with those before. The above indexes of the observation group had improved significantly compared with those of the control group (P<0.05). Moreover, in both groups, the concentration/attention factor and CRT scores increased dramatically and the scores of Conner's child behavior scale after the intervention had dropped significantly compared with those before. After intervention, the above indexes of the observation group showed greater improvements than those of the control group (P<0.05).
CONCLUSIONS: The musicotherapy combined with cognitive behavioral intervention can improve the cognitive functions of children with ADHD and has clinical application values

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Psychiatry Res. 2022 Aug;314:114674.

MEASURING AUTISM IN MALES AND FEMALES WITH A DIFFERENTIAL ITEM FUNCTIONING APPROACH: RESULTS FROM A NATION-WIDE POPULATION-BASED STUDY.

Mayrland C, Nilsson T, Larsson H, et al.

Existing screening instruments for Autism Spectrum Disorder (ASD) might be prone to detect a male manifestation of ASD. Here, we examined the 17 items from the ASD domain in the Autism-Tics, ADHD and other Comorbidities inventory (A-TAC) for Differential Item Functioning (DIF). Data were obtained from the Child and Adolescent Twin Study in Sweden (CATSS) in which parents have responded to the A-TAC. Information regarding a registered diagnosis of ASD were retrieved from the National Patient Register. The cohort was divided into a developmental sample for evaluation of DIF, and a validation sample for examination of the diagnostic accuracy of the total ASD domain, and a novel male and female short form. Our main finding included the identification of DIF for six items, three favouring males and three favouring females. The full, 17 item, ASD domain and the male and female short form showed excellent ability to capture ASD diagnoses in both males and females up to the age of nine years. The full ASD domain in A-TAC is psychometrically largely equivalent across sex and the limited differences between males and females diminish the need for a sex-specific scoring when utilizing the 17 item total score

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Psychiatry Res. 2022;313.

FAMILIAL RISK FOR BIPOLAR I DISORDER IS ASSOCIATED WITH ERYTHROCYTE OMEGA-3 POLYUNSATURATED FATTY ACID DEFICITS IN YOUTH WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

McNamara RK, Chen C, Tallman MJ, et al.

Although attention-deficit/hyperactivity disorder (ADHD) and a family history of bipolar I disorder (BD) increase the risk for developing BD, associated pathoetiological mechanisms remain poorly understood. One candidate risk factor is a neurodevelopmental deficiency in omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This study investigated erythrocyte EPA+DHA biostatus in psychostimulant-free ADHD youth with (ΓÇÿhigh-riskΓÇÖ, HR) and without (ΓÇÿlow-riskΓÇÖ, LR) a first-degree relative with BD, and healthy controls (HC). Erythrocyte EPA+DHA composition was determined by gas chromatography, and symptom ratings were performed. A total of n = 123 (HR, n = 41; LR, n = 42; HC, n = 40) youth (mean age: 14.4 -¦ 2.5 years) were included in the analysis. Compared with HC, erythrocyte EPA+DHA composition was significantly lower in HR (-13%) but not LR (-3%), and there was a trend for HR to be lower than LR (-11%). Both HR and LR differed significantly from HC on all symptom ratings. HR had greater ADHD hyperactivity/impulsive symptom severity, manic symptom severity, and higher parent-reported ratings of internalization, externalization, and dysregulation, compared with LR. ADHD youth with a BD family history exhibit erythrocyte EPA+DHA deficits and a more severe clinical profile, including greater manic and dysregulation symptoms, compared with ADHD youth without a BD family history

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Psychophysiology. 2022 Jun;59.

INNOVATIVE APPROACHES IN INVESTIGATING INTER-BEAT INTERVALS: GRAPH THEORETICAL METHOD SUGGESTS ALTERED AUTONOMIC FUNCTIONING IN ADOLESCENTS WITH ADHD.

Kvadsheim E, Fasmer OB, Fasmer EE, et al.

Cardiac inter-beat intervals (IBIs) are considered to reflect autonomic functioning and self-regulatory abilities and are often investigated by traditional time- and frequency domain analyses. These analyses investigate IBI fluctuations across relatively long time series. The similarity graph algorithm is a nonlinear method that analyzes segments of IBI time series (i.e., time windows)—possibly being more sensitive to transient and spontaneous IBI fluctuations. We hypothesized that the similarity graph algorithm would detect differences between Attention-Deficit/Hyperactivity Disorder (ADHD) and control groups. Resting electrocardiogram (ECG) recordings were collected in 10–18-year-olds with ADHD (n = 37) and controls (n = 36). IBIs were converted to graphs that were subsequently investigated for similarity. We varied the criterion for defining IBIs as similar, assessing which setting best distinguished ADHD and control groups. Using this setting, we applied the similarity graph algorithm to time windows of 2–5, 6–13 and 12–25 s, respectively. We also performed traditional IBI analyses. Independent samples t tests assessed group differences. Results showed that a 1.5% criterion of similarity and a time window of 2–5 s best distinguished adolescents with ADHD and controls. The similarity graph algorithm showed a higher number of edges, maximum edges and cliques, and lower edges10 + 10/edges2 + 2 in the ADHD group compared to controls. The results suggested more similar IBIs in the ADHD group compared to the controls, possibly due to altered vagal activity and less effective regulation of heart rate. Traditional analyses did not detect any group differences. Consequently, the similarity graph algorithm might complement traditional IBI analyses as a marker of psychopathology

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Qual Manag Health Care. 2022 Jul;31:154-59.

FACTORS ASSOCIATED WITH CHILDREN DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND 30-DAY FOLLOW-UP CARE WITH PRACTITIONERS AMONG MEDICAID RECIPIENTS IN GEORGIA.

Yin H, Ibe B, Parr TL, et al.

BACKGROUND AND OBJECTIVES: It is important that children prescribed attention-deficit/hyperactivity disorder (ADHD) medication get timely follow-up care. In 2018, only 44% of US Medicaid recipients attended a follow-up visit within 30 days of their first ADHD prescription. The objective of this study was to identify the member and practitioner-related predictors that were associated with children who were diagnosed with ADHD and had a follow-up visit within 30 days (initiation phase) of their first prescription of ADHD medication (Index Prescription Start Date, or IPSD).

METHODS: A cross-sectional study was conducted to identify the independent predictors of a follow-up visit within 30 days and 2 follow-up visits within 270 days after the initiation phase (continuation and maintenance phase, or C&M phase) for Medicaid recipients. Predictive factors examined included race, school age group, gender, geography of residence, Medicaid service region, newly diagnosed ADHD, hospital admission, emergency department (ED) visit, types of ADHD medication, other psychosocial or behavioral diagnoses, psychosocial or behavioral therapy, prescriber specialty, and school season.

RESULTS: There were 2369 members eligible for the initiation phase measure, of whom 330 members were eligible for the C&M phase measure. Multiple regression analysis found that unmet 30-day follow-up was significantly associated with African American children with an existing diagnosis of ADHD (adjusted odds ratio [AOR] = 2.13; 95% confidence interval [CI], 1.64-2.76), middle school-aged children (AOR = 1.49; 95% CI, 1.23-1.80), rural residence (AOR = 1.27; 95% CI, 1.05-1.55), no ED visit (AOR = 1.57; 95% CI, 1.16-2.12), no psychosocial or behavioral therapy prior to the IPSD (AOR = 2.30; 95% CI, 1.65-3.21), and primary care practitioners (AOR = 1.88; 95% CI, 1.45-2.44).

CONCLUSION: Pediatrics was the most common specialty prescribing ADHD medications. Managed care organizations can focus intervention efforts to improve compliance with 30-day follow-up among Medicaid children by targeting the high-risk categories identified above. They can also focus on facilitating communication between behavioral health practitioners and pediatricians about several key points: (1) the importance of using behavioral health therapy prior to prescribing medication; (2) the importance of timely follow-up care; and (3) the importance of medication management in combination with behavioral health therapy

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Res Dev Disabil. 2022 Aug;127:104262.

EVENT RATE EFFECTS ON CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER: TEST PREDICTIONS FROM THE MODERATE BRAIN AROUSAL MODEL AND THE NEURO-ENERGETICS THEORY USING THE DIFFUSION DECISION MODEL.

Zhou Q, Luo Y.

BACKGROUND: Converging evidence has found that the inhibitory control of children with attention-deficit/hyperactive disorder (ADHD) is context-dependent and particularly susceptible to the event rate. The Moderate Brain Arousal (MBA) model predicts a U-shaped curve between event rate and performance as a modulation of brain arousal. The neuroenergetics theory (NeT) proposes that a smaller event rate results in neuronal fatigue and subsequent descent performance. However, previous work applied the traditional one-dimensional index of performance, such as accuracy rate and response time, which might limit the exploration of the event rate effect on the specific underlying process. AIMS: We used a diffusion decision model (DDM) to study the influence of event rate on inhibition control in children with ADHD and verified the explanation of the MBA model and the NeT.

METHODS AND PROCEDURES: The Stop Signal Task manipulated by four event rate conditions was conducted with 24 children with ADHD (mean age=8.5, males=16) and 29 typical developmental children (TDC) (mean age=9.0, males=12). DDM was applied to compare the differences in the DDM parameters across different event rates.

OUTCOMES AND RESULTS: Compared with TDC, children with ADHD had a smaller drift rate, longer non-decision time, and smaller boundary separation. Although the event rate had little influence on ADHD, the drift rate of the TDC was approximately linear with an increased event rate, and the Ter had a quadratic function relationship with the event rate.

CONCLUSIONS AND IMPLICATIONS: The event rate effect may influence children's performance through dual mechanisms. Neuronal energy supply could regulate information processing and brain arousal to regulate the activation of primary stimuli encoding and motor control. Insight into the multi-mechanism of ADHD cognition deficits would be helpful for clinicians in making objective diagnoses and effective targeted treatments

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Res Dev Disabil. 2022 Aug;127:104270.

"EVENTUALLY I'M GONNA NEED PEOPLE": SOCIAL CAPITAL AMONG COLLEGE STUDENTS WITH DEVELOPMENTAL DISABILITY.

Hoyle JN, Laditka JN, Laditka SB.

BACKGROUND AND AIMS: About 18% of college students have disabilities. Social capital, resources we can tap from relationships, may be particularly valuable for students with disabilities. Yet, disabilities often limit the individual's ability to develop or use social capital. We studied how college students with developmental disabilities understand, develop, and use social capital.

METHODS AND PROCEDURES: We conducted in-depth semi-structured Zoom interviews with 10 women with developmental disabilities enrolled at a public university in the southeastern United States early in 2021. We examined the qualitative data with thematic analysis.

OUTCOMES AND RESULTS: Participants averaged age 20; 70% reported attention deficit disorder or attention deficit hyperactivity disorder; 90% reported multiple diagnoses. Most participants described COVID-19 pandemic-related isolation and stress, which magnified both the need for relationships and awareness of that need, prompting participants to become proactive in forming and maintaining relationships despite anxiety about them. Themes were: foundational relationships, reciprocity, expanding horizons, a need for new relationships, focus on the future and relationship barriers.

CONCLUSIONS AND IMPLICATIONS: Results highlight the importance of social relationships and the resources they provide to students with disabilities, particularly in stressful times. Colleges can help students by connecting them with others and providing strategies for building and maintaining social capital. WHAT THIS PAPER ADDS: College students with developmental disabilities often face challenges developing and maintaining social capital, resources derived from relationships with other people. These resources are key to success in school and after graduation, as students continue into adulthood. We studied how students with developmental disabilities build social capital. The students described their relationships with others and the types of support they contributed to and received from those relationships. We also extended previous

research by examining pandemic-related effects, interviewing participants nearly one year into the COVID-19 pandemic. We provide recommendations for further research and ways colleges and universities can encourage social capital development among all students

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Res Dev Disabil. 2022;128.

A SYSTEMATIC REVIEW OF THE USE OF ATOMOXETINE FOR MANAGEMENT OF COMORBID ANXIETY DISORDERS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Khoodoruth MAS, Ouanes S, Khan YS.

Background: Anxiety disorders are among the most common comorbid mental disorders in children and adolescents with attention-deficit hyperactivity disorder (ADHD). While the role of atomoxetine, a non-stimulant medication, is well-established in the management of ADHD symptoms since two decades, there is a dearth of evidence regarding its efficacy in the management of anxiety disorders in children and adolescents with ADHD.

Aims: We aimed to provide insights into (1) the comparative efficacy of atomoxetine in children and adolescents with comorbid ADHD and anxiety disorders, (2) change in severity of anxiety symptoms based on patients, parents, and clinicians ratings, (3) tolerability and side effects.

Methods: We searched PubMed, EMBASE, and PsycINFO for clinical trials that addressed the efficacy of atomoxetine for anxiety symptoms in children and adolescents with ADHD. All published literature was systematically reviewed.

Results: We included four studies, out of which two specifically addressed comorbid ADHD and anxiety disorder. The studies suggested that atomoxetine did not exacerbate and in fact reduced anxiety symptoms in young patients with comorbid ADHD.

Conclusions and implications: Overall, atomoxetine demonstrates good efficacy in improving anxiety symptoms in children and adolescents with ADHD. Further studies are needed to shed light on atomoxetine's efficacy for anxiety subtypes in ADHD

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Research on Child and Adolescent Psychopathology. 2022 Jun;50:809-22.

LONGITUDINAL ASSOCIATION OF SLUGGISH COGNITIVE TEMPO WITH DEPRESSION IN ADOLESCENTS AND THE POSSIBLE ROLE OF PEER VICTIMIZATION.

Fredrick JW, Langberg JM, Becker SP.

It is unknown whether sluggish cognitive tempo (SCT) is prospectively associated with depression in adolescence, and possible processes linking SCT to depression remain unexamined. Using a longitudinal study with three timepoints over a two-year period, the current study tested the indirect effects of SCT on depression via peer victimization, specifically physical, relational, and verbal victimization. Participants were 302 adolescents (Mage = 13.17 years; 44.7% female participants; 81.8% White; 52% with ADHD). In the fall of 8th grade, adolescents and parents completed measures of adolescents' SCT and ADHD symptoms. Adolescents completed a measure of peer victimization in spring of 8th grade and a measure of depressive symptoms in 10th grade. Models examining indirect effects were conducted with and without control of baseline ADHD and/or depressive symptoms. Across analyses, adolescent and parent ratings of SCT symptoms uniquely predicted greater depressive symptoms two years later when controlling for adolescent sex, study site, and either 8th grade depressive or ADHD symptoms. Further, adolescents' self-reported 8th grade SCT symptoms predicted 10th grade depressive symptoms via verbal victimization when controlling for 8th grade ADHD symptoms, but not in analyses incorporating 8th grade depressive symptoms. Findings underscore the predictive association of SCT on depressive symptoms, the possible role of adverse peer relationships as a mechanism linking SCT to depression, and the importance of considering ADHD and depressive symptoms in research on longitudinal correlates of SCT

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Research on Child and Adolescent Psychopathology. 2022 Jun;50:753-70.

CHILDHOOD ADHD AND EXECUTIVE FUNCTIONING: UNIQUE PREDICTIONS OF EARLY ADOLESCENT DEPRESSION.

Fenesy MC, Lee SS.

Given the increasing prevalence of adolescent depression, identification of its early predictors and elucidation of the mechanisms underlying its individual differences is imperative. Controlling for baseline executive functioning (EF), we tested separate ADHD dimensions (i.e., inattention, hyperactivity-impulsivity) as independent predictors of early adolescent depression, including temporally-ordered causal mediation by academic functioning and social problems, using structural equation modeling. At baseline, participants consisted of 216 children (67% male) ages 6–9 years old with (n = 112) and without (n = 104) ADHD who subsequently completed Wave 2 and 3 follow-ups approximately two and four years later, respectively. Predictors consisted of separate parent and teacher ratings of childhood ADHD and laboratory-based assessments of key EF domains. At Wave 2, parents and teachers completed normed rating scales of youth academic and social functioning; youth completed standardized assessments of academic achievement. At Wave 3, youth self-reported depression. Baseline inattention positively predicted early adolescent depression whereas childhood hyperactivity-impulsivity and EF did not. Neither academic nor social functioning significantly mediated predictions of depression from baseline ADHD and EF. We consider prediction of early adolescent depression from inattention, including directions for future intervention and prevention research

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Rev Colomb Psiquiatr. 2022.

ATTENTIONAL DIFFERENCES BETWEEN ISOLATED ATTENTION DEFICIT DISORDER AND ATTENTION DEFICIT DISORDER ASSOCIATED WITH NEUROFIBROMATOSIS TYPE 1.

Vaucheret Paz E, Ortol+í R, Cestari M, et al.

Introduction: The incidence of ADHD in patients with NF1 reaches 60%. Beyond the published literature on cognitive aspects in subjects with NF1, some studies suggest that the attentional profile of patients with NF1+ADHD is different from those with isolated ADHD.

Methods: A retrospective, analytical case-control study with the objective of comparing the intellectual and attentional profile in children with NF1+ADHD, NF1 and isolated ADHD in order to characterise them, noting similarities and differences.

Results: Neuropsychological evaluations from 2017 to 2021 were reviewed for all subjects with a diagnosis of NF1 (n = 46) with IQ >70 and ADHD (n = 180). In the ANOVA test, it was observed that patients with NF1+ADHD presented with greater visuospatial impairment (M = 84.66; F(2,210) = 7.84; P< 0.001; η2 = 0.07) and a lower total intellectual level (M = 84.20; F(2,223) = 4.35; P = 0.01; η2 = 0.04). In the attentional tests they showed more errors of omission (M = 72.66; F(2,223) = 18.13; P< .001; η2 = 0.14) and of commission (M = 57.87; F(2,223) = 4.68; P = 0.01; η2 = 0.04) and lower reaction speed (M = 66.58; F(2,223) = 19.24; P< 0.001; η2 = 0.15) compared to patients with NF1 and isolated ADHD.

Conclusions: Attention deficit in patients with NF1 is associated with lower performance in intellectual functioning and greater visuospatial impairment. The attentional pattern of patients with NF1+ADHD was different from those with isolated ADHD; the difference being not only quantitative but also qualitative, supporting the hypothesis that attention impairment has its own features of NF1 and independent of ADHD

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Revista Habanera de Ciencias Medicas. 2021;20.

PHYSICAL ACTIVITY, EXERCISE AND QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Castillo-Paredes A, Valenzuela FM, Miranda RN.

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects quality of life in children and adolescents, extending into adulthood. The literature indicates that the practice of physical activity and physical exercise establishes positive benefits for the human body at a physical, biological and psychological level.

Objective: To examine the effects of physical activity or physical exercise interventions on quality of life in children and adolescents diagnosed with ADHD.

Material and Methods: The search for research was carried out through Google Scholar, Scopus, Pubmed, Scielo, Web of Science, Dialnet and Redalyc, selecting only open access research in Spanish. The last 5 years were considered for the analysis of the research; they were searched using the words: Physical Activity and Quality of life in children and adolescents with attention deficit and hyperactivity disorder, Physical Exercise and Quality of life in children and adolescents with attention deficit disorder with hyperactivity, Physical Activity and Quality of life in children and adolescents with ADHD, Physical Exercise and Quality of life in children and adolescents with ADHD.
Development: The 8 articles selected and extracted from the databases agree with the inclusion criteria related to the physical, psychological, biological and social benefits on quality of life.
Conclusions: Physical activity and physical exercise interventions with a duration of 15-90 minutes in children and adolescents with ADHD can be beneficial on quality of life

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Sci Rep. 2022 Jun;12:9958.

A PILOT META-ANALYSIS ON SELF-REPORTED EFFICACY OF NEUROFEEDBACK FOR ADOLESCENTS AND ADULTS WITH ADHD.

Fan HY, Sun CK, Cheng YS, et al.

Self-reported effectiveness of electroencephalogram-based neurofeedback (EEG-NF) against the core symptoms of attention-deficit hyperactivity disorder (ADHD) in adolescents/adults remains unclear. We searched PubMed, Embase, ClinicalKey, Cochrane CENTRAL, ScienceDirect, Web of Science, and ClinicalTrials.gov from inception to August 2021 for randomized clinical trials (RCTs) of EEG-NF with self-reported ADHD symptom ratings. Comparators included participants on waitlist/treatment as usual (TAU) or receiving other interventions. Of the 279 participants (mean age=23.48; range: 6-60) in five eligible RCTs, 183 received EEG-NF treatment. Forest plot demonstrated no difference in inattention (SMD=-0.11, 95% CI -0.39-0.18, p=0.46), total score (SMD=-0.08, 95% CI -0.36-0.2, p=0.56), and hyperactivity/impulsivity (SMD=0.01, 95% CI -0.23-0.25, p=0.91) between EEG-NF and comparison groups. Nevertheless, compared with waitlist/TAU, EEG-NF showed better improvement in inattention (SMD=-0.48, 95% CI -0.9--0.06, p=0.03) but not hyperactivity/impulsivity (SMD=-0.03, 95% CI -0.45-0.38, p=0.87). Follow-up 6-12 months demonstrated no difference in inattention (SMD=-0.01, 95% CI -0.41-0.38, p=0.94), total score (SMD=0.22, 95% CI -0.08-0.52, p=0.15), and hyperactivity/impulsivity (SMD=-0.01, 95% CI -0.27-0.26, p=0.96) between the two groups. Dropout rate also showed no difference (RR=1.05, 95% CI 0.82-1.33, p=0.72). Our results support EEG-NF for improving inattention in adolescents/young adults, although its effectiveness against hyperactivity/impulsivity remains inconclusive

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Sci Rep. 2022 Jul;12:11367.

GRAY MATTER VOLUMETRIC CORRELATES OF ATTENTION DEFICIT AND HYPERACTIVITY TRAITS IN EMERGING ADOLESCENTS.

Li CS, Chen Y, Ide JS.

Previous research has demonstrated reduction in cortical and subcortical, including basal ganglia (BG), gray matter volumes (GMV) in individuals with attention deficit hyperactivity disorder (ADHD), a neurodevelopmental condition that is more prevalent in males than in females. However, the volumetric deficits vary across studies. Whether volumetric reductions are more significant in males than females; to what extent these neural markers are heritable and relate to cognitive dysfunction in ADHD remain unclear. To address these questions, we followed published routines and performed voxel-based morphometry analysis of a data set (n=11,502; 5,464 girls, 9-10 years) curated from the Adolescent Brain Cognition Development project, a population-based study of typically developing children. Of the sample, 634 and 2,826 were identified as monozygotic twins and dizygotic twins/siblings, respectively. In linear regressions, a cluster in the hypothalamus showed larger GMV, and bilateral caudate and putamen, lateral orbitofrontal and occipital cortex showed smaller GMVs, in correlation with higher ADHD scores in girls and boys combined. When examined separately, boys relative to girls showed more widespread (including BG) and stronger associations between GMV deficits and ADHD scores. ADHD traits and the volumetric correlates demonstrated heritability estimates (a(2)) between 0.59 and 0.79, replicating prior findings of the genetic

basis of ADHD. Further, ADHD traits and the volumetric correlates (except for the hypothalamus) were each negatively and positively correlated with N-back performance. Together, these findings confirm volumetric deficits in children with more prominent ADHD traits. Highly heritable in both girls and boys and potentially more significant in boys than in girls, the structural deficits underlie diminished capacity in working memory and potentially other cognitive deficits in ADHD

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Sensors (Basel). 2022 Jun;22.

A Systematic Review on Feature Extraction in Electroencephalography-Based Diagnostics and Therapy in Attention Deficit Hyperactivity Disorder.

Arpaia P, Covino A, Cristaldi L, et al.

A systematic review on electroencephalographic (EEG)-based feature extraction strategies to diagnosis and therapy of attention deficit hyperactivity disorder (ADHD) in children is presented. The analysis is realized at an executive function level to improve the research of neurocorrelates of heterogeneous disorders such as ADHD. The Quality Assessment Tool for Quantitative Studies (QATQS) and field-weighted citation impact metric (Scopus) were used to assess the methodological rigor of the studies and their impact on the scientific community, respectively. One hundred and one articles, concerning the diagnostics and therapy of ADHD children aged from 8 to 14, were collected. Event-related potential components were mainly exploited for executive functions related to the cluster inhibition, whereas band power spectral density is the most considered EEG feature for executive functions related to the cluster working memory. This review identifies the most used (also by rigorous and relevant articles) EEG signal processing strategies for executive function assessment in ADHD

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Sex Reprod Healthc. 2022 Jun;32:100727.

Knowledge, challenges, and standard of care of young women with ADHD at Swedish youth clinics.

Klint Carlander AK, Thorsell M, Demetry Y, et al.

OBJECTIVES: Sexual risk-taking and its consequences for young women with ADHD(attention deficit hyperactivity disorder) including sexually transmitted diseases, teenage pregnancies and underage parenthood constitute substantial challenges for individuals and midwives. The aim was to investigate current knowledge and specific challenges in reproductive health and contraceptive counselling for women with ADHD at Swedish youth clinics.

METHOD: Inductive qualitative interview study of ten midwives at six youth health clinics in Stockholm and Uppsala County. We used a semi-structured interview guide. The interviews were transcribed verbatim and analyzed with the NVivo 12 qualitative data analysis software.

RESULTS: Three main categories were identified: (1) challenges in provision of care of young women with ADHD, (2) standard of care and active adaptations towards women with ADHD and (3) organizational readiness for change;. Several challenges and frustrations, such as difficulties with attention with or without concomitant impulsivity and overactivity, in provision of reproductive health and contraceptive counselling for young women with ADHD were identified. Midwives reported high organizational readiness for improvement of standard of care.

CONCLUSIONS: Inadequate contraceptive counseling or lack of knowledge on specific challenges in the sexual and reproductive health of young women with ADHD may contribute to this group failing to access, inadequately respond to, or act upon counseling at youth clinics. Support for midwives with evidence-based interventions specifically developed for these women are imperative. Development of such tools should be a priority for research

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Sleep. 2022;45.

ASSOCIATION OF A NOVEL EEG METRIC OF SLEEP DEPTH/INTENSITY WITH ATTENTION-DEFICIT/HYPERACTIVITY, LEARNING, AND INTERNALIZING DISORDERS AND THEIR PHARMACOTHERAPY IN ADOLESCENCE.

Ricci A, Calhoun SL, He F, et al.

Study Objectives: Psychiatric/learning disorders are associated with sleep disturbances, including those arising from abnormal cortical activity. The odds ratio product (ORP) is a standardized electroencephalogram metric of sleep depth/intensity validated in adults, while ORP data in youth are lacking. We tested ORP as a measure of sleep depth/intensity in adolescents with and without psychiatric/learning disorders.

Methods: Four hundred eighteen adolescents (median 16 years) underwent a 9-hour, in-lab polysomnography. Of them, 263 were typically developing (TD), 89 were unmedicated, and 66 were medicated for disorders including attention-deficit/hyperactivity (ADHD), learning (LD), and internalizing (ID). Central ORP during non-rapid eye movement (NREM) sleep was the primary outcome. Secondary/exploratory outcomes included central and frontal ORP during NREM stages, in the 9-seconds following arousals (ORP-9), in the first and second halves of the night, during REM sleep and wakefulness.

Results: Unmedicated youth with ADHD/LD had greater central ORP than TD during stage 3 and in central and frontal regions during stage 2 and the second half of the sleep period, while ORP in youth with ADHD/LD on stimulants did not significantly differ from TD. Unmedicated youth with ID did not significantly differ from TD in ORP, while youth with ID on antidepressants had greater central and frontal ORP than TD during NREM and REM sleep, and higher ORP-9.

Conclusions: The greater ORP in unmedicated youth with ADHD/LD, and normalized levels in those on stimulants, suggests ORP is a useful metric of decreased NREM sleep depth/intensity in ADHD/LD. Antidepressants are associated with greater ORP/ORP-9, suggesting these medications induce cortical arousability

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Sleep Med. 2022 Sep;97:47-54.

A COMPARISON OF MOOD, QUALITY OF LIFE AND EXECUTIVE FUNCTION AMONG NARCOLEPSY TYPE 1 PATIENTS WITH OR WITHOUT ADHD SYMPTOMS IN CHINA.

Qu S, Wang P, Wang M, et al.

OBJECTIVE: To investigate the prevalence of core attention-deficit/hyperactivity disorder (ADHD) symptoms in Chinese narcolepsy type 1 (NT1) patients and to explore mood, quality of life, and executive function in narcolepsy patients with or without ADHD and the response to Methylphenidate Hydrochloride Extended-release tablets (ER-MPH) treatment.

METHOD: A total of 267 pediatric NT1 patients (194 males and 73 females, 5-17 years old) were evaluated for ADHD symptoms by a psychiatrist using the DSM-IV diagnostic criteria of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid) from February 2011 to July 2013 at Peking University People's Hospital. All patients underwent Stanford Sleep Inventory (SSI) evaluation and polysomnography followed by multiple sleep latency tests (MSLT) before ER-MPH treatment. Neuropsychological evaluations, including the Inventory of Subjective Life Quality (ISLQ), Depression Self-resting Scale for Children (DSRS-C), Screening for Child Anxiety-related Emotional Disorders (SCARED) and Barratt Impulsiveness Scale (BIS), were performed before and after 16 weeks of ER-MPH treatment. Executive abilities were assessed by the Behavior Rating Inventory of Executive Function-parent version (BRIEF-P). The narcolepsy symptoms, evaluated by the Pediatric Sleep Questionnaire (PSQ), and ADHD symptoms were assessed before and after treatment in NT1 patients with ADHD.

RESULT: Seventy-seven of 267 (28.8%) NT1 patients had ADHD symptoms, with 73 patients being inattentive type (ADHD-I) and 4 patients being combined type (ADHD-C). Despite similar objective sleep parameters, NT1 patients with ADHD symptoms experienced higher anxiety levels, more impulsive behaviors, lower health-related quality of life and worse executive functions than those without ADHD ($p<0.05$). Methylphenidate treatment was effective in improving daytime sleepiness in NT1 patients with ADHD (PSQ, 16.7± 2.1 vs 13.5 ± 1.9, $p<0.05$) but was ineffective on ADHD symptoms (ADHD-RS, 25.3 ± 9.1 vs 26.4± 8.9, $p>0.05$).

CONCLUSION: A high prevalence of ADHD (28.8%) was identified in children and adolescents with NT1. Comorbid ADHD symptoms were associated with increased levels of mood disorders and lower quality of

life. ER-MPH treatment could reduce daytime sleepiness but not ADHD symptoms in narcolepsy patients with ADHD, suggesting that new treatment strategies are needed for this group of patients

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Stud Health Technol Inform. 2022 Jun;290:655-59.

PREDICTIONS OF ACADEMIC PERFORMANCE OF CHILDREN AND ADOLESCENTS WITH ADHD USING THE SHAP APPROACH.

Balbino M, Jandre C, de MD, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neuro-developmental disorder characterized by inattention and/or impulsivity-hyperactivity symptoms. Through Machine Learning methods and the SHAP approach, this work aims to discover which features have the most significant impact on the students' performance with ADHD in arithmetic, writing and reading. The SHAP allowed us to deepen the model's understanding and identify the most relevant features for academic performance. The experiments indicated that the Raven_Z IQ test score is the factor with the most significant impact on academic performance in all disciplines. Then, the mother's schooling, being from a private school, and the student's social class were the most frequently highlighted features. In all disciplines, the student having ADHD emerged as an important feature with a negative impact but less relevance than the previous features

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Sultan Qaboos Univ Med J. 2022 May;22:206-11.

SOCIO-DEMOGRAPHIC AND CLINICAL PROFILES OF ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER PATIENTS IN A UNIVERSITY HOSPITAL IN OMAN.

Mirza H, Al-Huseini S, Al-Jamoodi S, et al.

OBJECTIVES: Although attention deficit hyperactivity disorder (ADHD) is typically considered a condition affecting children, there is evidence that children diagnosed with ADHD continue to suffer from this condition after the age of 18. This study aimed to describe the socio-demographic and clinical characteristics of adult ADHD patients in Oman and evaluate their association with the disorder's different subtypes.

METHODS: This retrospective study included adult patients with ADHD from the outpatient clinic at Sultan Qaboos University Hospital, Muscat, Oman. Data from medical records from January 2018 to April 2020 were collected. Socio-demographic characteristics, clinical profiles and psychiatric comorbidities were examined.

RESULTS: This study included 100 adults who fulfilled the standard diagnosis of ADHD, with 54.0% (n = 54) and 46.0% (n = 46) from the inattentive and combined subtypes, respectively. It was found that ADHD was more prevalent among males (64.0%) than females (36.0%), with the inattentive subtype being more predominant among females. The ADHD patients with the inattentive subtype were associated with comorbid substance use disorders (odds ratio [OR] = 11.29; P = 0.049), personality disorders (OR = 7.96; P = 0.017) and major depressive disorder (OR = 15.94; P = 0.002) compared to patients predominantly with the combined subtype.

CONCLUSION: This study echoes the findings from the current literature that adult patients with ADHD commonly have comorbid psychiatric disorders, leading to significant functional impairment. Psychiatric comorbidities must be identified and urgently treated for better clinical and functional outcomes in adult patients with ADHD

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Supportive Care in Cancer. 2022.

SLUGGISH COGNITIVE TEMPO PROFILES IN SURVIVORS OF CHILDHOOD CANCER AS COMPARED TO CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Peterson RK, Holingue C, Jacobson LA.

Purpose: Neurocognitive late effects including problems with attention have been reported in pediatric oncology survivors. While some researchers have characterized these late effects as similar to symptoms of attention-deficit/hyperactivity disorder, inattentive presentation (ADHD-I), there remains some controversy as to whether these concerns in oncology patients are best conceptualized according to an ADHD-I or sluggish cognitive tempo (SCT) framework. The aim of this study was to describe SCT symptoms in children

with ADHD-I or oncology diagnoses; identify groups of SCT symptoms among children with brain tumors (BT), acute lymphoblastic leukemia (ALL), or ADHD-I; and identify whether specific SCT profiles are associated with these diagnoses.
Methods: The sample was comprised of 364 youth (146 BT, 149 ADHD-I, 69 ALL) referred for a neuropsychological evaluation at an academic medical center. Caregivers completed the SCT scale as part of the clinical evaluation.
Results: Groups differed on mean scores for the SCT scales (Total, Sleepy/sluggish, Low initiation, and Daydreamy) by diagnosis (all $p < 0.05$), with the ADHD-I group having higher SCT symptoms on all scales. Latent profile analysis showed significant differences between latent SCT classes according to ADHD-I versus cancer diagnosis. The ADHD-I group was significantly more likely to be in the high SCT class compared to the oncology groups.
Conclusion: Findings add to the understanding of SCT symptoms in pediatric oncology survivors. There is utility in applying the SCT framework to the oncology population; however, pediatric survivors are likely to be rated differently than youth with ADHD-I. Implications and future directions are discussed

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Tokai J Exp Clin Med. 2022 Jul;47:72-74.
A Case of Nocturnal Enuresis Associated with Attention-deficit/hyperactivity Disorder Successfully Treated with Guanfacine Monotherapy.
Takahashi Y, Mikami K, Kimoto K, et al.
Nocturnal enuresis (NE) is a syndrome associated with abnormal nocturnal urine production, urination mechanism, and sleep arousal. NE is strongly associated with attention-deficit/hyperactivity disorder (ADHD), and it has been reported that NE occurs in approximately 30% of children with ADHD. There have been several reports on the efficacy of atomoxetine as treatment for NE with ADHD, while the efficacy of guanfacine is still limited. We report our experience of treating an 10-year-old girl with NE with ADHD with a single dose of guanfacine. The patient first visited our hospital because of difficulty concentrating, restlessness at home and school, and nocturnal incontinence. She was diagnosed with NE with ADHD based on a review of her personal history from her mother. Her NE symptoms improved with guanfacine monotherapy (1 mg/day. The patient weighed 28 kg)

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Toxics. 2022;10.
Perinatal Dioxin Exposure and Attention Deficit Hyperactivity Disorder (ADHD) Symptoms in Children Living in a Dioxin Contamination Hotspot in Vietnam.
Pham-The T, Nishijo M, Pham TN, et al.
We examined children in Da Nang, a dioxin contamination hotspot in Vietnam, twice at 5 and 8 years of age, and investigated sex-and age-dependent differences in the effects of dioxin exposure on attention deficit hyperactivity disorder (ADHD) symptoms. We also studied autistic traits in children with ADHD symptoms. A total of 163 children participated in follow-up surveys at 5 and 8 years of age and were included in the present analysis. ADHD symptoms were assessed using an ADHD rating scale with inattention and hyperactivity-and-impulsivity (hyperactivity) subscales. Autistic behaviors were evaluated using the Autism Spectrum Rating Scale (ASRS). Perinatal dioxin exposure was indicated by dioxin levels in maternal breast milk. In boys, hyperactivity scores were significantly higher in the high 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) group only at 5 years of age. In girls, hyperactivity scores at 8 years of age were significantly higher in the high TCDD group, which was significantly associated with those at 5 years of age. In girls, ASRS unusual behavior scores were significantly higher with higher TCDD exposure and hyperactivity scores at 8 years of age. These results suggest that high perinatal TCDD exposure may increase ADHD likelihood and autistic traits, particularly in girls of 7ΓÇô8 years of age

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Transl Psychiatry. 2022 Jun;12:225.

SEX-DIFFERENT INTERRELATIONSHIPS OF RS945270, CEREBRAL GRAY MATTER VOLUMES, AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A REGION-WIDE STUDY ACROSS BRAIN.

Luo X, Fang W, Lin X, et al.

Previous genome-wide association studies (GWAS) reported that the allele C of rs945270 of the kinectin 1 gene (KTN1) most significantly increased the gray matter volume (GMV) of the putamen and modestly regulated the risk for attention deficit hyperactivity disorder (ADHD). On the other hand, ADHD is known to be associated with a reduction in subcortical and cortical GMVs. Here, we examined the interrelationships of the GMVs, rs945270 alleles, and ADHD symptom scores in the same cohort of children. With data of rs945270 genotypes, GMVs of 118 brain regions, and ADHD symptom scores of 3372 boys and 3129 girls of the Adolescent Brain Cognition Development project, we employed linear regression analyses to examine the pairwise correlations adjusted for the third of the three traits and other relevant covariates, and examine their mediation effects. We found that the major allele C of rs945270 modestly increased risk for ADHD in males only when controlling for the confounding effects of the GMV of any one of the 118 cerebral regions ($0.026 \le p \le 0.059$: Top two: left and right putamen). This allele also significantly increased putamen GMV in males alone (left $p = 2.8 \times 10\text{-}5$, and right $p = 9.4 \times 10\text{-}5$; $\alpha = 2.1 \times 10\text{-}4$) and modestly increased other subcortical and cortical GMVs in both sexes ($\alpha < p < 0.05$), whether or not adjusted for ADHD symptom scores. Both subcortical and cortical GMVs were significantly or suggestively reduced in ADHD when adjusted for rs945270 alleles, each more significantly in females ($3.6 \times 10\text{-}7 \le p < \alpha$; Top two: left pallidum and putamen) and males ($3.5 \times 10\text{-}6 \le p < \alpha$), respectively. Finally, the left and right putamen GMVs reduced 14.0% and 11.7% of the risk effects of allele C on ADHD, and allele C strengthened 4.5% (left) and 12.2% (right) of the protective effects of putamen GMVs on ADHD risk, respectively. We concluded that the rs945270-GMVs-ADHD relationships were sex-different. In males, the major allele C of rs945270 increased risk for ADHD, which was compromised by putamen GMVs; this allele also but only significantly increased putamen GMVs that then significantly protected against ADHD risk. In females, the top two GMVs significantly decreasing ADHD risk were left pallidum and putamen GMVs. Basal ganglia the left putamen in particular play the most critical role in the pathogenesis of ADHD

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Transl Psychiatry. 2022 Jun;12:247.

CLINICAL AUTISM SUBSCALES HAVE COMMON GENETIC LIABILITIES THAT ARE HERITABLE, PLEIOTROPIC, AND GENERALIZABLE TO THE GENERAL POPULATION.

Thomas TR, Koomar T, Casten LG, et al.

The complexity of autism's phenotypic spectra is well-known, yet most genetic research uses case-control status as the target trait. It is undetermined if autistic symptom domain severity underlying this heterogeneity is heritable and pleiotropic with other psychiatric and behavior traits in the same manner as autism case-control status. In N=6064 autistic children in the SPARK cohort, we investigated the common genetic properties of twelve subscales from three clinical autism instruments measuring autistic traits: the Social Communication Questionnaire (SCQ), the Repetitive Behavior Scale-Revised (RBS-R), and the Developmental Coordination Disorder Questionnaire (DCDQ). Educational attainment polygenic scores (PGS) were significantly negatively correlated with eleven subscales, while ADHD and major depression PGS were positively correlated with ten and eight of the autism subscales, respectively. Loneliness and neuroticism PGS were also positively correlated with many subscales. Significant PGS by sex interactions were found-surprisingly, the autism case-control PGS was negatively correlated in females and had no strong correlation in males. SNP-heritability of the DCDQ subscales ranged from 0.04 to 0.08, RBS-R subscales ranged from 0.09 to 0.24, and SCQ subscales ranged from 0 to 0.12. GWAS in SPARK followed by estimation of polygenic scores (PGS) in the typically-developing ABCD cohort (N=5285), revealed significant associations of RBS-R subscale PGS with autism-related behavioral traits, with several subscale PGS more strongly correlated than the autism case-control PGS. Overall, our analyses suggest that the clinical autism subscale traits show variability in SNP-heritability, PGS associations, and significant PGS by sex interactions, underscoring the heterogeneity in autistic traits at a genetic level. Furthermore, of the three instruments investigated, the RBS-R shows the greatest evidence of genetic signal in both (1) autistic samples (greater heritability) and (2) general population samples (strongest PGS associations)

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Transl Psychiatry. 2022 Jun;12:231.

ASSOCIATIONS BETWEEN CHILDHOOD MALTREATMENT AND PSYCHIATRIC DISORDERS: ANALYSIS FROM ELECTRONIC HEALTH RECORDS IN HONG KONG.

Wong RS, Tung KTS, Ho FKW, et al.

There has been a lack of high-quality evidence concerning the association between childhood maltreatment and psychiatric diagnoses particularly for Axis II disorders. This study aimed to examine the association between childhood maltreatment exposure and Axis I and Axis II psychiatry disorders using electronic health records. In this study, the exposed group (n=7473) comprised patients aged 0 to 19 years with a first-time record of maltreatment episode between January 1, 2001 and December 31, 2010, whereas the unexposed group (n=26,834) comprised individuals of the same gender and age who were admitted into the same hospital in the same calendar year and month but had no records of maltreatment in the Hong Kong Clinical Data Analysis and Reporting System (CDARS). Data on their psychiatric diagnoses recorded from the date of admission to January 31, 2019 were extracted. A Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR, plus 95% CIs) between childhood maltreatment exposure and psychiatric diagnoses, adjusting for age at index visit, sex, and government welfare recipient status. Results showed that childhood maltreatment exposure was significantly associated with subsequent diagnosis of conduct disorder/ oppositional defiant disorder (adjusted HR, 10.99 [95% CI 6.36, 19.01]), attention deficit hyperactivity disorder (ADHD) (7.28 [5.49, 9.65]), and personality disorders (5.36 [3.78, 7.59]). The risk of psychiatric disorders following childhood maltreatment did not vary by history of childhood sexual abuse, age at maltreatment exposure, and gender. Individuals with a history of childhood maltreatment are vulnerable to psychiatric disorders. Findings support the provision of integrated care within the primary health care setting to address the long-term medical and psychosocial needs of individuals with a history of childhood maltreatment

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Transl Psychiatry. 2022 Jul;12:270.

ASSOCIATION BETWEEN CORD BLOOD METABOLITES IN TRYPTOPHAN PATHWAY AND CHILDHOOD RISK OF AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Raghavan R, Anand NS, Wang G, et al.

Alterations in tryptophan and serotonin have been implicated in various mental disorders; but studies are limited on child neurodevelopmental disabilities such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). This prospective cohort study examined the associations between levels of tryptophan and select metabolites (5-methoxytryptophol (5-MTX), 5-hydroxytryptophan (5-HTP), serotonin, N-acetyltrytophan) in cord plasma (collected at birth) and physician-diagnosed ASD, ADHD and other developmental disabilities (DD) in childhood. The study sample (n=996) derived from the Boston Birth Cohort, which included 326 neurotypical children, 87 ASD, 269 ADHD, and 314 other DD children (mutually exclusive). These participants were enrolled at birth and followed-up prospectively (from October 1, 1998 to June 30, 2018) at the Boston Medical Center. Higher levels of cord 5-MTX was associated with a lower risk of ASD (aOR: 0.56, 95% CI: 0.41, 0.77) and ADHD (aOR: 0.79, 95% CI: 0.65, 0.96) per Z-score increase, after adjusting for potential confounders. Similarly, children with cord 5-MTX 25th percentile (vs. <25th percentile) had a reduction in ASD (aOR: 0.27, 95% CI: 0.14, 0.49) and ADHD risks (aOR: 0.45, 95% CI: 0.29, 0.70). In contrast, higher levels of cord tryptophan, 5-HTP and N-acetyltryptophan were associated with higher risk of ADHD, with aOR: 1.25, 95% CI: 1.03, 1.51; aOR: 1.32, 95% CI: 1.08, 1.61; and aOR: 1.27, 95% CI: 1.05, 1.53, respectively, but not with ASD and other DD. Cord serotonin was not associated with ASD, ADHD, and other DD. Most findings remained statistically significant in the sensitivity and subgroup analyses

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Turk Psikiyatri Derg. 2022;33:90-96.

RELATIONSHIP BETWEEN SLEEP DISORDERS AND ATTENTION DEFICIT- HYPERACTIVITY DISORDER SYMPTOMS IN UNIVERSITY STUDENTS.

Eroylu EÃ, Aykut DS, Karahan S, et al.

OBJECTIVE: Sleep disorders increase the symptoms of attention deficit hyperactivity disorder (ADHD). The aim of this study was to investigate whether or not sleep related problems give rise to symptoms of attention deficit and hyperactivity-impulsivity in university students.

METHODS: The 252 university students between the ages of 18-25 years included in the study were assessed on the Pittsburgh Sleep Quality Index (PSQI), the Adult Attention-Deficit Hyperactivity Disorder Scale, the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI).

RESULTS: The participants of the study comprised 38.5% males and 61.5% females with a mean age of 22.39 (±1.93) years. The mean score data were 5.78 (± 2.72) on the PSQI, 41.77 (± 20.38) on the Adult Attention-Deficit Hyperactivity Disorder Scale, 8.53 (± 6.97) on the BDI and 9.05 (± 7.92) on the BAI. The total score and the scores on the attention-deficit and the general problems subsections of the Adult Attention-Deficit Hyperactivity Disorder Scale were significantly higher in participants with poor sleep quality (P<0.001). The PSQI and the Adult Attention-Deficit Hyperactivity Disorder Scale scores were significantly above the cut-off values in the participants with depression and anxiety symptoms as compared to those without these symptoms (P<0.001). The PSQI total score positively correlated with the Adult Attention-Deficit Hyperactivity Disorder Scale total score (P<0.001).

CONCLUSION: University students with sleep disorder have more ADHD symptoms and poor quality of sleep increase ADHD sypmtoms. Therefore it's important to evaluate quality of sleep in young people suffering from attention problems in terms of treatment approaches and interventions

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Ugeskr Laeger. 2022 Jun;184.

ADHD IN ADULTS IS STILL OVERLOOKED.

Rasmussen PD.

It is well known that ADHD extends into adulthood, but if left untreated, has consequences in a range of areas. In this case report, a young man is described who, since childhood, has tried to draw attention to his problems with attention management. He smoked 60 cigarettes a day to deal with inner turmoil and restlessness. His medical history, interview with DIVA 2.0 and testing with CPT-3 point to significant problems in executive functions. Initiating medical treatment improves his level of function markedly. The clinician must uncover potential use of coping strategies when screening for ADHD

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Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122:100-07.

EMOTIONAL AND BEHAVIORAL DYSREGULATION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chutko LS, Yakovenko EA, Surushkina SY, et al.

OBJECTIVE: To study disorders of emotional regulation in different types of attention deficit hyperactivity disorder (ADHD) in children.

MATERIAL AND METHODS: 58 children suffering from ADHD, aged 12 to 15 years were divided into 2 subgroups (38 children with a combined form of ADHD and 20 children with ADHD with a predominance of inattention). The control group consisted of 30 children without manifestations of neuropsychiatric disorders. The following research methods were used in the work: the SNAP-IY scale to assess the severity of the disease; the Strengths and Difficulties Questionnaire (SCT), a form for parents to assess emotional and behavioral impairments; Spielberger's self-assessment test in the processing of Khanin to assess the level of anxiety; spectral analysis of the EEG with the construction of graphical power spectra and registration of evoked potentials (EP) with the performance of an attention test in the Go/No-Go paradigm.

RESULTS: The results of the study showed the presence of emotional and behavioral disorders in children with ADHD, more pronounced in the combined form of the disease. Complaints of emotional lability, tearfulness, irritability were noted in 53 children with ADHD in the study group (61.6%). At the same time, these complaints were registered in 39 children from the first group (72.2%) and 14 children from the second group (43.8%). The level of inattention was approximately the same (3.21±0.64 and 3.43±0.56, respectively),

while the level of hyperactivity and impulsivity in adolescents from the first group was significantly higher (3.18±0.54, p<0.01). Indicators of the SCT scale, as a total indicator (3.4±1.6, p<0.01), and on the scales of «behavior problems» (7.4±1.6, p<0.01), «emotional problems» (8.0±1.6, p<0.01), «problems with peers» (7.6±1.3, p<0.01), «prosocial behavior» (3.4±1.6, p<0.01) were significantly higher in the subgroup of children from the first group. The performed statistical analysis of the test data for attention in the Go/No-Go paradigm revealed significant differences (p<0.01) in the number of omissions of significant pairs of stimuli between healthy children and a subgroup with ADHD with a predominance of inattention, between healthy children and a subgroup with combined form ADHD. When comparing evoked EEG synchronization in the theta range under Go conditions, we found a significant decrease in this parameter in the range of 200-400 ms in the subgroup of children with ADHD with a predominance of inattention and in the subgroup of ADHD with a combined form; under No-Go conditions, a significant decrease in the magnitude of evoked EEG synchronization was revealed in a subgroup of children with combined form ADHD.

CONCLUSION: In general, the results of this study allow us to conclude that impaired cognitive control has a large impact on the development of emotional disorders in children with ADHD

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APPLIED NEUROPSYCHOLOGY: CHILD
2022, VOL. 11, NO. 3, 553–560
https://doi.org/10.1080/21622965.2020.1852084

Hippotherapy in neurodevelopmental disorders: a narrative review focusing on cognitive and behavioral outcomes

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ABSTRACT

Hippotherapy (HT) is a rehabilitative tool inducing psychological and motor improvements using human-horse interaction. HT provides sensory stimulation to the rider through the rhythmic and repetitive movements of the horse, facilitating communication between patients and healthcare professionals, favoring the establishment of a therapeutic alliance. The purpose of this review is to evaluate the effects of HT treatment on cognitive-behavioral processes in neurodevelopmental disorders. We screened studies published between 2002 and 2020 on PubMed, Scopus, Cochrane, and Web of Sciences databases. The search combined the following terms: "hippotherapy"; "horseback riding"; "equine-assisted therapy"; "developmental disorder"; "autism spectrum disorder"; "dyspraxia"; "infantile cerebral palsy"; and "attention-deficit/hyperactivity disorder". This review shows that HT can be a valuable tool for the treatment of developmental disorders. The psychological, cognitive and relational areas could benefit from the animal-child interaction to promote child autonomy, self-esteem, self-efficacy and openness to others. Physical, motor and psychosocial benefits were found in adolescents with anxiety and/or depression disorders, in autism spectrum disorders, dyspraxia, as well as in infantile cerebral palsy and attention deficit hyperactivity disorder. HT could be considered an alternative therapeutic tool thanks to the relationship between patient-horse-instructor and to the sensory-motor and cognitive stimulation that enforce learning processes.

KEYWORDS

Hippotherapy; developmental disorders; equine-assisted therapy; psychological disorders

Introduction

The use of animals for therapeutic purposes has very ancient roots. Animal Assisted Interventions (AAI) include projects aimed at improving health and well-being of people with the help of animals (Della Mura & Del Gottardo, 2010). AAI consist of different types of therapeutic, rehabilitative, educational, and recreational services provided thanks to the involvement of different animals. The interventions involve people with physical, neuromotor, mental and psychic disorders (Portaro, Maresca, Naro, et al., 2020a; Portaro, Maresca, Raffa, et al., 2020b), but they can be used also in healthy individuals. AAI are classified into animal-assisted therapy (AAT), animal-assisted education (AAE) and animal-assisted activity (AAA) (Della Mura & Del Gottardo, 2010).

Hippotherapy (HT) is a type of AAT, which consists of a set of medical techniques that use the horse to improve both physical and mental health. HT allows inducing psychic and motor functional improvements using the human-horse interaction. Although Hippocrates was the first to describe the therapeutic benefits of HT (Mayberry, 1978; Riede, 1987), and, in 1875, Chassaignac recognized the value of HT to improve balance, muscle strength, joint flexibility and mood (Bertoti, 1988), it is only since the late 1970s that HT has become a standardized therapy (Maregillano, 2004; Silkwood-Sherer & Warmbier, 2007). In 1992, the American Hippotherapy Association (AHA) was founded and defined an official and international protocol for HT. In Italy, the Ministry of Health defined the HT guidelines only relatively recently in 2015 (De Santis et al., 2018).

HT has positive effects also on psychological, social, and educational areas, involving the sensory, musculoskeletal, limbic, vestibular and ocular systems (Champagne & Dugas, 2010; Silkwood-Sherer et al., 2012). Hippotherapy is considered a kind of physiotherapy, harnessing the sensory information produced by the horse's gait and motion to stimulate the patient's postural reflex mechanisms through motor and sensory inputs. It improves balance and coordination, and some researchers believe that one of the potential mechanisms of action may involve the rhythmic and repetitive movements and sensory feedback the person receives during HT (Benda et al., 2003; Portaro, Maresca, Naro, et al., 2020a). Horses may also positively affect psychological and mental health. Indeed, one of the main activities used to achieve therapeutic goals during HT is the grooming of the horse, an approach that induces a deep interaction between the patient and the horse. The non-verbal communication of the horse causes relaxation, due to the horse breathing and sharing its body warmth (Portaro, Maresca,

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Naro, et al., 2020a; Portaro et al., 2019). In fact, it is well known that petting an animal can reinforce social interaction, so that grooming may be considered a sort of "special communication" between animals, possibly building mutual trust. Such an interaction, defined as "total grooming," is somehow comparable to parental care, where the patient is lulled and pampered by parents. The positive effect of the mutual grooming might be related to the release of oxytocin, as evidence indicates that such neuropeptide and endogenous opioids affect maternal attachment to infants, including maintenance of contact, grooming, and responses to separation (Saltzman & Maestripieri, 2011). Some studies described that horses detect small changes in a human's body language, as well as give the participant a "mirror" to gain insight into their psyche (Schultz et al., 2006). Similarly, at the physiological level, behavioral and evolutionary biology indicate that there are universal mechanisms and structures supporting social behavior in both and horses, promoting the social relationships between the two different species, thus positively affecting human behavior (Beetz et al., 2011). Moreover, the environment where the therapy is performed is different from the "closed" settings of conventional physical therapy. The immersion in the nature and the contact with other people attending the riding school may represent a continuous stimulus for disabled people.

The beneficial physical and psychological effects of HT has been demonstrated in many acquired neurological (Erdman & Pierce, 2016; Shurtleff et al., 2009; Silkwood-Sherer et al., 2012; Sterba, 2007) and neurodegenerative diseases (Beinotti et al., 2013; Harris & Williams, 2017). However, psychiatric diseases and developmental disorders may also benefit from HT (Granados & Agís, 2011; Şik et al., 2012).

Horses could facilitate the opening of a communication channel between patients and healthcare professionals and favor the establishment of a therapeutic alliance, empathy, openness to others, caring, socialization, self-esteem, physical contact, play and relaxation (Delta Society Program for Animal-Assisted Activities & Therapy Paperback, 2016). Moreover, it has been shown that HT shortens recovery times, improving balance, mobility and posture (Silkwood-Sherer et al., 2012). Physical therapists have used horse movements for patient neurorehabilitation, while psychologists benefit from horse mobility to increase patient compliance (Champagne et al., 2010; Maregillano, 2004). In fact, the rhythmic and repetitive movements of the horse provide the patient with physical and sensory feedback, leading to improvement in both motor and behavioral outcomes (Portaro, Cacciola, et al., 2019).

Recently, attention has focused on the use of HT as a viable alternative method of intervention for a variety of neurodevelopmental disorders (ND), including autism spectrum disorder (ASD) (Kern et al., 2011), attention deficit hyperactivity disorder (ADHD) (Oh et al., 2018), infantile cerebral palsy (ICP) (Mutoh et al., 2019), dyspraxia (Hession et al., 2014) and other child psychological and behavioral disorders (Wilson et al., 2017).

ND occur in the early stages of life and are characterized by deficits in cognitive, motor, behavioral, social, academic and professional functioning. Deficits range from specific learning limitations to general impairment of social skills and intelligence (Ahn & Hwang, 2018). Children with ND often have difficulty in normal cognitive development (Spratt et al., 2012), have poor social function, and have difficulties in communication, social interaction, and behavior (Wiggins et al., 2015). In the last years, there has been a growing effort in developing cognitive interventions to improve symptoms or characteristics of ND, such as adaptive and communicative behavior and social skills (Reichow et al., 2012). The multifactorial nature of ND is the reason why a variety of therapies have been implemented, including educational, behavioral and pharmacotherapy. Traditional therapeutic methods are often not sufficient and frequently many parents of ND children seek alternative treatment to complement traditional rehabilitation therapy.

In recent years, HT has increasingly been considered a valuable way of treating motor, cognitive and relational deficits in children with ND. HT is a unique treatment for children with ND because it considers the context of therapy while offering the necessary support to challenge the cognitive-sensory-motor systems (Engel, 2007). It has been shown that commitment to therapeutic activities is crucial to improvements in adaptation and greater willingness to participate in daily activities in ND (Brown & Dunn, 2010), and using the movement and the positive and calm behavior of the horse can exert a positive influence in these children.

Although HT may positively affect cognition and behavior, few studies have investigated the relationship between HT, cognitive skills and psychological aspects in ND (Hession et al., 2014; Masini, 2010). Indeed, even if the relationship between humans and horse has old roots, there are few theoretical studies on the efficacy of HT and its psychological, physical, social and educational effects in such patients.

The purpose of this narrative review is to evaluate the effects of HT on cognitive and behavioral outcomes in children with ND.

Search strategy

Studies were identified by searching on Scopus, PubMed, Web of Science, and Cochrane databases. All studies fulfilling our selection criteria and published from January 2002 to May 2020 were evaluated for possible inclusion. Searches combined the following terms: "hippotherapy"; "horseback riding"; "equine-assisted therapy"; "developmental disorder"; "autism spectrum disorder"; "dyspraxia"; "infantile cerebral palsy"; and "attention deficit hyperactivity disorder." All articles were evaluated by title, abstract, and text after they fulfilled the following criteria. We selected only texts in English, and removed duplicates. The results of the search consisted of: (1) research published with peer review; (2) studies with the sample population including only pediatric patients; (3) studies evaluating cognitive-behavioral effects of

HT in developmental disorder; and (4) case studies were excluded.

Hippotherapy and autism spectrum disorder

Autism spectrum disorder (ASD) is a developmental disorder that impairs social and communication skills and induces repetitive and stereotyped behaviors (Park et al., 2014). Early treatment for ASD is important, as proper care can reduce patients' difficulties while helping them to learn new skills. ASD causes many different problems, and there is no single best treatment. Children with ASD should be referred to skilled clinicians to be provided with adequate behavioral, psychological and educational interventions (Wilson et al., 2017).

HT could represent an alternative rehabilitation method to learn social, communication and language skills and reduce maladaptive behaviors (Lanning et al., 2014; Tomchek & Dunn, 2007). In fact, research on children with ASD suggests that HT improves (i) severe motor and postural skills (Hawkins et al., 2014), (ii) spontaneous verbalization (Holm et al., 2014), (iii) irritability and hyperactivity, (iv) social cognition and (v) receptive communication skills (Gabriels et al., 2015), as well as quality of life (Trzmiel et al., 2019). Kang et al. (2013), in a longitudinal study of 26 adolescents (6 with cerebral palsy, 14 with intellectual disability and 6 with ASD), showed that HT could be considered a good method of improving physical functionality.

Some studies have highlighted the effectiveness of HT on the psychological and cognitive features of ASD (Atun-Einy & Lotan, 2017; Peters & Wood, 2017; Petty et al., 2017). In a case control study by Borgi et al. (2016), the effectiveness of HT in improving adaptive and executive functioning in 15 children with ASD (aged 6–12 years) was investigated using the Vineland Adaptive Behavior Scale and the Tower of London. Therapeutic sessions consisted of structured activities involving horses, and included both work on the ground and riding. Results showed an improvement in adaptive and executive functioning. In particular, HT activities can increase attention and the ability to focus on different tasks and can lessen distractibility (Borgi et al., 2016). Such results were confirmed by a case control study, which demonstrated that the riding experience, as well as touching the horse and moving to a syncopated rhythm, might help to reduce ASD symptoms and hyperactivity (Harris & Williams, 2017). Moreover, a recent systematic review confirmed the efficacy of HT on response time and attention span of young people with ASD (Yotchukiat et al., 2016). In another case control study, the authors found an association between HT, social communication and sensory processing skills (assessed using the Pedagogical Analysis and Curriculum -PAC-test) in children with ASD. In fact, after the HT program, the patients appeared more socially motivated to engage with others. Additionally, the parents reported an increase in their ASD children's sensory integration, attention and self-regulation, with a reduction of inattention and distractibility (Steiner & Kertesz, 2015).

As far as communication and social skills are concerned, some studies show that HT improves these abilities in ASD patients. Kwon et al. (2019), in a prospective case-control study of 29 children, compared a group treated with HT and a group receiving conventional therapy. Both groups showed improvements in language and cognition after the intervention. However, the experimental HT group showed statistically significant improvements in more domains, such as simultaneous and sequential processing, planning, and learning, than the control group.

A systematic review highlighted the effectiveness of HT on behavioral and social interactions in the treatment of children with ASD (Ward et al., 2013; Wiese et al., 2016). Coman et al. (2018) have confirmed these positive data in a randomized control trial, demonstrating the therapeutic effects of HT on social and sensory functioning of 50 children with ASD. Moreover, a randomized controlled trial has reported favorable long-term outcomes (i.e., at 6- month follow-up) of 64 children with ASD treated with HT. Specifically, the treatment group receiving HT maintained a reduction in irritability (effect size $= 0.32$, $p = 0.07$) and improvements in social and communicative behaviors, as per the Aberrant Behavior Checklist-Community scale; hyperactive behaviors did not follow the same trend (Gabriels et al., 2018). In a further randomized control trial, the same authors confirmed their interesting results, suggesting that the HT effectiveness on irritability and hyperactivity could be due to the modulation of plasma cortisol (Pan et al., 2018).

On the other hand, in their longitudinal study, Anderson and Meints (2016) found that HT did not significantly improve either social or communication functioning of the overall adaptive behaviors, assessed using a mix of parent-report questionnaires and semi-structured tests, including the Vineland Adaptive Behavior Scale. Indeed, their results suggested HT merely contributed to ASD patients' well-being and psychological health. Moreover, they demonstrated that the family has an important role in the management of ASD disorders: involving the parents in the rehabilitation programs, including HT, may be beneficial for both patients and family. Recently, in exploratory and qualitative research, Tan and Simmonds (2018) investigated parents' perceptions of the HT-related psychosocial outcomes of their children. They found that, after the training, children improved satisfaction as well as some emotional and psychological aspects, such as self-esteem and self-regulation, achieving benefits for all of the family members.

As there is evidence for positive impact of HT on several outcomes, such as improvement in mood and behavior, in children with ASD, we believe that HT may be an effective strategy to improve social communication and motor skills in such patient populations. Unfortunately, the effects of HT on cognitive functioning and quality of life have been poorly investigated (Ajzenman et al., 2013). Moreover, there are a few studies of adolescents or young adults with ASD evaluating the impact of HT on emotional regulation and/or the level of stress (O'Haire, 2017; Yotchukiat et al., 2016). High stress levels and a lack of coping strategies (Plessow et al.,

2011) can influence psychological well-being (Bishop-Fitzpatrick et al., 2016). In this regard, Kemeny (2019) compared HT and standard stress management techniques on the stress levels of 27 adolescents with ASD. This comparative research demonstrated that HT might be promising in decreasing stress levels.

To summarize, a number of studies have investigated the effect of HT on the behavior and social interactions of patients with ASD, although many are limited by the small sample sizes and the lack of standardized measurement of the results. Thus, empirical investigations and systematic research are needed to confirm the efficacy of HT in children with ASD. Nonetheless, the current data may provide support for the use of HT programs as complementary intervention strategies for children with ASD.

Hippotherapy and attention-deficit/hyperactivity disorder

HT has been used to treat the attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder characterized by inattention, impulsiveness and hyperactivity. ADHD requires symptom onset by age of 12, and causes significant impairment in social, academic or work functioning. Based on the prevalence of the attention peoblems, there are different presentations of ADHD: inattentive, hyperactive-impulsive and combined presentations (Willcutt, 2012).

In a case control study, García-Gómez et al. (2016) have empirically evaluated the effects of a program of HT on quality of life and various psychosocial variables, assessed using the Behavioral Assessment System for Children, of a group of 14 students diagnosed with ADHD (7–14 years of age). The program consisted of 24 bi-weekly sessions, and lasted 3 months. The results showed the experimental group showed improvement in interpersonal relationships, maybe due to the calm temperament of the horses.

A recent systematic review examined the effectiveness of HT on behavioral, psychological and physical symptoms of ADHD. The work concluded that, although HT may offer some positive benefits to these children, further methodologically robust research is needed before definitive hypotheses can be formulated (White et al., 2020).

Children with ADHD often have cognitive abnormalities, including deficits in executive functions with a diminished capacity to regulate themselves, as well as significant social/emotional and behavioral difficulties with a higher risk of educational failure. In a longitudinal study, Gilboa and Helmer (2020) provide preliminary evidence of the effectiveness of HT interventions for attention and executive function deficit among children with ADHD, using the Behavior Rating Inventory of Executive Function and the Canadian Occupational Performance Measure. Some authors claim that HT can be used as a non-pharmacological adjunctive treatment option for physical and psychological rehabilitation in ADHD. In this regard, in a randomized controlled study, Oh et al. (2018) analyzed the effects of HT compared to pharmacotherapy in 34 children with ADHD, showing that HT was useful in improving attention, impulsivity/hyperactivity and quality of life, as per the Child Behavior Checklist, the Self-Esteem Scale and Pediatric Quality of Life Inventory. The efficacy of HT in ADHD was demonstrated in a pilot study that compared the functional magnetic resonance imaging signals at rest (rs-fMRI) and the clinical correlates in 10 patients (Yoo et al., 2016). Notably, the authors found that HT was associated with a short-range functional connectivity in the regions related to the default mode network and the behavioral inhibition system, which in turn correlated with the symptom improvement (Yoo et al., 2016).

Lee et al. (2015) examined the effects of HT on both brain function and levels of brain - derived neurotrophic factor (BDNF) in 40 children with ADHD. After completion of the HT program, there was a significant decrease in body fat in the HT group compared to the baseline. However, there was no significant changes in BDNF levels and activated brain function scanned by fMRI in the HT group. This suggests that HT training should be modified and developed to increase its efficacy in children with ADHD.

In conclusion, it would seem that it is currently possible to recommend HT as a sporting activity that provides similar benefits to other physical activities, but which is still far from being able to be recognized as a therapeutic activity for ADHD, due to the lack of research in this area.

Infantile cerebral palsy: beyond motor impairment

Infantile cerebral palsy (ICP) is a persistent and non-progressive disorder affecting postural stability and dynamic movement. ICP is the result of an acquired injury, occurring in the prenatal, perinatal or postnatal period, and involving different functional circuitries, which necessitate partial compensatory reorganization of the brain.

There is evidence that children with ICP might benefit from HT (Zadnikar & Kastrin, 2011), which can be considered a good rehabilitation tool for these patients. However, the scientific basis underpinning its efficacy remains unknown. Mutoh et al. (2019) carried out a prospective trial to determine how HT affects motor function and gait in children with ICP, also assessing caregivers' quality of life. After 1-year HT training, performed once a week, the 24 children with ICP enrolled in the study improved their walking ability. Moreover, psychological health and quality of life of their caregivers improved.

The case control study conducted by Park et al. (2014) investigated the effects of HT on gross motor function and functional performance in 34 children with ICP. Children were treated with HT for 45 min twice a week for 8 weeks. The data demonstrated that HT enhanced children's motivation and willingness to engage more meaningfully in the functional activities of daily life, also potentiating self-confidence, motivation and other emotional areas.

On the other hand, other studies showed that quality of life or health did not significantly improve after HT. Indeed, neither Davis et al. (2009) nor Deutz et al. (2018) demonstrated any positive effect of HT on quality of life of children with ICP, as measured by two different instruments

(i.e., CHQ—physical and psychosocial sub scores, and KIDSCREEN −27 parental version). However, these conclusions must be interpreted within the context of the tools used, because they may fail to cover the different daily life situations sufficiently, and they have not yet been demonstrated to be sensitive enough to detect a real change in children with CP.

Hippotherapy and dyspraxia

Dyspraxia affects about 6% of children and can be managed positively using HT. Dyspraxia is a motor coordination disorder characterized by difficulty in planning and executing intentional actions. This disorder may be present alone (primary dyspraxia) or associated with other neurodevelopmental disorder, such as autism or Down syndrome (secondary dyspraxia). A longitudinal study performed by Hession et al. (2014) demonstrated that the rhythmic physical movement of a horse during HT combined with the audiovisual feedback of this movement was effective in terms of improved cognition, mood arousal and gait variability in a group of 40 children (6–15 years) with primary dyspraxia.

Nonetheless, no definitive conclusions can be made, as there are no other published data on this important issue.

Hippotherapy in other child psychological and behavioral disorders

Many young children can suffer from psychosomatic problems (idiopathic intestinal colic, laryngospasm, asthma), while the older ones may have sleep, eating, language, attention or affective disorders. HT as "psychotherapy" is a specialized field that uses horses as a therapeutic tool leading to empowerment of emotions and feelings, mind-body control and psychological well-being (McConnell, 2002). Children's emotional responses, such as self-efficacy and self-esteem (Beck & Katcher, 1996), could be promoted by equine-facilitated psychotherapy (Mayberry, 1978). According to Barker (1999), the child–horse bond could promote empathy, acceptance, security, reliability, autonomy and self-control. Indeed, HT interventions can be a valid therapeutic alternative or a complementary means to treat psychological disorders. In recent qualitative research, Wilson et al. (2017) applied HT in adolescents with anxiety and/or depression disorders, reporting significant improvements in confidence, self-esteem and assertiveness, as well as a decrease in dysfunctional behaviors.

Equine-assisted learning is an experiential way that uses horses to provide a unique learning experience for personal growth. Frederick et al. (2015), in their randomized controlled study, investigated the impact of HT in a sample of at-risk teens. After five weeks of training, the adolescents undergoing HT showed better outcomes (as measured by the Adolescent Domain Specific Hope Scale and the Major Depression Inventory) than those submitted to traditional training. Although the intervention was short, HT had a positive impact on the lives and attitudes of adolescents at risk, increasing hope levels and reducing depressive symptoms. Promotion of social skills in young people is an effective strategy to prevent mental, emotional and behavioral disorders in adulthood. Pendry et al. (2014) carried out a randomized controlled trial to build social and emotional skills of 131 young people (aged 10–14 years) through interaction with the horses in educational contexts. The HT program consisted of once-weekly, 90-min sessions of individual and team-focused activities. The results indicated a moderate effect of the treatment on social competencies, as per the Devereux Student Strength Assessment administered to the children's parents.

An interesting case control study described the theoretical-conceptual frame of equine-facilitated psychotherapy, the features of intervention, and its implementation. In this paper, Bachi et al. (2012) assessed the efficacy of HT as psychotherapy on self-image, self-control, confidence and general satisfaction of life in 15 at-risk adolescents, reporting a trend of positive changes in all of the investigated parameters.

Psychological disorders are found also in children who have other experiences, such as violence between parents. These children are considered at risk for behavioral and mental disorders, including anxiety, anger, depression and suicidal ideation, withdrawal, low self-esteem, and attention-deficit/hyperactivity disorders. Hameury et al. (2011) reported on 63 children with a history of physical abuse and abandonment who received HT as psychotherapy. The authors demonstrated rapid response to such treatment, especially in younger children.

Finally, with regard to Down's syndrome, the authors did not find any study investigating the relationship between HT and cognitive, behavioral or psychological aspects. Indeed, the few studies carried out in these patients focused on balance, postural control and motor functions (Moriello et al., 2020; Portaro, Cacciola, et al., 2019).

Limitation of the study

Although the articles analyzed in this review demonstrate the effectiveness of HT under some circumstances, the results are inconclusive because literature on this issue often lacks metodologically sound papers. Indeed, it includes qualitative studies, comparative and longitudinal studies, with short reports, with limited statistics (small sample size, likely low power, no effect size calculations, and various other methodological issues) or subjective parental perception of the improvement. On the contrary, there are few case controls or randomized controlled studies. Only the results concerning ASD are mostly supported by methodologically valid and replicable research, using standardized outcome measures. However, this assumption cannot be extended to other ND.

Our review suggests that there might be few RCT with specific intervention and outcome measures, which can be used pre- and post-intervention, that are sensitive enough to document changes in the children receiving HT. Furthermore, as far as we know, there are no blinded RCT of HT, as the raters of the changes in behavior usually have

knowledge about the inclusion of the person in the used therapy. Therefore, it is mandatory to standardize HT procedures in relation to the different dysfunctions and pathologies, identifying reliable outcome measures and adequate treatment protocols.

Authors' point of view and conclusions

This narrative review underlines the potential therapeutic efficacy of HT for pediatric psychological and cognitive/behavioral deficits. HT could be considered a valid alternative treatment tool thanks to the strong relationship between patient-horse-instructor and to the multimodal sensory-motor and cognitive stimulations that enforce learning processes. The psychological, cognitive and relational areas might greatly benefit from the contact between animal and child, thanks to natural empathy established between them. It is thought that horses are extremely sensitive to changes in their environment, and they will react relatively strongly to any negative interaction with them. Because they calm down and are responsive to gentle handling, they provide positive feedback to people who are interacting with them. Therefore, learning new competencies, specific to the equestrian world but generalizable to daily living, could promote the development of child autonomy, self-esteem, self-efficacy and openness to others.

Disclosure statement

The authors declare that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-022-01428-2

ORIGINAL PAPER

Omega-3/6 supplementation for mild to moderate inattentive ADHD: a randomised, double-blind, placebo-controlled efficacy study in Italian children

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Received: 15 November 2021 / Accepted: 9 May 2022

Abstract

Recently there has been a growing interest in non-pharmacological treatments for ADHD. We evaluated the efficacy of a specific Omega-3/6 dietary supplement (two capsules containing 279 mg eicosapentaenoic acid [EPA], 87 mg Docosahexaenoic Acid [DHA], 30 mg gamma linolenic acid [GLA] each) in ameliorating inattentive symptoms in inattentive-ADHD children (6–12 years) with a baseline ADHD-RS-Inattention score ≥ 12. Secondary objectives included changes in global functioning, severity of illness, depression, and anxiety symptoms, learning disorders and in the fatty acids blood levels. The study was a randomised, double-blind, placebo-controlled efficacy and safety trial with a 6-month double-blind evaluation of Omega-3/6 vs placebo (Phase-I) and a further 6-month-open-label treatment with Omega-3/6 on all patients (Phase-II). In total 160 subjects were enrolled. No superiority of Omega-3/6 supplement to placebo was observed on the primary outcome (ADHD-RS-inattention score) after the first 6-months, with 46.3% of responders in the Omega-3/6 group and 45.6% in the placebo group; a slight (not statistically significant) reduction in Omega-6/3 ratio blood levels was measured in the active treatment group. Twelve months after enrolment, percentages of responders were similar between groups. A mild statistical, although not clinically significant, improvement was observed on the ADHD-RS-total score in the Omega-3/6 group but not on the ADHD-RS-Inattention score; a slight (not-statistically significant) reduction in Omega-6/3 ratio was observed in the group taking active treatment only during Phase II. In conclusion, no clinical beneficial effects of Omega-3/6 were detected on inattentive symptoms, suggesting a limited role of Omega-3/6 dietary products in children with mild ADHD-I. *Trial registration*: At the time of the Ethical submission, according to the clinical trial Italian law, registration was not mandatory for food additive as Omega 3/6 were then classified. The trial was approved by the Ethical Committee of the Cagliari University Hospital (resolution n. 662; September 22nd, 2011).

Keywords ADHD · Randomized controlled trial · Fatty acids · Child and adolescent psychiatry

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Published online: 07 June 2022

Introduction

ADHD is one of the most common neurodevelopmental disorder in child psychiatry [1]. It can have a debilitating impact on normal development, with high risk of comorbidities with other psychiatric disorders as well as emotional and social difficulties persisting also in adulthood [2]. According to international guidelines, treatment is based on a multimodal approach that combines behavioural and pharmacological treatment [3–5].

In the last decade there has been a growing interest in dietary supplementation of polyunsaturated fatty acids (PUFAs) such as Omega 3 (Ω-3) and Omega 6 (Ω-6). PUFAs are involved in different neural processes, including oxidative stress and inflammation, and their deficiency may play a putative role in ADHD pathogenesis [6, 7]. Ω-3 and Ω-6 fatty acids are integral parts of the neuronal cell membranes in the brain, and both contribute to neural transmission [8]. Ω-3 PUFAs have anti-inflammatory, antithrombotic, and vasodilatory functions, whereas Ω-6 PUFAs have pro-inflammatory properties and are known for increasing thrombosis and vasoconstriction. The western diet is rich in Omega-6 fatty acids and relatively poor in Omega-3 fatty acids. Lower plasma levels of Ω-3 and an increased Ω6/3 ratio [9] have been reported in patients with ADHD, with Omega supplementation playing a role in the improvement of clinical symptoms [10].

RCTs on the effect of PUFAs supplementation in ADHD have shown contrasting results [10–14], probably related to a significant methodological heterogeneity. RCTs reporting positive results (Hedges's g range varying from 0.50 to 1.22 estimated according to evaluation of efficacy on specific symptoms [9]) generally have higher sample sizes with a minimum study duration of 15 weeks and the administration of both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [15]. Significant results have also been observed with a combination of EPA and DHA Omega-3 and the gamma linolenic acid (GLA) Omega-6 [16, 17]. Randomized Clinical Trials (RCTs) reporting negative results may have been affected by a higher number of limitations such as smaller sample sizes, shorter study duration, or the exclusive administration of either DHA or EPA [15].

A link between ADHD symptoms, learning difficulties and Omega 3/6 fatty acid deficiency has also been highlighted [18]. Trials using a combination of EPA and DHA in children with reading and writing disorder, dyspraxia, and ADHD-related symptoms have reported significant symptom reductions in all areas [19–21]. Three RCTs studies conducted in populations including a possible comorbidity with learning disorders [22–24] showed that Omega 3/6 fatty acids may reduce ADHD symptoms in treated patients: the largest improvement was observed in children and adolescents with ADHD inattentive subtype (ADHD-I). Very few RCTs have, however, been specifically performed in children with dyslexia, preventing any firm conclusion about the effect of PUFAs on learning abilities in children with specific learning disorders [25].

Ω3 PUFAs effects have also been examined as add-on therapy to methylphenidate (MPH) or atomoxetine (ATX). When prescribed as add-on treatment, Omega supplementation has proved effective in reducing the MPH dosage needed to achieve the same clinical improvement and in lowering incidence of medication adverse events [26, 27].

More recently, Crippa et al. [28] showed no evidence of benefit from a 6 months DHA supplementation on behaviour and cognition in ADHD children, although a slightly significant improvement in psychosocial functioning and a decrease of parent-rated emotional problems was detected. In their systematic review and meta-analysis, Cooper et al. did not find any significant improvement in emotional lability (EL), oppositional and conduct problems or aggression with PUFA, although when restricting the analysis to higher quality studies a reduction of oppositional behaviours and EL was found [29].

Considering the current available contrasting results about the efficacy of dietary supplements in the ADHD population, a growing interest in identifying patient subsamples more likely to respond to PUFA has been reported, although data from single studies and meta-analysis are still insufficient to draw firm conclusions. In terms of different ADHD presentations some studies show that inattentive patients appear to be more sensitive to PUFA supplementation [18, 30] and that the combination with EPA and GLA is more efficacious in reducing inattention symptoms [13], while subjects with predominantly hyperactivity/impulsivity presentation appear to be more responsive to higher dosages of EPA (> 500 mg per day) [9].

Although sex-specific differences in essential fatty acid metabolism have been studied [31], information about different responses in the two genders are insufficient, probably because of the scarce representation of females in the ADHD clinical population. Two studies found a greater improvement in ADHD scores in male participants [32, 33] while one other showed a better response to treatment in the following subgroups: male sex, age 13–18 years, inattentive ADHD type, and the presence of a reading or writing disorder [24]. In contrast, Raz et al. [34] found none between age, sex, comorbidities, or ADHD severity to be relevant moderators. No significant differences have been detected according to age [12] although further trials are surely needed to answer this question [11].

Finally, very few supplementation trials have included blood PUFA analysis. Considering that serum, plasma, or erythrocyte PUFA contents are biomarkers of PUFA intake

and bioavailability [35], the inclusion of PUFA status, and particularly the Ω6/3 ratio, have been suggested as putative predictive parameters for efficacy in children with a low baseline Ω-3 PUFA level or in those who exhibit the greatest increase in PUFA levels over the supplementation period [36].

Based on this evidence, we hypothesized that dietary PUFAs could improve inattention symptoms in ADHD-I children possibly according to changes in blood PUFA levels. With this aim in mind, we performed a sufficiently powered, randomised, placebo-controlled trial, to verify the efficacy of an Omega-3/6 supplement in reducing inattentive symptoms. Blood PUFA status (Ω3, Ω6 and Ω6/3 ratio) at baseline, the changes in blood PUFA levels, and their correlation with behavioural changes were also examined over the whole study period.

Objectives

Primary objective: to evaluate the efficacy of a specific Omega-3/6 combination in reducing the ADHD core inattentive symptoms.

Secondary objectives: to assess the improvement in global functioning, behavioural problems, mood and anxiety, motor coordination and specific learning skills. Another secondary objective was to evaluate baseline essential fatty acids plasma levels (Ω 6, Ω 3 and Ω 6/3 ratio) and their changes at the different time-points, as well as the possible correlation between this variation and the clinical improvement assessed by the ADHD-RS.

Experimental procedures

Study design

A randomised, double-blind, multicentre, placebo controlled, efficacy study, divided into three periods: (a) Screening and baseline assessment; (b) Phase I double-blind evaluation of dietary supplement vs placebo (6 months); c) Phase II open label treatment period (6 months).

The trial was approved by the Ethical Committee of the Cagliari University Hospital (resolution n. 662; September 22nd, 2011). At the time of the Ethical submission, according to the clinical trial Italian law, registration was not mandatory for Omega 3/6 since they were classified as food additives.

Participation to the study was on voluntary basis. Before any study procedure, parents or a legally authorized representative of the subject signed the informed consent. Children provided their written assent.

Participants

The participants were mainstream school children aged 6–12 years, recruited from four Italian sites: Unit of Child and Adolescent Neuropsychiatry, Cagliari University Hospital; Stella Maris Scientific Institute for Child and Adolescent Neuropsychiatry, Pisa; Unit of Pediatric Neurology Tor Vergata, Rome; Division of Child Neuropsychiatry, Messina University Hospital. Baseline characteristics are shown in Table 1.

Patients had to meet DSM-IV criteria for a primary diagnosis of mild to moderate ADHD-I (i.e.: not as severe as to require immediate pharmacological treatment), based on a detailed psychiatric evaluation and the semi-structured diagnostic interview Schedule for Affective Disorders and Schizophrenia for school-age children-present and lifetime version (Kiddie-SADS-Present and Lifetime—K-SADS-PL) [37]. Participants were considered eligible if they were drug-naïve, if they had a baseline ADHD-RS-IV [38] subscale inattention score ≥ 12 (i.e., reporting the score of 2 in at least 6 questions) and a global functioning between 45 and 59 by the Children's Global Assessment (C-GAS) [39]. As for the primary diagnosis, the presence of any comorbidity was assessed according to DSM-IV criteria by K-SADS [37]. Subjects out of a healthy weight range between 20 and 50 kg at the initial visit and/or with IQ < 70 were not eligible to enter the trial. Other exclusion criteria were: somatic (serious internal conditions like chronic renal failure, severe liver disease, cardiovascular disorders, uncontrolled hypertension with systolic blood pressure > 170 and diastolic blood pressure > 100 mm Hg, malignant tumours, HIV infection, epilepsy) and psychiatric (alcoholism, history of Bipolar I or II Disorder or psychosis) comorbidities; Autism Spectrum Disorder (ASD) subjects were excluded because the dual diagnosis of ADHD and ASD was not permitted according to DSM-IV criteria. Subjects were not allowed to enter the

Table 1 Baseline characteristics of participants

	Total sample, *n* (%)	Ω 3/6, *n* (%)	Placebo, *n* (%)
	160 (100)	79 (49.4)	81 (50.6)
Males	118 (73.7)	59 (74.7)	59 (72.8)
Females	42 (26.3)	20 (25.3)	22 (27.2)
Age (mean ± SD)	9.7 ± 1.9	9.6 ± 1.8	9.8 ± 2.1
Psychiatric comorbidities			
ODD	13 (8.1)	3 (3.8)	10 (12.3)
GAD	5 (3.1)	3 (3.8)	2 (2.5)
SAD	11 (6.8)	5 (6.3)	6 (7.4)
Specific phobias	8 (5)	5 (6.3)	3 (3.7)
OCD	1 (0.6)	1 (1.3)	–
Mood disorders	2 (1.2)	1 (1.3)	1 (1.2)
SLD	91 (56.9)	47 (59.5)	44 (54.3)

trial also if they had a documented allergy, hypersensitivity, or intolerance to any of the excipients of the test or placebo product; if they were treated with fish oil or derivatives during the last three months; or if they were on any antipsychotics, anxiolytics or sedative/hypnotic drugs, antidepressants and anticoagulants. Concomitant psychoeducational interventions were not considered an exclusion criterion.

Randomization and blinding

Eligible subjects were randomised in a 1:1 ratio (dietary supplement: placebo) and assigned to one of the two treatment arms. Random allocation sequence was generated by the Clinical Research Organization (CRO) based at the Clinical Pharmacology Unit of the Cagliari University Hospital, using a block randomization (block size: 4) and an allocation ratio of 1:1 to ensure a good balance of the characteristics of the patients in each group. To avoid interference in the efficacy evaluation it was decided to stratify for specific factors (gender and age). Capsules, sent by the producer to the CRO, were then packaged into bottles that, in turn, were sent to each participant site. A code list identifying active and placebo bottles, inaccessible to the study staff, was kept by the Clinical Pharmacology Unit, until the end of the study. All participants and investigators were blinded. Investigators were unblinded only when all subjects had completed the study and all data had been collected.

Randomized subjects were treated with two capsules each containing 279 mg EPA, 87 mg DHA, 30 mg GLA (gamma linolenic acid) or placebo, per day, to be taken with the meal. Dosage was selected according to the literature data available when the study was designed (2010) suggesting that a daily dose of 558 mg EPA, 174 mg DHA and 60 mg GLA could be effective in reducing inattentive symptoms without significant adverse events [24]. In phase II, all patients were given open active treatment at the same dosage. The placebo capsules matched the FA supplementary ones in touch, smell, and size.

Outcomes

Clinical assessments have been performed at 5 time points: baseline and after 3, 6, 9 and 12 months. After 1 month, a psycho-educational support and clinical monitoring visit was guaranteed for each patient to obtain a better compliance with the study protocol.

Primary outcome

The primary outcome measure was the Inattention Score of the clinician administered ADHD-RS-IV [38]. ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0 to 54. The scale is sub-divided into two sub-scales of 9 items each: hyperactivity/impulsivity and inattentiveness.

Subjects with a 25% reduction in the ADHD-RS-Inattention score were considered "*responders*", according to a definition previously used in other trials with Omega supplements (e.g. Johnson et al., 2009) [24].

Secondary outcomes (see Supplementary Information SI for details)

- ADHD-RS-IV total score [38],
- Clinical Global Impressions Rating Scale (CGI) [40],
- Children's Global Assessment (C-GAS) [39],
- Conner's Parent and Teacher Rating Scale-Revised (CPRS-RS and CTRS) [41],
- Children's Depression Rating Scale (CDRS) [42],
- Multidimensional Anxiety Scale for Children (MASC) [43],
- The Developmental Coordination Disorder Questionnaire (DCDQ) [44],
- Reading and Writing Tests [45]
- Diet Information (information about food intake of the previous seven days before each applicable visit was collected through a diary).
- EFA blood levels [46]

ADHD-RS-IV, CGI-I and C-GAS change from baseline was evaluated at each visit.

CGI-S, CPRS, CTRS, CDRS, MASC, DCDQ, reading and writing tests, blood measurement of fatty acids and diet information were assessed at baseline and after 6 and 12 months.

Additionally, a physical examination including height and weight, pulse and blood pressure, as well as a general and neurological examination, were conducted and the safety of Omega supplementation was assessed.

At baseline assessment, the investigator provided a psychoeducational training both to the parents and the participants, of about one hour, with the purpose of helping the parents and their children to learn appropriate techniques to better manage invalidating inattention symptoms and to reinforce children's strengths.

At each appointment subjects were interviewed about possible adverse events (AE); all symptoms not related to the subjects' psychiatric condition were considered an AE.

Compliance (defined as taking at least the 70% of the prescribed dosage) was assessed at each applicable visit by direct questioning of parents and/or patient. To allow the clinical staff to evaluate the adherence to treatment and discontinue non-compliant subjects, participants were also

asked to return both used (including empty) and unused bottles distributed at the previous visit.

Statistical analyses

All randomized patients with at least one post-baseline assessment were included in the analysis.

All randomized subjects who completed a study period were included in the Per Protocol (PP) analyses. The primary outcome (ADHD-RS) and the secondary outcomes C-GAS and CGI-S were confirmed by Intention-To-Treat (ITT) analysis with the Last Observation Carried Forward (LOCF) method.

The primary efficacy measure of the study was the ADHD-RS_IV Inattention score change from baseline. In each arm of the study (Omega and Placebo), the variation of the ADHD-RS_IV Inattention score over the 3 study periods (baseline, 6 months, and 12 months), has been analysed through Friedman test separately for the patients treated with Omega and the patients treated with Placebo.

The variation of the secondary outcomes, including the ADHD-RS_IV total score, the C-GAS, the CGI-S, the CPRS-RS and CTRS scores over the three study periods, was analysed through Friedman test separately for the patients treated with Omega and the patients treated with Placebo.

The variation of the ADHD RS-IV Inattention score in patients treated with the active supplement was compared with the one observed in patients treated with placebo, at baseline, at 6 months, and at 12 months through repeated measures ANOVA. The same statistical method was used to assess the variation of the other clinical measures in patients treated with Omega and placebo, at baseline, at 6 months and at 12 months. The selected measure of effect size was the partial eta squared (η^2p): this measure reflects the percentage of the variance in the dependent variable explained by the independent variables in a sample, *i.e. a* $\eta^2p = 0.050$ explains the 5.0% of variance.

Finally, Pearson's correlations were used to investigate the correlation between the PUFA blood levels and the ADHD-RS scores. Statistical significance was set at $p < 0.05$. Data were analysed using the Statistical Package for the Social Sciences (version 20; SPSS Inc., Chicago, IL, USA).

Power analysis

Power calculations were based on the comparable previous studies by Johnson et al. 2009 [24] and by Richardson and Montgomery 2005 [19] where a group size of 42 participants per group gave a > 80% power at the 0.05 level. A target sample size of 80 subjects per group was therefore considered more than appropriate for this study.

Results

A total of 160 patients (118 boys and 42 girls; mean age 9.7 ± 1.9 years; active treatment, $n = 79$; placebo, $n = 81$) were enrolled. Of these, 135 completed the first 6 months double blind evaluation of Omega-3/6 vs placebo (Phase I; PP population analysed for the primary outcome was: Omega supplement n = 67, Placebo $n = 68$) and 122 completed the further 6 months open label treatment with Omega-3/6 on all patients (Phase II; PP population analysed was: Omega supplement $n = 62$, Placebo $n = 60$). The dropout rate was about 23% (38 subjects: 21 placebo and 17 Omega group) essentially for poor motivation. None of the enrolled subjects discontinued the study due to an adverse event. Two subjects reported difficulties in swallowing capsules. No significant socio-demographic and clinical differences were found between the drop out population and the participants who ended the study (Fig. 1).

ADHD-RS

At baseline, the two randomized groups resulted similar in the mean inattention subscale and the mean total ADHD-RS scores. A significant change in the inattention and total score was found through the Friedman test, over the 3 study timepoints (baseline, 6 months, and 12 months) within each group. ADHD-RS_IV Inattention score: Omega-3/6, 16.02 ± 4.53 at baseline, 11.98 ± 5.36 at 6 months, 11.61 ± 4.88 at 12 months, $p < 0.001$. Placebo, 17.07 ± 4.83, 13.17 ± 4.95, 13.08 ± 5.47, $p < 0.001$ [Fig. 2a]. ADHD-RS_IV total score: Omega-3/6, 24.27 ± 8.63 at baseline, 19.97 ± 9.69 at 6 months, 18.59 ± 8.57 at 12 months, $p < 0.001$; Placebo, 28.53 ± 9.53 at baseline, 23.07 ± 10.11 at 6 months, 22.55 ± 10.45 at 12 months, $p < 0.001$ [Fig. 2b].

No significant statistical differences were found between Omega-3/6 and placebo groups, across baseline and 6 months follow up visit, through repeated measures ANOVA, both for the ADHD-RS_IV Inattention score ($F = 1.778$; $p = 0.185$; $\eta^2p = 0.013$) and the ADHD-RS_IV total score ($F = 3.437$; $p = 0.066$; partial eta squared (η^2p) = 0.025).

Considering the three times points (baseline, 6 months, and 12 months) across the whole study period, no significant differences were observed for the ADHD-RS_IV Inattention score ($F = 2.899$; $p = 0.091$; $\eta^2p = 0.024$) through repeated measures ANOVA, while a small significant statistical difference between Omega-3/6 and placebo groups was found for the ADHD-RS_IV total score ($F = 6.245$; $p = 0.014$, $\eta^2p = 0.051$); the $\eta^2p = 0.051$ explains the 5.1% of variance [Fig. 2a and b].

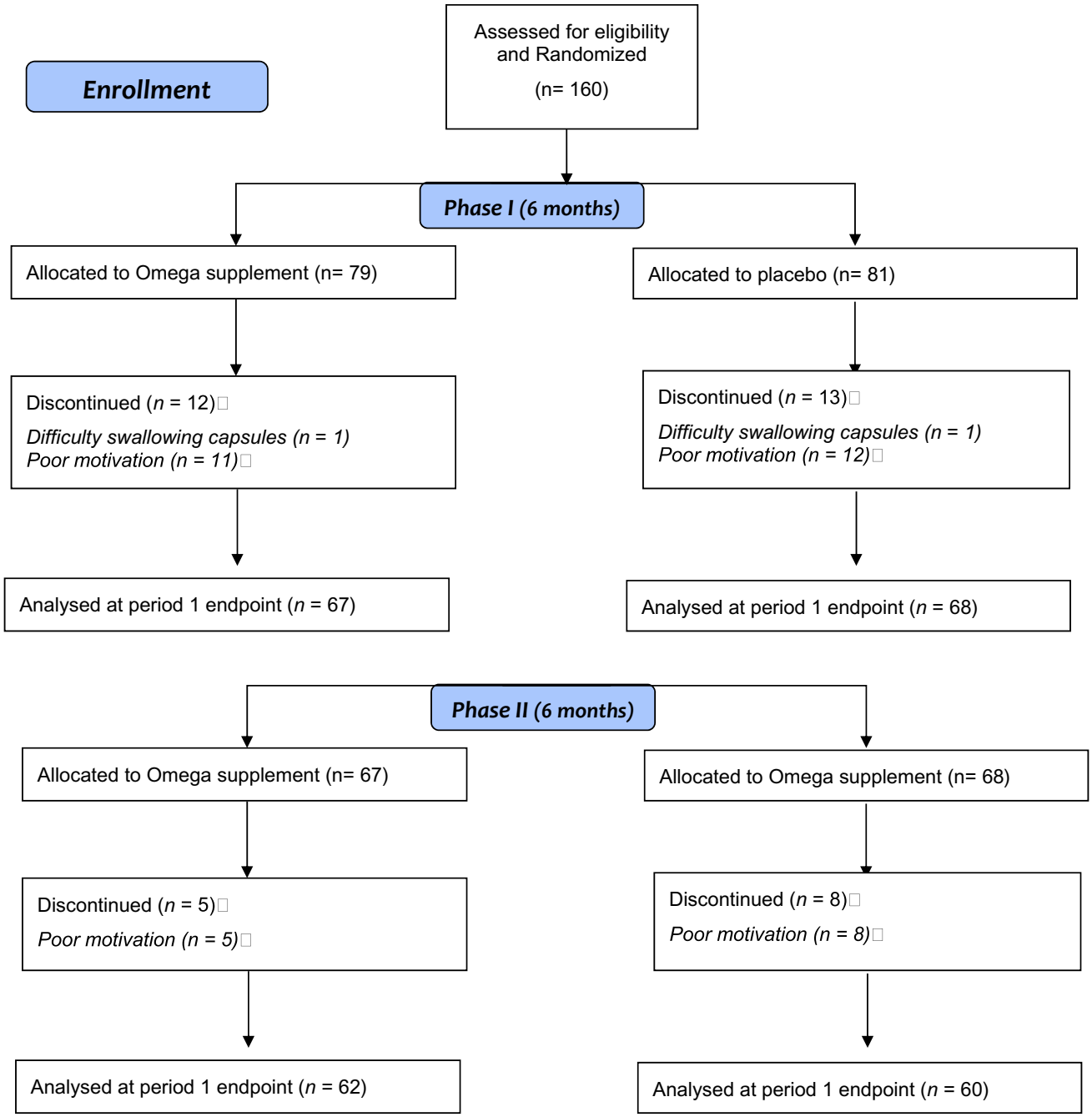

Fig. 1 Flow chart of participants

Baseline to 6- and 12-months changes analysed for the ITT population with LOCF were comparable to the PP population analyses: ADHD-RS_IV Inattention score ($F = 1.931$; $p = 0.167$; $\eta^2 p = 0.012$) and ADHD-RS_IV total score ($F = 4.452$; $p = 0.036$, $\eta^2 p = 0.028$; see Table 2).

According to the ADHD-RS- Inattention score, after six months, we found 31 (46.3%) responders in the Omega-3/6 group and 31 (45.6%) in the placebo group; at the end of the study, we found 36 (58.1%) responders in the Omega group and 32 (53.3%) in the placebo one. No significant differences were found between the two groups of responders in terms of symptoms reduction (Table S1). Analysis according to gender, age, comorbidities, and clinical severity of symptoms revealed no significant differences between the two groups of responders.

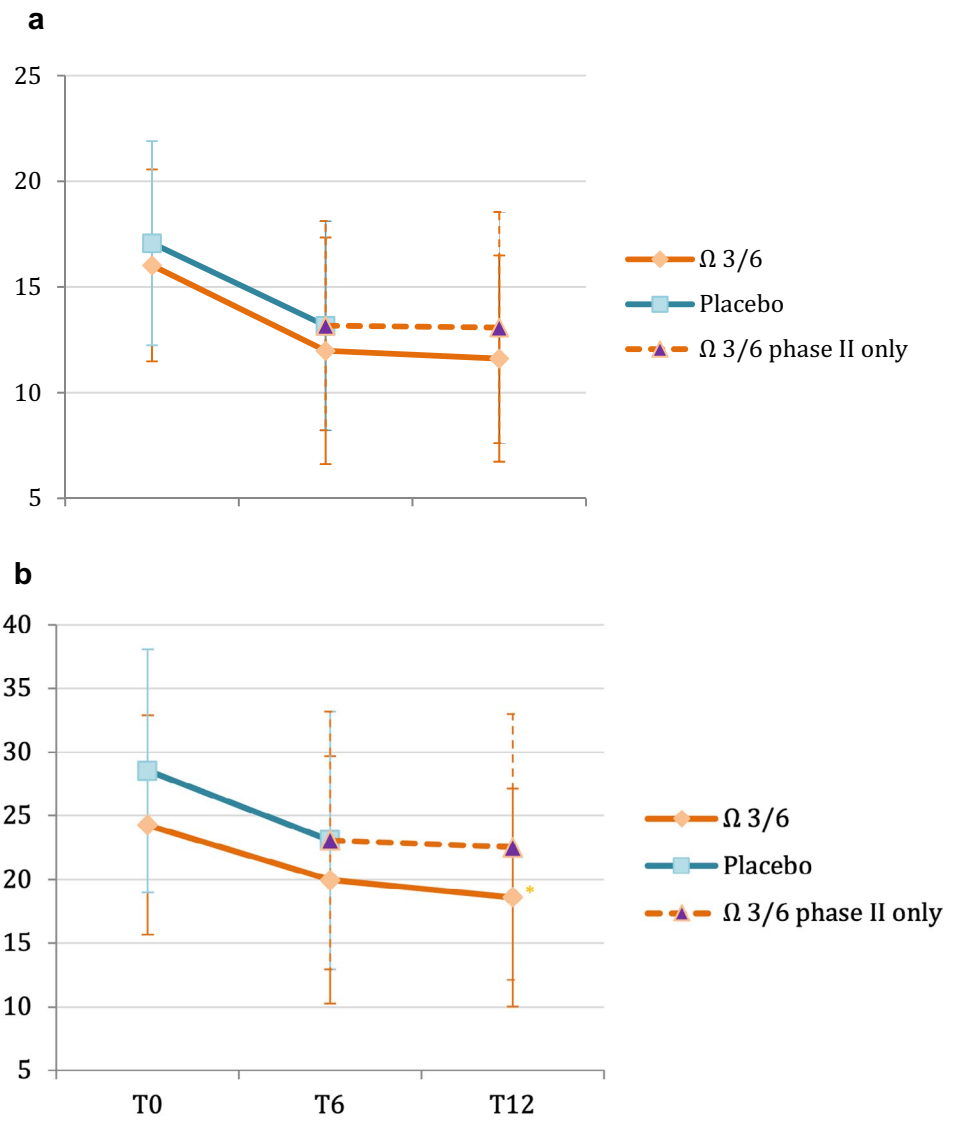

Fig. 2 **a** Baseline to 6 and 12 months Mean and SD changes of ADHD-RS-Inattention score (PP population). No significant differences between omega-3/6 and placebo groups were found in the change of the inattention score of ADHD-RS across the whole study period (considering the three time points baseline, 6 months and 12 months) through repeated measures ANOVA ($F=2.899$; $p=0.091$; $\eta^2p=0.024$). **b** Baseline to 6 and 12 months Mean and SD changes of ADHD-RS total score (PP population). No significant statistical differences were found between Omega-3/6 and placebo groups, across baseline and 6 months follow up visit. A slight significant change in the total score of ADHD-RS-IV Total score was found across the whole study period (baseline, 6 months and 12 months), with a statistically significant difference between Omega-3/6 and placebo groups through repeated measures ANOVA ($p=0.014$; $\eta^2p=0.051$)

Table 2 Baseline to 6 and 12 months Mean and SD changes of ADHD-RS-Total and ADHD-RS-Inattention score (ITT population with LOCF)

	Baseline Mean (SD)	6 months Mean (SD)	12 months Mean (SD)	p 0 vs 12 months	Repeated measures ANOVA
ADHD-RS-Inattention					
Ω 3/6	15.91 (4.32)	13.01 (5.56)	12.63 (5.30)	<0.001	0.167 ($\eta^2p=0.012$)
Placebo	16.99 (4.52)	13.69 (4.96)	13.60 (5.54)	<0.001	
ADHD-RS total					
Ω 3/6	25.06 (8.48)	21.90 (10.08)	20.58 (9.58)	<0.001	0.036 ($\eta^2p=0.028$)
Placebo	28.31 (9.05)	24.10 (10.02)	23.75 (10.55)	<0.001	

ITT intention-to-treat, *LOCF* Last Observation Carried Forward, *n.s.* not significant

A mild but significant improvement in the primary outcome measure ADHD-RS-Inattention score and in the ADHD-RS- Total score over the 3 study timepoints (baseline, 6 months and 12 months) was found within each group. A slight statistically significant difference between Omega-3/6 and placebo groups was found across the three times considered through repeated measures ANOVA for the ADHD-RS_IV total score ($F=4.452$; $p=0.036$, partial eta squared (η^2p) $=0.028$) while no significant differences were met for the primary outcome measure ADHD-RS_IV Inattention score ($F=1.931$; $p=0.167$; $\eta^2p=0.012$)

Global functioning and clinical impression

A significant change in CGAS score was found, through the Friedman test, over the 3 study periods (baseline, 6 months, and 12 months) within each group. Omega-3/6, 51.44 ± 3.84 at baseline, 56.03 ± 5.98 at 6 months, 61.19 ± 9.52 at 12 months, $p < 0.001$; Placebo, 51.14 ± 4.22 at baseline, 55.2 ± 5.28 at 6 months, 59.68 ± 8.60 at 12 months, $p < 0.001$.

Also, a significant change in CGI-S scores was found over the 3 study periods (baseline, 6 months, and 12 months) within each group: Omega-3/6, 3.67 ± 0.6 at baseline, 3.38 ± 0.74 at 6 months, 3.03 ± 0.9 at 12 months, $p < 0.001$. Placebo, 3.68 ± 0.6 at baseline, 3.47 ± 0.67 at 6 months, 3.08 ± 0.83 at 12 months, $p < 0.001$).

Although CGAS and CGI-S scores improved in both groups no significant difference was found through repeated measures ANOVA between the two randomised groups across the three-time period considered: CGAS $p = 0.36$, $\eta^2 p = 0.007$; CGI-S $p = 0.643$, $\eta^2 p = 0.002$) (Table 3). Baseline to 6- and 12-month changes analysed for the ITT population with LOCF were, also in this case, comparable to the PP population analyses: CGAS ($F = 0.464$; $p = 0.497$; $\eta^2 p = 0.003$), CGI-S ($F = 0.304$; $p = 0.582$; $\eta^2 p = 0.002$).

Conner's Parent and Teacher Rating Scale-Revised (CPRS-RS and CTRS)

Parent's ratings showed a mild but significant improvement in the subscales "inattention symptoms" and "ADHD index" over the 3 study periods (baseline, 6 months, and 12 months) within each group. CPRS-RS Inattention: Omega-3/6, 75.79 ± 12.74 at baseline, 65.71 ± 11.09 at 6 months, 66.67 ± 12.31 at 12 months, $p = 0.002$; Placebo 75.24 ± 11.06 at baseline, 67.61 ± 12.57 at 6 months, 66.28 ± 12.41, $p < 0.001$; Table S2). No significant differences between Omega-3/6 and placebo groups across the three times considered (baseline, 6 months, and 12 months) were found through repeated measures ANOVA ($F = 0.035$; $p = 0.852$; $\eta^2 p = 0.000$).

No significant results were found for teacher's ratings; it is worth noting however that CTRS were less numerous in consideration of the impossibility in having completed questionnaires at visits during school holidays.

Learning abilities

In our sample the prevalence of SLD (Specific Learning Disorders) was not significantly different between the active and placebo group (Tot SLD = 91; Omega-3/6 = 47 vs Placebo = 44). Baseline mean scores of reading accuracy and speed and writing abilities did not significantly change for all tests within and between the two groups after 6 and 12 months. Active treatment was not superior to placebo in improving reading and writing difficulties (Tables S3, S4 and S5).

Anxious and depressive symptoms

No effect was found on mood and anxiety symptoms in both groups, although a slight reduction of anxiety has been observed from baseline to the end of the study.

Developmental Coordination Disorder Questionnaire (DCDQ)

No effect was found on global motor abilities in both groups.

EFA blood levels

Seventy-one subjects (active treatment n = 35 and placebo n = 36) agreed to participate to collection of a drop of blood from their finger for PUFA blood level analyses. PUFA plasma blood levels at baseline resulted similar between the Omega supplement and the placebo groups respectively as following: Ω6 25.77 ± 4.1 vs 26.82 ± 4.9; Ω3 3.32 ± 1.6 vs 2.55 ± 1.0 and Ω6/3 ratio 9.49 ± 4.1 vs 11.9 ± 4.2.

Table 3 CGAS and CGI-S (Omega vs Placebo)

	Baseline mean (SD)	6 months, mean (SD)	12 months, mean (SD)	P 0 vs 12 months	Repeated measures ANOVA
CGAS					
Ω 3/6	51.44 (±3.84)	56.03 (±5.98)	61.19 (±9.52)	< 0.001	0.36 (η^2p = 0.007)
Placebo	51.14 (±4.22)	55.2 (±5.28)	59.68 (±8.60)	< 0.001	
CGI-S					
Ω 3/6	3.67 (±0.6)	3.38 (±0.74)	3.03 (±0.9)	< 0.001	0.643 (η^2p = 0.002)
Placebo	3.68 (±0.6)	3.47 (±0.67)	3.08 (±0.83)	< 0.001	

The difference in CGAS and in CGI-S score between the randomized groups (Omega vs Placebo) at baseline, 6 months, and 12 months, were compared through repeated measures ANOVA showing no significant differences between the two groups. Baseline to 6- and 12-months changes analysed for the ITT population with LOCF were comparable to the PP population analyses: CGAS ($F = 0.464$; $p = 0.497$; $\eta^2 p = 0.003$), CGI-S ($F = 0.304$; $p = 0.582$; $\eta^2 p = 0.002$)

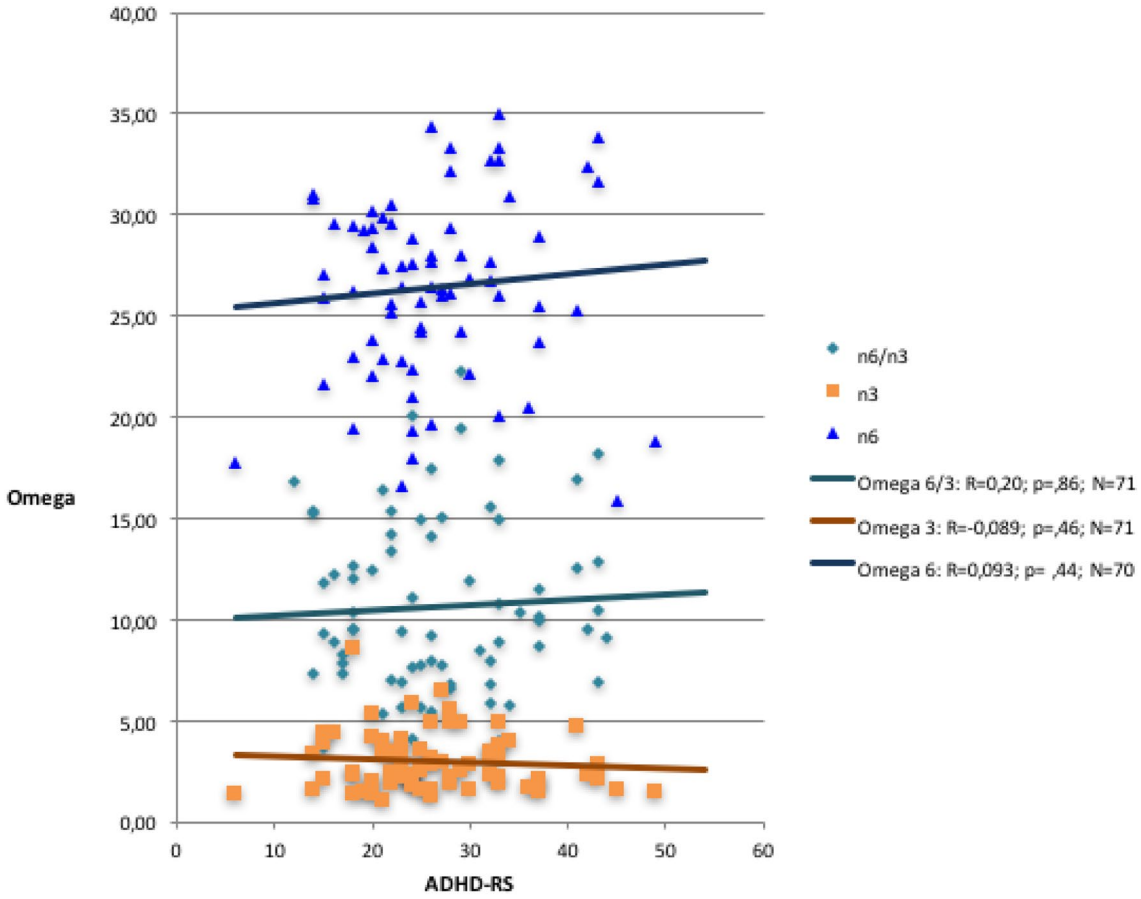

Fig. 3 Correlation between PUFA plasma levels and ADHD-RS scores at baseline. No significant correlation was found between FA blood levels and clinical symptoms at baseline in the total sample

Furthermore, no significant correlation was found, at baseline, in the total sample, between the plasma levels of essential fatty acids and the severity of symptoms measured by the ADHD-RS (Fig. 3).

Forty-six subjects (24 randomised to the omega group and 22 to the placebo group) agreed to repeat their blood exam after 6 and 12 months. There were no differences in ADHD-RS scores between those who provided blood samples and those who did not.

No significant differences of fatty acids blood levels (Ω3, Ω6 and Ω6/3 ratio) were found at baseline between the two groups. The variation of plasmatic levels of FA at three time

Table 4 FA levels in the Omega (n = 24) and Placebo (n = 22) groups

	Baseline, mean (SD)	6 months, mean (SD)	12 months, mean (SD)
Omega 6			
Ω 3/6	26.40 (4.2)	25.4 (4.5)	25.40 (4.4)
Placebo	27.52 (5.6)	25.0 (5.2)	24.08 (6.2)
Omega 3			
Ω 3/6	3.8 (± 1.7)	3.5 (± 1.2)	3.1 (± 1.1)
Placebo	2.8 (± 1.0)	2.3 (± 0.9)	3.3 (± 1.3)
Omega 6/3			
Ω 3/6	8.5 (4.2)	8.1 (2.7)	8.9 (2.9)
Placebo	10.9(3.7)	11.8 (4.0)	8.2 (2.9)

No significant differences of fatty acids blood levels (Ω3, Ω6 and Ω6/3 ratio) were found at the three time points of the study (baseline and after 6 and 12 months) both within and between the two groups

points of the study (baseline and after 6 and 12 months) revealed no significant differences within and between the two randomized arms (Table 4). No correlation from baseline to the end of the study was found between the change in the FA plasma profile and the clinical improvement measured by the variation ADHD-RS score (Fig. 4).

Safety

Dietary supplementation was well tolerated, and no subjects reported severe adverse effects. A total of 5 patients showed mild adverse events, none of which related to the discontinuation of the study: 2 subjects on the Omega 3/6 supplement referred diarrhoea, while 3 subjects on placebo reported one each respectively abdominal pain, itch and somnolence with difficulty in waking up in the morning.

Discussion

Within the present study, we found a similar mild within-group improvement in global functioning and inattentive symptoms, with no significant difference between the placebo and omega groups.

The improvement of the ADHD-RS inattentiveness subscale scores at the different time points was significant within both groups, but the comparison between groups was not significant. These results are in line with three recent similar RCTs. A total of 50 ADHD subjects, aged 7–14, were enrolled in a 6-month randomized, placebo-controlled clinical trial and received either DHA or placebo. After 6-month DHA supplementation no beneficial effect on ADHD symptoms was found [28]. Cornu et al. [47] highlighted the lack of beneficial effect of omega-3 supplement (DHA + EPA) in a population of French children (mean age 9.90 ± 2.62 years) with mild ADHD symptoms. In this case the total ADHD-RS-IV score reduction was greater in the placebo group than in the DHA–EPA group. Also, when used as an add-on therapy, Omega-3 failed to improve mean scores of Conner's scales compared to zinc with no further significant difference between omega-3 group compared to placebo group ($p = 0.89$) [48].

Over the past two decades, many studies have shown a significant reduction in ADHD symptoms following food supplementation [19–21], but most of these trials were conducted in subjects without a formal diagnosis of ADHD. More recent studies, performed in subjects with ADHD, have reported a potential efficacy of supplements in specific subgroups of patients, such as subjects with predominant

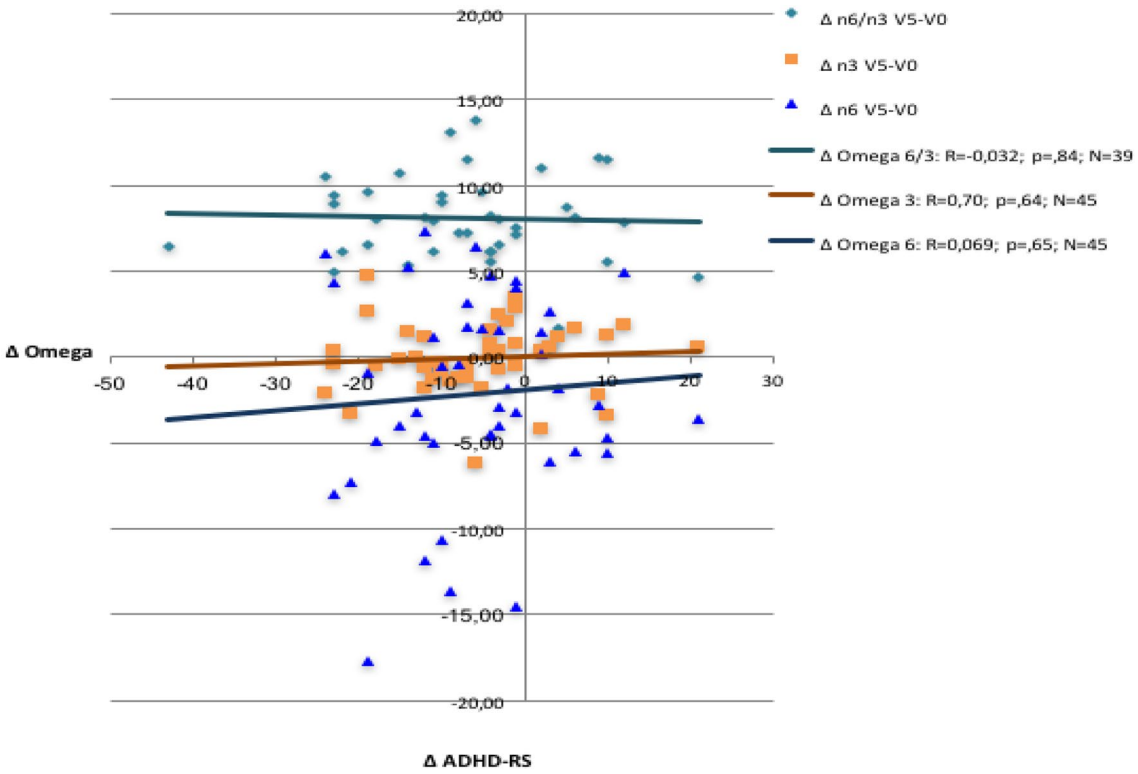

Fig. 4 Correlation between changes in PUFA plasma levels and ADHD-RS scores improvement from baseline to the end of the study. No significant correlation was found between FA and clinical symptoms and their variations during the whole study period in the total sample

inattention symptoms and neurodevelopment disorders [49, 50]. Bloch and Qawamasi [10] showed a significant improvement in both inattentive and the other ADHD core symptoms in those taking the supplement compared to those randomized to placebo, but these results, authors wrote, must be considered with caution due the limited statistical power of the study. In our trial we also found a small statistical difference between groups on the ADHD-RS total score after 12 months of treatment, indicating a possible effect on hyperactivity/impulsivity symptoms. It should be considered, however, that difference in ADHD-RS-Total score (PP population $\eta^2p = 0.051$; ITT population $\eta^2p = 0.028$) appears to be leaded by the difference in the ADHD-RS-Hyperactivity score which at baseline was, by inclusion criteria, within the normal range; it should also be considered that a $\eta^2p = 0.051$ explains only the 5.1% of variance. Taken together these two considerations strongly suggest that the small difference in the ADHD-RS-Total score (a secondary outcome measure in the present study) should be considered clinically not significant.

A significant placebo effect has been reported in other developmental disorders such as autism [51] or paediatric depression: milder baseline illness severity, younger age and a high number of study sites were predictors for high placebo response in paediatric depression [52], while increased response to the active intervention, outcome ratings by clinicians (as compared with caregivers), trials of pharmacological and adjunctive interventions and specific trials location predicted higher placebo responses in autism [51]. In the present study, there were only four recruiting sites, no differences were observed between clinician and caregiver ratings and omega supplementation was the only treatment compared to placebo. It is worth noting, however, that the severity of core symptoms in the present sample, measured by the ADHD-RS-Inattention subscale (16.02) and CGI-S scale (3.67), was within the range of "mild disease", as in many studies with a high placebo effect.

The improvement observed in both groups reinforces the hypothesis that caring for patients and caregivers, through constant and precise clinical monitoring and educational support, can itself guarantee a better management and reduction of ADHD core symptoms that negatively impact on global functioning [53, 54].

In recent years, several meta-analyses were published to clarify the efficacy of dietary supplementation with essential fatty acids especially in children and adolescents [55], all of them generally reporting low effect sizes. The systematic review conducted by the EAGG group [14] showed a slight reduction in ADHD symptoms with polyunsaturated fatty acids (SMD 0.21), in contrast with the recent systematic review and meta-analysis by Chang et al. [9] which suggests that mono-therapy with Omega 3-based supplements appears to be associated with a moderate improvement in both clinical symptoms (SMD 0.38) and cognitive performance (SMD 1.09). According to Agostoni et al. [15], the current available evidence is not always consistent, probably due to the heterogeneity of the methods (different and not homogenous sample sizes, different inclusion criteria, different combination, and dosage of PUFAs, various length of study supplementation and various neuropsychological tests and scales). All these elements make it difficult to compare the findings to draw any firm conclusions about Omega supplementation efficacy.

In their recent systematic review, Abdullah et al. [56] examined the effectiveness of omega-3 supplementation at reducing ADHD symptoms in children and adolescents, with changes on Conners' rating scale (CRS) as primary outcome measure. Both experiment and control groups had similar reductions in CRS score, confirming the insufficient evidence to recommend omega-3 supplementation as of any benefit in improving ADHD symptoms.

Measuring the secondary outcomes, we found in both groups a significant improvement in terms of global functioning and a statistically significant change in the CGI-S scale, although, as for the primary outcome, the comparison between groups was not significant (CGI-S $p = 0.94$; CGAS $p = 0.32$).

When examining family and school functioning, we found a significant difference within each study group in the change of CPRS' inattention and ADHD index score, with a change from the clinically significant to the subclinical threshold at the end of the study. No significant variations were found in CTRS' score and between the two groups. Our results are in contrast with previous studies showing the efficacy of omega-3 on ADHD symptoms in the family environment [9] and on inattention symptoms in school settings [57], but they confirm the results of another study [58] showing a lack of efficacy of an omega-3 supplementation compared to placebo, on CTRS scores.

Within our sample all subjects were also assessed for school learning skills. 91 enrolled subjects, 47 belonging to the omega group and 44 to the placebo one, had a comorbid specific learning disorder. No statistically significant changes emerged from the comparison between the two groups in terms of accuracy and reading speed or writing skills. Our data are in contrast with the previous study published by Raz and Gabis [59], and the recent randomized, placebo-controlled trial performed in typically developmental children aged 9–10 years old. In this case, 3 months of Omega 3/6 treatment appeared to improve reading ability, specifically the clinically relevant 'phonologic decoding time' and 'visual analysis time', in mainstream schoolchildren [18]. On the other hand, our results are in line with a recent Cochrane review [25] where none of the two included studies reported effects of PUFAs on reading, writing, spelling or mathematical abilities of the examined children.

A secondary objective of the present work was to evaluate baseline EFA plasma levels (Ω 6, Ω 3 and Ω 6/3 ratio) and their changes at the different time-points, as well as the possible correlation between this variation and the clinical improvement assessed by the ADHD-RS.

By comparing the two randomisation groups, there was no significant variation in the mean values of fatty acids at the different follow-up times. However, in the placebo group, a slight, although not statistically significant, reduction of the Ω 6/3 ratio in the Phase II of the study (from the sixth to the twelfth month) was observed on patients starting the active treatment. In our sample, EFA blood levels were not significantly correlated to ADHD severity at baseline nor at the different study time points, Omega-3/6 dietary supplementation did not significantly modify the FA plasmatic levels during the whole study with no correlation with clinical and functional improvement. This is in contrast with several studies, that suggest a relation between omega 3/6 deficiency and inattention and hyperactivity symptoms, learning difficulties [12, 60, 61] and neurodevelopmental disorder [44].

When examining these results, it is also essential to identify the range of plasma essential fatty acid levels assumed as "pathological" and which variables (dietary and individual) may be responsible for these levels. In recent studies an extreme variability of the plasma levels was reported in the different samples confirming that several factors including the country of origin and diet may influence the mean values in the blood. Omega-3 blood levels (placebo group: 2.8 ± 1.0; Ω3/6 group: 3.8 ± 1.7) and Omega-6 blood levels (placebo: 27.52 ± 5.6; Ω3/6: 26.40 ± 4.2) in our sample, were quite similar to those of the normal Italian population (Ω3: 2.31 ± 0.50, Ω6: 28.97 ± 2.19) [62], evidencing therefore possible limited room for improvement in a mild impaired population.

Doses and specific composition of PUFA administration should also be considered in explaining heterogeneity of results. When we designed the present study (approved in 2011 and performed between March 2012 and September 2015) the available literature data suggested that the following composition of Omega 3 and Omega 6 and dose (558 mg EPA, 174 mg DHA and 6 0 mg GLA), could be effective in reducing inattentive symptoms [24]. Studies using lower doses (345 mg of DHA) did not produce a significant improvement of ADHD symptoms [63], while other studies using 635 mg of EPA and 195 mg of DHA and even higher doses (EPA 1.2 g) reported a significant clinical and functional improvement [64, 65]. Current recommendation of experts advises for a dosage of at least 750 mg of both EPA and DHA per day for at least 12 weeks before evaluating the response [66].

As in previous studies, omega supplementation was well tolerated: no significant adverse events were reported and the drop-out rate (about 23%) was similar in the two groups and comparable to the majority of the trials included in recent meta-analyse s. Considered the limited side effects, it may be reasonable to consider Omega-3/6 supplementation as a possible option for families of children with mild symptoms who cannot be tightly clinically monitored with a proper psychoeducational intervention, or for those patients with resistant symptoms that, for different reasons, reject a pharmacological approach. In these cases, health care professionals should prescribe PUFA supplements by primarily indicating that, although well tolerated, PUFA supplements typically do not have as much effect as stimulants on ADHD symptoms and secondly defining the duration of treatment before starting any other effective medication [66].

Strengths and limitations

The main strengths of this study are the enrolment of one of the largest sample size of all clinical trials published so far in the field; the duration of the trial (6 months double blind phase followed by a 6 months open label phase); appropriate dose (two capsules each containing 279 mg EPA, 87 mg DHA, 30 mg GLA) and the measurement of EFA blood levels, although in a subsample of subjects.

The main limitations of our study include the selection of subjects with ADHD inattentive subtype and only a “mild” presentation of the disorder. These criteria were selected based on previous literature and ethical reasons (children with moderate or severe presentation were excluded since participation excluded administration of effective medications for the duration of the whole study). Other important limitations include the limited range of age (with exclusion of the adolescent population), the small subsample of subjects that agreed in participating to the blood test collection, and the lack of detailed information about concomitant psycho-educational intervention.

Conclusions and future directions

In the present study, Omega-3/6 dietary supplementation was not significantly correlated with the clinical improvement in ADHD symptoms, nor with EFA blood levels. The efficacy of Omega-3/6 dietary products in children with mild ADHD-I resulted significantly lower compared to that of drug therapies currently indicated for the treatment of ADHD, such as psychostimulants, atomoxetine, or alpha-2 agonists [11, 47, 67] with a proportion of responders varying from about 70–83% for lisdexamfetamine, 53–80% for MPH and around 63% for ATX in randomized clinical trials [68]. The possible action of Omega-3/6 as supplement combined to standard drug therapy remains to be studied, in particular as an add-on treatment for reducing side effects and doses of traditional active drugs [27].

To establish the real efficacy of Omega supplementation in reducing inattentive and hyperactivity/impulsivity symptoms in ADHD children, as well as its utility in add-on to standard pharmacological therapies, it will be essential to establish the target characteristics of potentially "responders" patients in terms of basal level of FA and individual variables (clinical symptoms, comorbidities, diet, optimal age and duration of PUFA treatment, ethnicity). In future studies it will be important to establish the length of treatment and the minimum treatment dosage and to regularly check for the baseline essential fatty acids blood levels and their change over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-022-01428-2.

Acknowledgements The study presented in this paper was funded by Vifor Pharma under an unrestricted educational research grant to Dr. S. Carucci and Prof. A. Zuddas. Vifor Pharma had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors would like to thank the participants and their families for taking part in the research and Dr. Tiziana Cauli for reading the manuscript and providing helpful suggestions.

Author contributions SC, GM and AZ designed the study and wrote the protocol. SC, RR, GD and AZ managed the literature searches. SC coordinated the four participant Italian sites and was responsible for the national data management and collection. AM and PC performed the statistical analysis. SC and RR wrote the first draft of the manuscript. All authors contributed to collection of data and have approved the final manuscript.

Availability of data and materials On request to the corresponding author.

Declarations

Conflict of interest Dr. Carucci had collaborations within projects from the European Union (7th Framework Program) and as sub- investigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen Cilag and Angelini. Travel support from Fidia Farmaceutici. Prof. Contu has no conflicts of interest to declare. Prof. Curatolo has no conflicts of interest to declare. Dr. Demuru has no conflicts of interest to declare. Prof. Gagliano was in the advisory boards for Eli Lilly and Shire. She is/has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen and Otsuka. She has been speaker for Novartis, Eli Lilly and Shire. Dr. Grelloni has no conflicts of interest to declare. Dr. Lamberti has a collaboration as subinvestigator in sponsored clinical trial by Janssen Cilag. Dr. Liboni has no conflicts of interest to declare. Dr. Masi has received institutional research grants from Lundbeck and Humana, was in an advisory board for Angelini, and has been speaker for Angelini, FB Health, Janssen, Lundbeck, and Otsuka. Prof. Mereu has no conflicts of interest to declare. Dr. Romaniello had a collaboration as sub-investigator in sponsored clinical trial by Lundbeck. Prof. Zuddas served in an advisory or consultancy role for Angelini, EduPharma, Servier, Taked. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier and Shire. He received royalties from Giunti OS, Oxford University Press. The present work is unrelated to the above grants and relationships.

Ethics approval This study was performed in line with the principles of the 1964 Declaration of Helsinki and its later amendments. The trial was approved by the Ethical Committee of the Cagliari University Hospital (resolution n. 662; September 22nd, 2011). At the time of the Ethical submission, according to the clinical trial Italian law, registration was not mandatory for food additive as Omega 3/6 were then classified.

Consent to participate Participation in the study was on voluntary basis. Before any study procedure, parents or a legally authorized representative of the subject signed the informed consent. Children provided their written assent.

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International Journal of
Environmental Research and Public Health

MDPI

Article

The Strengths and Difficulties Questionnaire as a Valuable Screening Tool for Identifying Core Symptoms and Behavioural and Emotional Problems in Children with Neuropsychiatric Disorders

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Abstract: The Strengths and Difficulties Questionnaire (SDQ) is a worldwide questionnaire used for the early identification of behavioural/emotional symptoms in children and adolescents with neuropsychiatric disorders. Although its prognostic power has been studied, it has not yet been tested whether SDQ: (i) can identify pathognomonic symptoms across a variety of neurodevelopmental and neuropsychiatric disorders, (ii) can capture emotional and behavioural problems associated with the main diagnosis, as well as shared transdiagnostic dimensions, and (iii) can detect changes in symptomatology with age. The present study evaluated nearly 1000 children and adolescents overall with Global Developmental Delay (GDD), Intellectual Disability (ID), Language Disorder (LD), Specific Learning Disorder (SLD), Autism Spectrum Disorder (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), Mood Disorder (MD), Anxiety Disorder (AD), and Eating Disorders (ED). We found that SDQ: (i) can identify the core symptoms in children with ASD, ADHD, MD, and AD via specific subscales; (ii) can capture the associated emotional and behavioural symptoms in children with LD, GDD, ID, SLD, and ED; and (iii) can detect changes in the symptomatology, especially for GDD, LD, ASD, ADHD, and AD. SDQ is also able to recognise the transdiagnostic dimensions across disorders. Our results underscore the potential of SDQ to specifically differentiate and identify behavioural/emotional profiles associated with clinical diagnosis.

Keywords: transdiagnostic; mental health; assessment; psychopathology; screening

Citation: Grasso, M.; Lazzaro, G.; Demaria, F.; Menghini, D.; Vicari, S. The Strengths and Difficulties Questionnaire as a Valuable Screening Tool for Identifying Core Symptoms and Behavioural and Emotional Problems in Children with Neuropsychiatric Disorders. *Int. J. Environ. Res. Public Health* **2022**, *19*, 7731. https://doi.org/10.3390/ijerph19137731

Academic Editors: Jorge Osma, María Vicenta Navarro-Haro and Amanda Díaz-García

Received: 12 May 2022
Accepted: 21 June 2022
Published: 23 June 2022

1. Introduction

Childhood and adolescence are sensitive periods characterised by determinant changes in the physical, emotional, and social domains [1,2]. During these periods, individuals are often exposed to high levels of psychological distress that may compromise their psychophysics well-being and make them more vulnerable to the development of neuropsychiatric disorders [3]. Neuropsychiatric disorders are often described as the leading cause of disability in youths worldwide, with significant costs to families, individuals, and national health systems [4] and harmful consequences during development.

Globally, an estimated 10–20% of youths usually experience mental health conditions that often remain underdiagnosed and undertreated [3], with detrimental consequences during development. An example is Attention Deficit/Hyperactivity Disorder (ADHD), one of the most common and disabling neurodevelopmental disorders of childhood. When misdiagnosed and never treated, ADHD persists into adulthood in association with aggravating comorbidities, including mood disorders (MD) and anxiety disorders (AD),

conduct disorder, antisocial personality and substance abuse, bipolar disorder, impulse control disorders, and even suicidal behaviour [5–9]. Similarly, if left unrecognised and untreated during the developmental ages, neuropsychiatric disorders such as MD and AD are likely to be steady or even to become more acute from adolescence to midlife, becoming increasingly difficult to treat as time goes on [10–12].

Of importance, most neurodevelopmental disorders, including Autism Spectrum Disorders (ASD) and Intellectual Disability (ID), as well as Specific Learning Disorders (SLD) and Language Disorders (LD), are commonly associated with poorly recognised behavioural and emotional problems [13–20] and not infrequently result in psychiatric disorders.

Early screening offers an important opportunity to rapidly detect and treat behavioural and emotional symptoms. Therefore, it is not surprising that, over the past two decades, several studies [21–25] have attempted to identify the early neuropsychiatric symptoms in children and adolescents via psychological questionnaires.

One worldwide screening tool used to detect neuropsychiatric symptoms in children and adolescents is the Strengths and Difficulties Questionnaire (SDQ) [26]. With good psychometric properties [23,27,28], the SDQ is a brief flexible questionnaire used for the early screening and identification of pathognomonic symptoms or behavioural and emotional symptoms associated with neuropsychiatric disorders, which require further evaluation with a structured neuropsychiatric examination. The SDQ has been employed in several studies to screen for neuropsychiatric disorders, including ADHD [29,30] and ASD [31], or to identify emotional and behavioural problems in children and adolescents with neurodevelopmental disorders [21,22,25,32], such as SLD [33] and ID [34].

Furthermore, a recent longitudinal study [35] demonstrated the predictive validity of the SDQ in a population of 1176 children. Specifically, pre-schoolers with the highest scores on the SDQ were at a higher risk of having symptoms of ADHD, behavioural disorders (oppositional defiant disorder or conduct disorder), and emotional disorders (depression or AD) in preadolescence.

A recent study by Vugteveen et al. [36] investigated to what extent specific SDQ profiles were associated with neuropsychiatric diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria [37] among diagnosed adolescents. The results showed that SDQ identified pathognomonic symptoms that matched the DSM-IV diagnoses for almost 90% of adolescents (i.e., ADHD, conduct disorder/oppositional defiant disorder, ASD, MD, and AD). Moreover, SDQ recognised additional emotional and behavioural problems that were comorbid with the core diagnoses and were shared transdiagnostically. However, the study considered only a selected range of age (12–17 years) and disregarded several neurodevelopmental disorders, such as SLD, ID, and LD, and neuropsychiatric disorders, such as Eating Disorders (ED) [36].

The present study aimed to investigate whether the SDQ is a reliable and valid tool for identifying the relevant symptoms in nearly one thousand children and adolescents diagnosed with a variety of neurodevelopmental and neuropsychiatric disorders. The present study also aimed to explore whether the SDQ could be considered a screening tool for the recognition of shared transdiagnostic dimensions in terms of the behavioural and emotional problems associated with neurodevelopmental and neuropsychiatric disorders. Finally, the present study aimed to test whether the SDQ is a sensitive measure to capture changes in symptomatology with age.

If the SDQ were a reliable and valid screening questionnaire, we would expect that it could detect symptoms of neuropsychiatric disorders (e.g., hyperactive symptoms for ADHD; emotional problems for MD and AD; and peer and prosocial problems for ASD), as well as associated behavioural and emotional problems (e.g., conduct disorders for ADHD, emotional problems for ADHD and ED, and peer and prosocial problems for ID).

2. Materials and Methods

2.1. Participants and Procedures

Out of 1000 children and adolescents attending the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital for an initial screening neuropsychiatric visit, a group of 952 participants were further referred for an in-depth neuropsychiatric examination and selected between December 2016 and March 2019 (Males, M/Females, F: 606/346; age range: 0.7–19.1 years; mean age ± standard deviation (SD): 8.9 ± 4.8 years).

Participants underwent a child neuropsychiatric examination conducted by experienced developmental neuropsychiatrists. The clinical diagnosis derived from the developmental history and the clinical examination based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria [38].

Participants were divided into nine groups based on the clinical diagnosis according to the DSM-5 criteria [38] as follows: 113 participants showed Global Developmental Delay (GDD; M/F: 89/24; 4.2 ± 1.8 years), 45 participants had ID (M/F: 27/18; 12.4 ± 4.5 years), 172 LD (M/F: 122/50; 4.3 ± 1.6 years), 187 SLD (M/F: 96/91; 12 ± 3 years), 69 ASD (M/F: 54/15; 7.3 ± 4.4. years), 131 ADHD (M/F: 110/21; 8.5 ± 3.7 years), 51 MD (M/F: 20/31; 13.7 ± 3.6 years), 151 AD, including obsessive-compulsive disorder and tic disorder (M/F: 82/69; 12 ± 4.1 years), and 33 ED (M/F: 6/27; 14 ± 3.7 years).

2.2. Measures

Strengths and Difficulties Questionnaire

SDQ [39] is a brief 25-item behavioural screening questionnaire for children and adolescents asking the parent to what extent both the positive and negative psychological attributes of the child were true in the past six months using a 3-point Likert scale (0 = not true, 1 = somewhat true, and 2 = certainly true). The SDQ consists of five subscales, each consisting of five items: Emotional Problems, Conduct Problems, Hyperactivity/Inattention, Peer Problems, and Prosocial Behaviour. In the study, we used raw SDQ scores, according to the original three-band categorisation (normal, borderline, and clinical) [39]. We chose the parent form of SDQ, because it would seem that the parents, as informants, are more cautious in describing their children's problems compared to the self-reports of youngers [40].

The SDQ has been validated for use in many countries across different languages, and it is commonly adopted in many European and Extra-European countries, including the United Kingdom [27], Finland [40], Germany [41], Sweden [42], and Italy [43,44]. All published studies confirmed the good psychometric properties of the instrument and the excellent balance between the time taken to fill it in and the amount of information collected. The SDQ can be obtained without charge from a website (https://www.sdqinfo.com) (accessed on 1 December 2016), and therefore, it is practical and free to use within clinical settings.

2.3. Statistical Analysis

The percentage of participants who obtained normal, borderline, and clinical scores in each SDQ subscale was calculated.

Diagnostic groups (GDD vs. ID vs. LD vs. SLD vs. ASD vs. ADHD vs. MD vs. AD vs. ED) were compared on the SDQ subscales (Emotional Problems vs. Conduct Problems vs. Hyperactivity/Inattention vs. Peer Problems vs. and Prosocial Behaviour) using the Kruskal–Wallis ANOVA, because the assumption of normality was not fulfilled. Bonferroni's correction for multiple comparisons was applied to account for the five comparisons of diagnostic groups on each SDQ subscale, and a p-value ≤ 0.01 was considered significant (p-value = 0.05/5 SDQ subscales = 0.01). Post hoc comparisons across the diagnostic groups on each SDQ subscale were run by using the mean ranks of all pairs of groups [45].

To test whether the scores on the SDQ subscales were age-dependent, Spearman's correlations (*rho*) between age and the scores on the SDQ subscales were run separately for each diagnostic group. Bonferroni's correction for multiple comparisons was applied to account for the nine

comparisons of the diagnostic groups within each SDQ subscale, and a p-value ≤ 0.0055 was considered significant (p-value = 0.05/9 and the diagnostic groups = 0.0055).

3. Results

Table 1 shows the percentage of children and adolescents who showed normal, borderline, and clinical scores on the SDQ subscales in each Diagnostic Group, as well as the mean and standard deviations (SD) of the scores in the SDQ subscales and post hoc comparisons.

The Diagnostic Groups differed in each SDQ subscale analysed: the Emotional Problems Subscale ($H(8) = 166.15$, $p < 0.001$), Conduct Problem Subscale ($H(8) = 87.39$, $p < 0.0001$), Hyperactivity/Inattention Subscale ($H(8) = 144.11$; $p < 0.001$), Peer Problems Subscale ($H(8) = 110.47$; $p < 0.001$), and Prosocial Behaviour Subscale ($H(8) = 132.47$; $p < 0.001$).

3.1. Global Developmental Delay

With the exception of the Emotional Problems Subscale, at least half of the participants with GDD showed a prevalence of clinical/borderline scores in the remaining SDQ subscales.

Comparisons between groups revealed that participants with GDD showed significantly worse scores in the Hyperactivity/Inattention Subscale than the groups with LD ($p < 0.0001$), AD ($p < 0.001$), and ED ($p < 0.0001$) but not compared to ID ($p = 0.99$), ASD ($p = 0.99$), MD ($p = 0.99$), SLD ($p = 0.03$), and ADHD ($p = 0.04$) groups.

In the Peer Problems Subscale, they also obtained worse scores than the SLD group ($p = 0.009$) and better scores than groups with ASD ($p < 0.0001$) but did not significantly differ from ID ($p = 0.90$), LD ($p = 0.03$), ADHD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

Further, they obtained significantly worse scores in the Prosocial Behaviour Subscale than the groups with LD ($p < 0.0001$), SLD ($p < 0.0001$), MD ($p = 0.005$), AD ($p < 0.0001$), and ED ($p < 0.001$) but not than with ID ($p = 0.95$), ASD ($p = 0.99$), and ADHD ($p = 0.02$).

Conversely, they obtained significantly better scores in the Emotional Problems Subscale than the groups with MD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p < 0.001$) but not than ID ($p = 0.05$), LD ($p = 0.40$), SLD ($p = 0.04$), ASD ($p = 0.99$), and ADHD ($p = 0.48$) groups.

In addition, they obtained significantly better scores in the Conduct Problems Subscale only compared to the ADHD group ($p < 0.0001$) but did not differ from the ID, LD, SLD ASD, MD, AD, and ED (p always = 0.99) groups.

3.2. Intellectual Disability

With the exception of the Prosocial Behaviour Subscale, the majority of the participants with ID showed clinical or borderline scores in the Emotional Problems, Conduct Problems, Hyperactivity/Inattention, and Peer Problem Subscales. Of note, the highest percentage of clinical scores was in the Peer Problems Subscale (60%).

A comparison between the groups revealed that participants with ID exhibited significantly worse scores in the Emotional Problems Subscale than the groups with only LD ($p < 0.0001$) but not compared to GDD ($p = 0.05$), SLD ($p = 0.99$), ASD ($p = 0.99$), ADHD ($p = 0.99$), AD ($p = 0.99$), ED ($p = 0.99$), and MD ($p = 0.02$) groups.

Similarly, in the Hyperactivity/Inattention Subscale, they exhibited significantly worse scores than the groups with only ED ($p = 0.002$) but did not differ from the groups with GDD ($p = 0.99$), LD ($p = 0.12$), SLD ($p = 0.99$), ASD ($p = 0.99$), ADHD ($p = 0.08$), MD ($p = 0.99$), and AD ($p = 0.37$).

In the Peer Problems Subscale, they obtained significantly worse scores than the groups with LD ($p < 0.0001$) and SLD ($p < 0.0001$) but did not differ from the groups with AD ($p = 0.01$), GDD ($p = 0.90$), ASD ($p = 0.99$), ADHD ($p = 0.20$), MD ($p = 0.99$), and ED ($p = 0.45$).

Table 1. Prevalence (%) and number of children and adolescents who showed normal, borderline, and clinical scores in the SDQ subscales for each diagnostic group, as well as the mean and standard deviation (SD) of the scores in the SDQ subscales and Post hoc comparisons.

Diagnostic Groups	**Emotional Problems** normal (0–3) borderline (4) clinical (5–10)	**Conduct Problems** normal (0–2) borderline (3) clinical (4–10)	**Hyperactivity/Inattention** normal (0–5) borderline (6) clinical (7–10)	**Peer Problems** normal (0–2) borderline (3) clinical (4–10)	**Prosocial Behaviour** normal (0–4) borderline (5) clinical (6–10)
	M (SD) Post hoc comparisons	M (SD) Post hoc comparisons	M (SD) Post hoc comparisons	M (SD) Post hoc comparisons	M (SD) Post hoc comparisons
Global Developmental Delay	N = 64.6% (73) B = 13.3% (15) C = 22.1% (25)	N = 50.4% (57) B = 17.7% (20) C = 31.9% (36)	N = 48.7% (55) B = 13.3% (15) C = 38% (43)	N = 40.7% (46) B = 17.7% (20) C = 41.6% (47)	N = 56.6% (64) B = 11.5% (13) C = 31.9% (36)
	2.8 (2.15) <MD *** <AD *** <ED **	2.9 (2.17) <ADHD ***	5.5 (2.76) >LD *** >AD ** >ED ***	3.1 (2.06) >SLD * <ASD ***	4.4 (2.66) >LD *** >SLD *** >MD * >AD *** >ED **
Intellectual Disability	N = 44.4% (20)B = 6.7% (3) C = 48.9% (22)	N = 40% (18)B = 11.1% (5) C = 48.9% (22)	N = 53.3% (24)B = 11.1% (5) C = 35.6% (16)	N = 24.4% (11)B = 15.6% (7) C = 60% (27)	N = 66.7% (30)B = 6.6% (3) C = 26.7% (12)
	4.3 (2.80) >LD ***	3.4 (2.44)	5.2 (3.03) >ED *	4.2 (2.56) >LD *** >SLD ***	3.6 (3.01) <ASD *
Language Disorder	N = 78.5% (135) B = 11% (19) C = 10.5% (18)	N = 57.6% (99) B = 18% (31) C = 24.4% (42)	N = 75.6% (130) B = 9.9% (17) C = 14.5% (25)	N = 58.7% (101) B = 17.4% (30) C = 23.9% (41)	N = 80.2% (138) B = 9.3% (16) C = 10.5% (18)
	2.0 (1.87) <ID *** <SLD *** <ASD * <ADHD *** <MD *** <AD *** <ED ***	2.4 (1.89) <ADHD ***	3.8 (2.50) <GDD *** <ASD *** <ADHD ***	2.2 (1.88) <ID *** <ASD *** <MD ***	2.7 (2.23) <GDD *** <ASD ***

Table 1. *Cont.*

Specific Learning Disorder	N = 46% (86) B = 15.5% (29) C = 38.5% (72)	N = 56.2% (105) B = 16.5% (31) C = 27.3% (51)	N = 67.4% (126) B = 10.7% (20) C = 21.9% (41)	N = 64.7% (121) B = 13.9% (26) C = 21.4% (40)	N = 88.2% (165) B = 4.8% (9) C = 7% (13)
	3.7 (2.41) >LD *** <MD ***	2.5 (2.03) <ADHD ***	4.4 (2.70) <ASD ** <ADHD ***	2.2 (2.14) <GDD * <ID *** <ASD *** <MD ***	2.1 (2.10) <GDD *** <ASD *** <ADHD ***
Autism Spectrum Disorder	N = 53.6% (37) B = 18.8% (13) C = 27.6% (19)	N = 55.1% (38) B = 15.9% (11) C = 29% (20)	N = 34.8% (24) B = 24.6% (17) C = 40.6% (28)	N = 11.6% (8) B = 18.8% (13) C = 69.6% (48)	N = 39.1% (27) B = 11.6% (8) C = 49.3% (34)
	3.4 (2.47) >LD * <MD ***	2.7 (1.93) <ADHD ***	6.1 (1.94) >LD *** >AD *** >ED *** >SLD **	4.9 (2.06) >GDD *** >LD *** >SLD *** >ADHD *** >AD *** >ED **	5.3 (2.46) >ID * >LD *** >SLD *** >ADHD *** >MD *** >AD *** >ED ***
Attention Deficit/ Hyperactivity Disorder	N = 51.9% (60) B = 9.9% (13) C = 38.2% (50)	N = 19.8% (26) B = 13% (17) C = 67.2% (88)	N = 29% (38) B = 15.3% (20) C = 55.7% (73)	N = 47.3% (62) B = 13.7% (18) C = 39% (51)	N = 70.2% (92) B = 14.5% (19) C = 15.3% (20)
	3.6 (2.62) >LD *** <MD ***	4.5 (2.19) >GDD *** >LD *** >SLD *** >ASD *** >AD *** >ED **	6.7 (2.44) >LD *** >SLD *** >AD *** >ED ***	2.9 (2.18) <ASD ***	3.1 (2.37) >SLD ** <ASD ***
Mood Disorder	N = 13.7% (7) B = 11.8% (6) C = 74.5% (38)	N = 31.4% (16) B = 27.4% (14) C = 41.2% (21)	N = 62.7% (32) B = 9.8% (5) C = 27.5% (14)	N = 27.5% (14) B = 19.6% (10) C = 52.9% (27)	N = 82.4% (42) B = 7.8% (4) C = 9.8% (5)
	6.5 (2.50) >GDD *** >LD ***>SLD *** >ASD *** >ADHD ***	3.5 (2.10)	5.1 (2.70) >ED *	4.0 (2.40) >LD *** >SLD ***	2.6 (1.90) <GDD * <ASD ***

Table 1. *Cont.*

	N = 33.8% (51) B = 11.2% (17) C = 55% (83)	N = 48.3% (73) B = 19.2% (29) C = 32.5% (49)	N = 72.8% (110) B = 9.3% (14) C = 17.9% (27)	N = 51.6% (78) B = 13.3% (20) C = 35.1% (53)	N = 83.4% (126) B = 6.6% (10) C = 10% (15)
Anxiety Disorder	4.8 (2.83) >GDD *** >LD ***	2.9 (2.11) <ADHD ***	4.0 (2.64) <GDD ** <ASD *** <ADHD ***	2.7 (2.26) <ASD ***	2.4 (2.18) <GDD *** <ASD ***
	N = 27.3% (9) B = 18.2% (6) C = 54.5% (18)	N = 45.5% (15) B = 24.2% (8) C = 30.3% (10)	N = 87.9% (29) B = 3% (1) C = 9.1% (3)	N = 51.5% (17) B = 15.2% (5) C = 33.3% (11)	N = 90.9% (30) B = 3% (1) C = 6.1% (2)
Eating Disorders	5.1 (2.46) >GDD ** >LD ***	2.8 (2.37) <ADHD *	2.6 (2.60) <GDD *** <ID ** <ASD *** <ADHD *** <MD *	2.8 (2.24) <ASD **	2.0 (1.83) <GDD ** <ASD ***

After Bonferroni's correction: * p-value < 0.01; ** p-value < 0.001; *** p-value < 0.0001. Only significant differences are reported. N: normal; B: borderline; C: clinical; <: better scores than those of other groups; >: worse scores than those of other groups.

Conversely, they obtained significantly better scores in the Prosocial Behaviour Subscale than the groups with only ASD ($p = 0.006$) but did not differ from the SLD ($p = 0.04$), GDD ($p = 0.95$), LD ($p = 0.99$), ADHD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.80$), and ED ($p = 0.90$) groups, while, in the Conduct Problems Subscale, their scores did not significantly differ from the GDD ($p = 0.99$), LD ($p = 0.21$), SLD ($p = 0.50$), ASD ($p = 0.99$), ADHD ($p = 0.23$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.3. Language Disorder

In all SDQ Subscales, the majority of the participants with LD showed normal scores.

A comparison between groups revealed that participants with LD exhibited significantly better scores in the Emotional Problems Subscale than the group with ID ($p < 0.0001$), SLD ($p < 0.0001$), ASD ($p < 0.01$), ADHD ($p < 0.0001$), MD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p < 0.0001$) but did not differ from the group with GDD ($p = 0.40$).

In the Conduct Problems Subscale, they obtained significantly better scores than the group with only ADHD ($p < 0.0001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.21$), SLD ($p = 0.99$), ASD ($p = 0.99$), MD ($p = 0.05$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

Similarly, they showed significantly better scores in the Hyperactivity/Inattention Subscale than the group with GDD ($p < 0.0001$), ASD ($p < 0.0001$), and ADHD ($p < 0.0001$) but did not differ from the ID ($p = 0.12$), SLD ($p = 0.99$), MD ($p = 0.21$), AD ($p = 0.99$), and ED ($p = 0.86$) groups.

Further, they exhibited significantly better scores in the Peer Problems Subscale than the group with ID ($p < 0.0001$), ASD ($p < 0.0001$), and MD ($p < 0.0001$) but did not differ from the GDD ($p = 0.03$), SLD ($p = 0.99$), ADHD ($p = 0.23$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

In the Prosocial Behaviour Subscale, they obtained significantly better scores than the group with GDD ($p < 0.0001$) and ASD ($p < 0.0001$) but did not differ from the ID ($p = 0.99$), SLD ($p = 0.17$), ADHD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.4. Specific Learning Disorder

With the exception of the Emotional Problems Subscale, participants with SLD obtained normal scores in the remaining SDQ subscales.

A comparison between groups revealed that the participants with SLD exhibited significantly better scores in the Emotional Problems Subscale than the group with MD ($p < 0.0001$), while obtaining significantly worse scores than the LD group ($p < 0.0001$). However, they did not differ from the GDD ($p = 0.04$), ID ($p = 0.99$), ASD ($p = 0.99$), ADHD ($p = 0.99$), AD ($p = 0.05$), and ED ($p = 0.50$) groups.

In the Conduct Problems Subscale, they displayed significantly better scores than the group with ADHD ($p < 0.0001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.50$), LD ($p = 0.99$), ASD ($p = 0.99$), MD ($p = 0.15$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

Similarly, they obtained significantly better scores in the Hyperactivity/Inattention Subscale than the group with ASD ($p < 0.001$) and ADHD ($p < 0.0001$) but did not differ from the GDD ($p = 0.03$), ID ($p = 0.99$), LD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.02$) groups.

In the Peer Problems Subscale, they also showed significantly better scores than the group with GDD ($p = 0.009$), ID ($p < 0.0001$), ASD ($p < 0.0001$), and MD ($p < 0.0001$) but did not differ from the LD ($p = 0.99$), ADHD ($p = 0.07$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

Further, in the Prosocial Behaviour Subscale, they obtained significantly better scores than the group with GDD ($p < 0.0001$), ASD ($p < 0.0001$), and ADHD ($p = 0.001$) but did not differ from the ID ($p = 0.04$), LD ($p = 0.17$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.5. Autism Spectrum Disorder

The majority of participants with ASD showed clinical/borderline scores in the Hyperactivity/Inattention, Peer Problems, and Prosocial Behaviour Subscales. Especially in the Problems with Peers Subscale, the percentage of clinical scores was particularly substantial, reaching 69.6%.

A comparison between the groups revealed that participants with ASD exhibited significantly worse scores than the group with LD ($p = 0.003$) and better scores than the MD group ($p < 0.0001$) in the Emotional Problems Subscale, while they did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), SLD ($p = 0.99$), AD ($p = 0.03$), and ED ($p = 0.16$) groups.

In the Hyperactivity/Inattention Subscale, they displayed significantly worse scores than the groups with LD ($p < 0.0001$), AD ($p < 0.0001$), ED ($p < 0.0001$), and SLD ($p < 0.001$), but they did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), ADHD ($p = 0.99$), and MD ($p = 0.99$) groups.

In the Peer Problems Subscale, they also obtained significantly worse scores than the groups with GDD ($p < 0.0001$), LD ($p < 0.0001$), SLD ($p < 0.0001$), ADHD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p < 0.001$), but they did not differ from the MD group ($p = 0.99$).

Further, they showed significantly worse scores in the Prosocial Behaviour Subscale than the groups with ID ($p = 0.006$), LD ($p < 0.0001$), SLD ($p < 0.0001$), ADHD ($p < 0.0001$), MD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p < 0.0001$) but did not differ from the GDD group ($p = 0.99$).

Conversely, they obtained significantly better scores in the Conduct Problems Subscale than the group with ADHD ($p < 0.0001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), LD ($p = 0.99$), SLD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.6. Attention Deficit/Hyperactivity Disorder

On the Conduct Problems and Hyperactivity/Inattention Subscales, more than two-thirds of the children and adolescents with ADHD showed borderline and clinical scores.

A comparison between the groups revealed that participants with ADHD exhibited significantly worse scores in the Emotional Problems Subscale than the group with LD ($p < 0.0001$) and significantly better scores than the group with MD ($p < 0.0001$). However, no other differences were found with the GDD ($p = 0.48$), ID ($p = 0.99$), SLD ($p = 0.99$), ASD ($p = 0.99$), AD ($p = 0.02$), and ED ($p = 0.22$) groups.

In the Conduct Problems Subscale, they displayed significantly worse scores than the groups with GDD ($p < 0.0001$), LD ($p < 0.0001$), SLD ($p < 0.0001$), ASD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p = 0.003$), but they did not differ from the ID ($p = 0.23$) and MD ($p = 0.34$) groups.

Similarly, in the Hyperactivity/Inattention Subscale, they obtained significantly worse scores than the groups with LD ($p < 0.0001$), SLD ($p < 0.0001$), AD ($p < 0.0001$), and ED ($p < 0.0001$) but did not differ from the GDD ($p = 0.04$), ID ($p = 0.08$), ASD ($p = 0.99$), and MD ($p = 0.01$) groups.

In the Prosocial Behaviour Subscale, the group with ADHD displayed significantly worse scores than the group with SLD ($p = 0.001$) and significantly better scores than the group with ASD ($p < 0.0001$). However, in the Prosocial Behaviour Subscale, they did not differ from the GDD ($p = 0.01$), ID ($p = 0.99$), LD ($p = 0.99$), MD ($p = 0.99$), AD ($p = 0.22$), and ED ($p = 0.72$) groups.

Conversely, they displayed significantly better scores in the Peer Problems Subscale than the group with ASD ($p < 0.0001$) but not compared to the GDD ($p = 0.99$), ID ($p = 0.20$), LD ($p = 0.23$), SLD ($p = 0.07$), MD ($p = 0.32$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.7. Mood Disorder

With the exception of the Hyperactivity/Inattention and Prosocial Behaviour Subscales, the majority of the participants with MD obtained clinical or borderline scores in the Emotional Problems, Conduct Problems, and Peer Problems Subscales. Of note, the percentage of clinical scores reached 74.5% on the Emotional Problems Subscale.

A comparison between the groups revealed that the participants with MD exhibited significantly worse scores in the Emotional Problems Subscale than the groups with GDD ($p < 0.0001$), LD ($p < 0.0001$), SLD ($p < 0.0001$), ASD ($p < 0.0001$), and ADHD ($p < 0.0001$) but did not differ from the groups with ID ($p = 0.02$), AD ($p = 0.03$), and ED ($p = 0.99$).

In the Hyperactivity/Inattention Subscale, they displayed significantly worse scores than the ED group ($p = 0.004$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), LD ($p = 0.99$), SLD ($p = 0.99$), ASD ($p = 0.99$), ADHD ($p = 0.01$), and AD ($p = 0.66$) groups.

Further, in the Peer Problems Subscale, they showed significantly worse scores than the groups with LD ($p < 0.0001$) and SLD ($p < 0.0001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), ASD ($p = 0.99$), ADHD ($p = 0.32$), AD ($p = 0.02$), and ED ($p = 0.68$) groups.

Conversely, in the Prosocial Behaviour Subscale, they showed significantly better scores than the groups with GDD ($p = 0.005$) and ASD ($p < 0.0001$) but did not differ from the ID ($p = 0.99$), LD ($p = 0.99$), SLD ($p = 0.99$), ADHD ($p = 0.99$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

In the Conduct Problems Subscale, no differences were found for the MD group compared to the GDD ($p = 0.99$), ID ($p = 0.99$), LD ($p = 0.05$), SLD ($p = 0.15$), ASD ($p = 0.99$), ADHD ($p = 0.34$), AD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.8. Anxiety Disorder

As expected, two-thirds of the participants with AD obtained clinical or borderline scores in the Emotional Problems Subscale. Approximately half of them also obtained clinical or borderline scores in the Conduct Problems Subscale.

A comparison between the groups revealed that participants with AD exhibited significantly worse scores only in the Emotional Problems Subscale than the groups with GDD ($p < 0.0001$) and LD ($p < 0.0001$), but they did not differ from the groups with ID ($p = 0.99$), SLD ($p = 0.05$), ASD ($p = 0.03$), ADHD ($p = 0.02$), MD ($p = 0.03$), and ED ($p = 0.99$).

Conversely, they showed significantly better scores in the Conduct Problems Subscale than the ADHD group ($p < 0.0001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.99$), LD ($p = 0.99$), SLD ($p = 0.99$), ASD ($p = 0.99$), MD ($p = 0.99$), and ED ($p = 0.99$) groups.

Similarly, in the Hyperactivity Subscale, they obtained significantly better scores than the groups with GDD ($p < 0.001$), ASD ($p < 0.0001$), and ADHD ($p < 0.0001$), but no differences emerged compared to the groups with ID ($p = 0.36$), LD ($p = 0.99$), SLD ($p = 0.99$), MD ($p = 0.66$), and ED ($p = 0.41$).

In the Peer Problems Subscale, they also displayed significantly better scores than the group with ASD ($p < 0.0001$) but not compared to the GDD ($p = 0.99$), ID ($p = 0.01$), LD ($p = 0.99$), SLD ($p = 0.99$), ADHD ($p = 0.99$), MD ($p = 0.02$), and ED ($p = 0.99$) groups.

Further, they obtained significantly better scores in the Prosocial Behaviour Subscale than the groups with GDD ($p < 0.0001$) and ASD ($p < 0.0001$), but they did not differ from the ID ($p = 0.80$), LD ($p = 0.99$), SLD ($p = 0.99$), ADHD ($p = 0.22$), MD ($p = 0.99$), and ED ($p = 0.99$) groups.

3.9. Eating Disorders

Three-quarters of the participants with ED obtained clinical or borderline scores in the Emotional Problems Subscale, and more than half of them also obtained clinical or borderline scores in the Conduct Problems Subscale.

A comparison between the groups revealed that the participants with ED displayed significantly worse scores in the Emotional Problems Subscale than the groups with GDD ($p < 0.001$) and LD ($p < 0.0001$) but did not differ from the groups with ID ($p = 0.99$), SLD ($p = 0.49$), ASD ($p = 0.16$), ADHD ($p = 0.22$), MD ($p = 0.99$), and AD ($p = 0.99$).

Conversely, they obtained significantly better scores in the Conduct Problems Subscale than the group with only ADHD ($p < 0.003$), while they were not different from the GDD ($p = 0.99$), ID ($p = 0.99$), LD ($p = 0.99$), SLD ($p = 0.99$), ASD ($p = 0.99$), MD ($p = 0.99$), and AD ($p = 0.99$) groups.

In the Hyperactivity/Inattention Subscale, they also showed significantly better scores than the groups with GDD ($p < 0.0001$), ID ($p = 0.002$), ASD ($p < 0.0001$), ADHD ($p < 0.0001$), and MD ($p < 0.01$) but did not differ from the LD ($p = 0.86$), SLD ($p = 0.02$), and AD ($p = 0.41$) groups.

Similarly, they obtained significantly better scores in the Peer Problems Subscale than the group with ASD ($p < 0.001$) but did not differ from the GDD ($p = 0.99$), ID ($p = 0.45$), LD ($p = 0.99$), SLD ($p = 0.99$), ADHD ($p = 0.99$), MD ($p = 0.68$), and AD ($p = 0.99$) groups.

They also exhibited significantly better scores in the Prosocial Behaviour Subscale than the groups with GDD ($p < 0.001$) and ASD ($p < 0.0001$), but they did not differ from the ID ($p = 0.90$), LD ($p = 0.99$), SLD ($p = 0.99$), ADHD ($p = 0.72$), MD ($p = 0.99$), and AD ($p = 0.99$) groups.

3.10. Correlations between Age and SDQ Subscales

As shown in Table 2, age was significantly and positively correlated to the scores in the Emotional Problems Subscale in the groups with GDD ($p < 0.0001$), LD ($p < 0.001$), ASD ($p < 0.001$), ADHD ($p < 0.001$), and AD ($p < 0.001$), meaning that they displayed worse scores in the Emotional Problems Subscale as they grew older.

Table 2. Correlations (Spearman's rho) between age and scores on the SDQ subscales for each diagnostic group.

		Emotional Problems *rho*	Conduct Problems *rho*	Hyperactivity/ Inattention *rho*	Peer Problems *rho*	Prosocial Behaviour *rho*
Age	Global Developmental Delay	0.45 ***	0.07	0.13	0.11	−0.40 ***
	Intellectual Disability	0.033	0.04	−0.19	0.30	0.06
	Language Disorders	0.25 **	−0.23 *	−0.03	−0.14	−0.41 ***
	Specific Learning Disorders	0.06	0.05	−0.04	0.07	0.02
	Autism Spectrum Disorder	0.43 **	0.13	0.22	0.35 *	−0.14
	Attention Deficit/Hyperactivity Disorder	0.33 ***	0.10	0.22	0.06	0.05
	Mood Disorder	0.13	0.12	−0.10	0.19	−0.07
	Anxiety Disorders	0.40 ***	0.05	−0.02	0.26 *	−0.18
	Eating Disorders	0.20	0.18	−0.08	−0.06	0.06

After Bonferroni's correction: * p-value < 0.005; ** p-value < 0.001; *** p-value < 0.0001.

Age was significantly and negatively correlated to the scores in the Conduct Problems Subscale in the group with LD ($p < 0.005$), meaning that they showed better scores in the Conduct Problems Subscale as they grew older.

Moreover, age was significantly and positively correlated to the scores in the Peer Problems Subscale in the groups with ASD and AD (p always < 0.005), meaning that they displayed worse scores in the Peer Problems Subscale as they grew older.

Last, age was significantly and negatively correlated to the scores in the Prosocial Behaviour Subscale in the groups with GDD and LD (p always < 0.0001), meaning that they displayed better scores in the Prosocial Behaviour Subscale as they grew older.

No further correlations were found in the other diagnostic groups between age and scores on the SDQ subscales, as well as in the Hyperactivity/Inattention Subscale (p always > 0.005).

4. Discussion

The current study demonstrated that the SDQ is a valid tool for identifying relevant symptoms in our children and adolescents in accordance with neurodevelopmental and neuropsychiatric diagnosis, as well as their changes with age.

Firstly, the SDQ has the potential to detect the core symptoms of both ASD and ADHD, as it includes subscales that detect the core symptoms of ASD (e.g., peer and prosocial behaviour problems), as well as the core symptoms of ADHD (e.g., hyperactivity/attention problems). Indeed, we found that children and adolescents with ASD generally scored significantly worse than other groups on the subscales assessing difficulties in communication and social cognition, such as the Peer Problems and Prosocial Behaviour Subscales, and that, in the same subscales, the majority of them exhibited at-risk or clinically relevant scores. Our results are in line with previous findings [31] that showed the sensitivity of the Peer Problems Subscale in identifying the core symptoms of ASD, a subscale in which children with ASD generally tend to score worse than other groups.

It has been widely recognised that children with ASD have severe problems with peers, as supported by studies documenting fewer friends at school, less reciprocity of friendship, and narrower social networks than their classmates [46,47]. The vast majority of the studies reported that youths with ASD are less liked by peers and more likely to be rejected, ignored, and purposely excluded by their peer group. We also found that problems with peers have a significant and positive association with age, meaning that such problems seem to increase with age. Accordingly, the evidence indicated that behavioural problems are usually augmented during development and that, even, the majority of adults with ASD present with significant, ongoing social impairments [48]. Of note, more than half of the participants with ASD also had borderline or clinical scores on the Hyperactivity/Inattention subscale, indicating that the SDQ is sensitive to detecting symptoms that are highly associated with ASD but, before the DSM-5, could not be diagnosed in a comorbidity. Indeed, while DSM-IV-TR [37] gave mutually exclusive diagnoses of ADHD and ASD, DSM-5 allows a dual diagnosis of ASD and ADHD behaviours, admitting the possibility of a comorbidity. Accordingly, the literature described that ASD co-occurs with ADHD in 40–70% of cases [49,50], especially in pre-schoolers. Moreover, we found that difficulties in emotional symptoms have a significant and positive association with age, meaning that these symptoms seem to be augmented along with age. Our findings on correlations seem to agree with a wide range of studies that support the high rates of psychiatric disorders in ASD, such as depression and anxiety, occurring more in adulthood [51].

Considering ADHD, we found that children and adolescents with ADHD generally scored significantly worse than other groups on the subscales assessing hyperactive behaviour/inattention and conduct problems and that, in the same subscales, more than two-thirds of them exhibited at-risk or clinically relevant scores. Our results provided evidence that the Hyperactivity/Inattention Subscale of the SDQ showed good agreement with the diagnostic criteria for ADHD, in agreement with previous studies [30,31]. Consistent with our findings on conduct problems, many studies have documented that ADHD and oppositional defiant disorder or conduct disorder often cooccur in about 40–60% of cases [52]. Previous studies examining the covariations between ADHD, oppositional defiant disorder, and conduct disorder emphasised that a common genetic risk factor explains more than half of the variance among the disorders [52,53].

The SDQ also detected symptoms that are highly associated with ADHD, such as well-documented dysfunctional social abilities. Accordingly, we found that more than half of children and adolescents with ADHD obtained at-risk or clinically relevant scores on the Peer Problems Subscale. According to previous studies [31], this subscale of the SDQ allows us to highlight an aspect that is often associated with ADHD and is one of the main factors responsible for the impaired quality of life of individuals with ADHD. It has been widely reported that one of the main problems of children with ADHD are difficulties in establishing mutual friendships, peer rejection, and bullying—mainly due to impulsivity and a poor attention span, leading to serious problems in developing satisfactory social relationships with peers [54,55].

In addition, we found that the emotional symptoms increase with age, as documented by our results on correlations. Several studies have demonstrated a high likelihood of finding the psychopathological conditions associated with ADHD, including emotional problems such as anxiety and major depression [56,57]. These conditions are documented especially in adolescence and adulthood [56]. Our findings on correlations are in line with these studies in ADHD documenting the emotional symptoms during childhood and adolescence that worsen and are accompanied by an increased risk of depression in adulthood [56].

Considering neuropsychiatric disorders, we found that the SDQ has the potential to also detect the core symptoms of both MD and AD. Indeed, the majority of our children and adolescents with MD and AD obtained at-risk or clinically relevant scores and scored significantly worse than other groups on the Emotional Problems Subscale of the SDQ. This subscale measures negative physical or cognitive symptoms (i.e., headache and worries) and mood state (i.e., sadness, tension for new situations, fears, and easily scared), in

accordance with the MD and AD diagnostic DSM-5 criteria [38]. Moreover, we observed that more than half of the participants with MD and AD exhibited at-risk or clinically relevant scores on the Conduct Problems Subscale, which assesses for disrupted behaviours, irritability, and emotional dysregulation symptoms, such as difficulties in managing anger and mood. In line with previous studies [58], we found that participants with MD and AD showed a similar profile in this subscale, obtaining worse scores than the other diagnostic groups. Besides the core symptoms of MD, we found that a relevant percentage of the children and adolescents with MD obtained at-risk or clinically relevant scores on the Peer Problems Subscale. It has been shown that children and adolescents with high levels of emotional problems, such as MD patients, have difficulty establishing meaningful and special relationships with peers [59].

Of note, correlations revealed that emotional and peer problems have significant and positive associations with age in participants with AD. This finding is in line with studies documenting that AD symptoms are greater with increasing age [60] and are accompanied by a change in social skills and motivation to socialise, which affects the creation, maintenance, and termination of social ties [61].

Considering children and adolescents with ED, we found that three-quarters of them had clinical scores on the Emotional Problems Subscale in agreement with studies reporting severe depressive symptoms, especially during adolescence in this population [62,63].

Regarding the other diagnostic groups for which the core symptoms could not be captured directly by the SDQ subscales, the tool was able to identify the transdiagnostic dimensions of neurodevelopmental and neuropsychiatric disorders, as well as changes in symptomatology with age.

Considering neurodevelopmental disorders, we found that scores on emotional problems in LD have a significant and positive association with age. Our results were in line with studies indicating that one area of particular vulnerability for children and adolescents with LD is emotional difficulties [64–66] that increase in symptomatology with age [67].

In addition, we found that participants with GDD and ID showed a rather similar profile on the Conduct Problems, Hyperactivity/Inattention, and Peer Problems Subscales. From a developmental perspective, we must consider that children presenting with GDD often result in ID, as is evident from the overlap in their symptomatology. The GDD and ID did not differ from the other neurodevelopmental disorders, such as ADHD and ASD, in the Hyperactivity/Inattention Subscale. Studies documented that children and adolescents with developmental disabilities were at a heightened risk for developing ADHD [68] and conduct problems [69]. In fact, behaviour disorders are common in children with cognitive delays, are often chronically disabling and can create problems in daily life. The SDQ has allowed us to also highlight these behavioural problems associated with disability and to guide parents toward the appropriate management and treatment of them. Similar to the other neurodevelopmental disorders we have discussed (i.e., ASD and ADHD), in groups with ID and GDD, developmental disabilities led to impaired social and relationship aspects, as documented by the worse scores on the Peer Problems Subscale. It should be noted that relational problems in GDD improve with growth, perhaps because the relational aspects are considered in therapeutic interventions [70]. In fact, for children whose cognitive abilities are impaired, the degree of relational problems can often be the difference between dependency and self-sufficiency, and interventions aimed at decreasing an individual's vulnerability through social skill development are commonly critical components of any therapeutic plan. Differently from GDD, participants with ID did not differ from psychopathological disorders, such as MD, AD, and ED, in the Emotional Problems Subscale. This result was in line with previous evidence showing in individuals with ID levels of emotional symptoms approximately three to four times higher than those of typically developing children [71]. Indeed, children with ID are at greater risk for MD and AD, especially AD, one of the most common forms of social distress found in ID [72,73].

Regarding SLD, more than half of the participants with SLD showed borderline or clinical scores in the Emotional Problems Subscales. The presence of internalising symptoms (i.e., depression and anxiety) in SLD have been well-documented in the literature [74–76]. Emotional problems in SLD are usually a consequence of many years of academic frustrations and negative experiences during the school years, especially when appropriate accommodations, support services, or individualised and specialised teachings are not provided. The SDQ was able to capture these emotional symptoms in children and adolescents with SLD and adequately handle these associated problems as well.

Our study has some limitations.

A first limitation was the lack of a control group, which should be included in future studies to compare the prevalence of the symptoms we found with that of the typically developing population.

Another limitation was the absence of a complete description of our patients' characteristics. Future studies should include a detailed description, including the demographic (e.g., socioeconomic status) and clinical characteristics of the patients (e.g., whether they are taking medication or not).

An additional limitation was the wide age range of participants. Including participants with a more homogeneous age range or stratifying them by age could better clarify the relationship between age and symptom development.

In addition, the number of participants considering each diagnostic group was limited, but the results are encouraging and useful for designing and executing a large-scale study using the SDQ.

Finally, future studies should include multi-informant analysis, considering self-reporting and teacher report questionnaires. It should augment the generalisability of the results into the daily professional's routine.

Overall, our results highlighted the clinical utility of using the SDQ as a potential tool to conduct the initial screening, and then further refer to patients for more structured neuropsychiatric evaluation. This is especially true for the early identification of core symptoms of ASD, ADHD, MD, and AD. Clinical assessments, such as the neuropsychiatric assessment, are complex and expensive. The SDQ can be integrated into daily clinical practice as an initial filter and then refer for the structured assessment only patients who score at-risk or clinical on the SDQ and who need further investigation.

Our results also showed that SDQ can detect behavioural and emotional problems that may be associated, with GDD, ID, SLD, and ED. Without a doubt, research on comorbid neuropsychiatric disorders has advanced in recent decades. However, because the comorbidity is associated with the cognitive and behavioural deficits of the primary disorder and influences its development; treatment should also focus on the comorbidities. The SDQ can bring precisely more attention to the associated symptoms to develop intervention plans that also address the comorbid problems.

5. Conclusions

In summary, our results indicated that the SDQ is a valid parent report questionnaire for identifying diagnostic and associated symptoms in the children and adolescents assessed in our study.

Specifically, the SDQ allowed us to detect specific symptoms for ascertaining the diagnosis in children and adolescents with ADHD, ASD, MD, and AD. In addition, SDQ can detect transdiagnostic emotional and behavioural problems associated with neurodevelopmental and neuropsychiatric disorders to better guide parents in their management.

Author Contributions: Conceptualisation, M.G., G.L., F.D., D.M., and S.V.; methodology, G.L., D.M., and S.V.; formal analysis, G.L., D.M., and S.V.; investigation, M.G., F.D., D.M., and S.V.; data curation, M.G., G.L., and D.M.; writing—original draft preparation, M.G., G.L., F.D., D.M., and S.V.; writing—review and editing, M.G., G.L., D.M., and S.V.; supervision, D.M. and S.V.; and project administration, S.V. and D.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study, due to its retrospective nature.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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

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International Journal of
Environmental Research and Public Health

MDPI

Article

Sleep Disturbances in Children with Attentional Deficit Hyperactivity Disorder and Specific Learning Disorders

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Abstract: Sleep disturbances may be a significant source of distress for children with neurodevelopmental disorders, and consequently also for their families. Crucially, sleep disturbances might be influenced by comorbidity. Attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD) often co-occur, and consequently, investigating sleep disturbances in children with comorbidity of ADHD and SLD is essential. Our study aimed at detecting sleep difficulties in a group of 74 children with ADHD, 78 children with SLD, and 76 children with ADHD and SLD by using the Sleep Disturbances Scale for Children. The results showed that sleep difficulties emerge more clearly in children with comorbid ADHD and SLD compared to children with only ADHD or SLD. These sleep difficulties were not due to differences in ages and behavioral/emotional problems. In conclusion, evaluating sleep disturbances is important when assessing and managing children with ADHD, SLD, and particularly with the two comorbid conditions, to better understand their difficulties and develop tailored interventions.

Keywords: neurodevelopmental disorders; ADHD; dyslexia; insomnia

Citation: Saccani, M.S.; Ursumando, L.; Di Vara, S.; Lazzaro, G.; Varuzza, C.; Vicari, S.; Menghini, D. Sleep Disturbances in Children with Attentional Deficit Hyperactivity Disorder and Specific Learning Disorders. *Int. J. Environ. Res. Public Health* **2022**, *19*, 6411. https://doi.org/10.3390/ijerph19116411

Academic Editor: Paul B. Tchounwou

Received: 21 March 2022
Accepted: 23 May 2022
Published: 25 May 2022

1. Introduction

Sleep disturbances are common in children with neurodevelopmental disorders and might become a significant source of distress, compromising the quality of life of both children and families [1]. Insufficient sleep is associated with emotional problems, such as depressed mood and anxiety traits, behavioral problems, such as impulsivity, hyperactivity, and aggressiveness, and cognitive problems, such as memory difficulties, learning difficulties, reduced attention, and reduced executive functioning [2–4].

Sleep disturbances have been unevenly studied in neurodevelopmental disorders. In children with attention deficit hyperactivity disorder (ADHD), 55% to 74% of sleep difficulties have been documented [5,6], such as decreased sleep efficiency, daytime sleepiness, delayed sleep onset, difficulty falling asleep, bedtime resistance problems, sleep-related breathing problems, motor restlessness during sleep, nocturnal enuresis, nocturnal awakenings, and difficulty waking up in the morning [7–10]. In addition, it has been noted that ADHD-like behavioral and cognitive symptoms may actually be consequences of sleep difficulties [11–13].

However, findings documenting atypical sleep and reduced sleep quality in children with ADHD are controversial [3,14,15]. Among the confounding factors, the most important are [7,8]: the greater intra-individual variability of the sleep/wake cycle in children with ADHD compared with controls, even when controlling for gender, medication, number

of days with data, and social jetlag [16]; age groups, as younger children with ADHD tend to have shorter sleep and older children longer sleep than controls [17]; and ADHD presentation, as children with ADHD with combined presentation show greater sleep problems than controls in initiating and maintaining sleep, breathing, sleep–wake transition, excessive daytime sleepiness, and sleep hyperhidrosis [18]. Discrepancies in results may also be due to the measures used. Most studies have used subjective measures, such as questionnaires, and only a few studies have employed objective measures, such as polysomnography or actigraphy [7].

When sleep measures were collected via actigraphy [19], children with ADHD presented similar sleep duration to controls and only moderately altered sleep patterns compared to controls, with increased activity during sleep. Children with ADHD who underwent a comprehensive sleep assessment [12,13] using multiple methodologies (e.g., blood tests, sleep questionnaires, laboratory video-polysomnographic recordings, multiple sleep latency tests, and one-week actigraphy) showed a much higher percentage of sleep problems than previous studies (of 30 children, 28 had poor sleep quality) and multiple sleep phenotypes, such as narcolepsy, delayed sleep onset insomnia, obstructive sleep apnea, periodic limb movements, and epileptiform discharges in sleep. In general, when studies controlled for various confounding factors, children with ADHD did not differ from controls in sleep patterns and had only alterations in sleep quality, such as greater daytime sleepiness, more motor restlessness during sleep, and more breath-related sleep disturbances than controls [8].

Unlike ADHD, sleep difficulties in children with specific learning disorders (SLD) have been overlooked. In the pioneering study by Mercier et al. [20], the sleep patterns of children with reading difficulties were measured for four consecutive nights using polysomnography. The results showed that children with reading difficulties, compared to controls, had an increase in stage 4 sleep, a decrease in sleep with rapid eye movements (REM sleep), a delayed onset of REM sleep, and a prolonged initial cycle of non-REM sleep [20].

Bruni et al. [21] measured sleep patterns by recording brain activity with EEG and analyzed spectral power in children with reading difficulties. The results showed that children with reading difficulties had increased EEG power of the frequency bands between 0.5–3 and 11–12 Hz (slow sigma) in stage 2 and between 0.5–1 Hz in stage 3. In addition, an increase in spindle density was found during stage 2. Importantly, these indices were correlated with the degree of reading impairment. In more recent studies, the association between sleep patterns and learning problems in children with reading difficulties has also been demonstrated [22,23].

Sleep disorders may be exacerbated in the case of comorbidity [9,24–27]. For example, ADHD and Tic disorder have been shown to be characterized by specific sleep difficulties that add up in comorbidity [25]. In addition, several studies have reported that symptoms of depression and anxiety contribute to sleep difficulties in ADHD, regardless of the severity of ADHD symptoms [9,26,27]. Finally, ADHD in combination with oppositional defiant disorder has been found to be associated with increased resistance to going to bed and waking up in the morning [24].

Sleep disorders have never been investigated for comorbidity between ADHD and SLD, despite the two disorders having a very high co-occurrence [28,29] with comorbidity rates ranging from 8% to 76% [30] and resulting in attention problems more severe than ADHD alone and learning problems more severe than SLD alone [31].

The present study aimed to investigate sleep disturbances in ADHD and SLD and to clarify how sleep disturbances are affected by ADHD and SLD comorbidity. To this end, we compared a group of children with ADHD and SLD comorbidity (ADHD+SLD), a group with ADHD, and a group with SLD on the scores of the Sleep Disturbances Scale for Children (SDSC, [32]).

2. Materials and Methods

2.1. Participants

Children and adolescents with ADHD+SLD, ADHD, and SLD were retrospectively selected on the basis of age and IQ from a large database. This database consisted of several hundred outpatients with behavioral problems and/or learning difficulties referred to the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital in Rome for in-depth diagnostic investigation. All participants were evaluated between 2017 and 2020 by expert neuropsychiatrists and developmental neuropsychologists.

The criteria for inclusion in the study consisted of having a diagnosis of ADHD and/or SLD (reading disorder and/or math disorder and/or writing disorder) according to DSM-5 [33] criteria and national guidelines or recommendations [34]; while the exclusion criteria were as follows: (1) having an intellectual disability or autism spectrum disorder according to DSM-5 [33] criteria; (2) having a personal history of neurological or neurosensory disorders; and (3) having been on drug treatment for at least 6 months.

The diagnosis of ADHD was made according to DSM-5 criteria [33] based on developmental history and an extensive clinical examination. To obtain separate information from children and parents about ADHD symptoms, the semi-structured interview, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version [35], was also administered by an experienced clinician.

The diagnosis of SLD, reading disorder, and/or math disorder and/or writing disorder was diagnosed when the performance (level of accuracy or speed) was at least 2 SDs below the mean for school-age on norm-referenced measures [36–44].

The final sample consisted of: 74 participants with ADHD (12 females and 62 males; mean age ± SD: 9.5 ± 2.3 years; age range: 6.4–15 years), 78 participants with SLD (35 females and 43 males; mean age ± SD: 9.89 ± 1.86 years; age range: 7.4–14.6 years), and 76 participants with ADHD+SLD (17 females and 59 males; mean age ± SD: 10 ± 2 years; age range: 7–14.8 years).

The IQ scores were obtained using the Wechsler Intelligence Scale for Children-IV [45] or the colored/standard progressive matrices [46] as follows: ADHD group, mean IQ ± SD: 112.57 ± 12.84; SLD group, mean IQ ± SD: 108.81 ± 10.32; ADHD+SLD group, mean IQ ± SD: 109.05 ± 12.8.

In accordance with matching criteria, children with ADHD+SLD, ADHD, and SLD did not differ for chronological age ($F_{2,225} = 1.01$, $p = 0.36$, $\eta p^2 = 0.01$) and for IQ ($F_{2,225} = 2.31$, $p = 0.11$, $\eta_p{}^2 = 0.02$).

Participants' anonymity and data confidentiality were ensured. All procedures performed in the study involving human participants were in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Ethical review and approval were waived for this study because of the retrospective design and the fact that the data used were anonymous.

2.2. Measures of Sleep Disturbances

The Sleep Disturbances Scale for Children (SDSC, [31]) is an easy, short, and well-validated questionnaire completed by parents and used to assess sleep difficulties over the past 6 months in children and adolescents. The SDSC consists of 26 items with values ranging from 1 to 5 (higher numerical values reflect greater symptom severity). Items are grouped into six disorder subscales: disorders in initiating and maintaining sleep (DIMS), sleep breathing disorders (SBD), disorders of arousal (DA), sleep–wake transition disorder (SWTD), disorders of excessive somnolence (DES), and nocturnal hyperhidrosis (NH).

The SDSC provides a standardized measure of sleep disturbance in childhood and adolescence through a sleep index score. The development of the SDSC was based on a database of a large population in order to define normal values and identify children with disturbed sleep [32]. Therefore, raw scores are converted to T-scores based on normative data. T-scores are clinically significant when they are ≥70, whereas 60 to 70 are considered

borderline scores. To have a measure of sleep disturbance, we analyzed the results of all six subscales of the disorder.

2.3. Measure of Behavioral and Emotional Symptoms

The Child Behavior Checklist for Ages 6–18 [47] is a widely used questionnaire completed by parents and used to identify behavioral and emotional problems over the past 2 months in children and adolescents. Raw scores were converted to T-scores based on normative data. We analyzed the results of two broadband scales: internalizing problems and externalizing problems.

2.4. Statistical Analyses

A Chi-square test for association with the odd ratios (ORs) and 95% confidence intervals (95% CI) was conducted to compare the number of participants with clinical scores of each group (ADHD+SLD, ADHD, SLD) in each SDSC subscale (DIMS, SBD, DA, SWTD, DES, NH). To take into account multiple comparisons (3 Group × 6 SDSC Subscale), the Benjamini–Hochberg procedure was adopted (False Discovery Rate was set at 0.1).

A repeated-measure analysis of variance (RMANOVA) with the Group (ADHD, SLD, ADHD+SLD) as between-subject factors and SDSC Subscales (DIMS, SBD, DA, SWTD, DES, NH) as within-subject factors was run to test whether scores of SDSC subscales differed among groups.

Another RMANOVA with the Group (ADHD, SLD, ADHD+SLD) as the between-subject factor and CBCL broadband scales (Internalizing Problems and Externalizing Problems) as the within-subject factor was run to verify whether the scores of CBCL broadband scales differed between groups.

For both RMANOVAs, post hoc analyses were conducted by means of Tukey's HSD tests. Partial eta squares (ηp^2) were reported as measures of the effect size.

Additionally, Pearson's correlation was used to measure the relation between scores of SDSC subscales (DIMS, SBD, DA, SWTD, DES, NH) and scores of CBCL broadband scales (internalizing problems and externalizing problems). To take into account multiple comparisons (2 CBCL Broadband Scale × 6 SDSC Subscales), Bonferroni correction was applied ($p = 0.05/12 = 0.004$).

Finally, in order to take into account the possible influence of emotional and behavioral symptoms in comparing the three groups on sleep disturbances, a repeated-measure analysis of variance controlling for CBCL broadband scales scores (RMANCOVA) was run, with the Group (ADHD, SLD, ADHD+SLD) as between-subject factors, the SDSC subscale (DIMS, SBD, DA, SWTD, DES, NH) as within-subject factors, and the CBCL broadband scale as the covariate.

3. Results

As shown in Table 1, the number of children with ADHD+SLD who obtained clinical scores in DIMS, DA, SWTD, and DES subscales was higher than that of children with SLD. Furthermore, children with ADHD+SLD compared to children with ADHD showed higher clinical scores in SWTD and NH subscales. Conversely, the comparisons between children with ADHD and children with SLD in all SDSC subscales were not significant.

By comparing the three groups on SDSC subscales scores, a significant main effect of Group ($F_{2,225} = 11.43$, $p = 0.001$, $\eta p^2 = 0.09$) was found. Post hoc analyses (Tukey's HSD tests) showed that children with ADHD+SLD had significantly higher scores than children with ADHD ($p = 0.011$) and children with SLD ($p = 0.001$). Coversely, children with ADHD and children with SLD did not differ ($p = 0.157$) (Figure 1).

Table 1. Frequencies of children and adolescents with clinical (T-scores ≥ 70) and non-clinical (T-scores < 70) scores and group comparisons on Sleep Disturbances Scale for Children.

	ADHD+SLD		ADHD		SLD		ADHD+SLD vs. ADHD				ADHD+SLD vs. SLD				ADHD vs. SLD			
	M (SD)	c/nc (#)	M (SD)	c/nc (#)	M (SD)	c/nc (#)	OD	95% CI	Z	*p*-Value	OD	95% CI	Z	*p*-Value	OD	95% CI	Z	*p*-Value
DIMS	67 (14.91)	33/43	63 (14.88)	24/50	58 (14.92)	15/63	1.59	0.82–3.19	1.38	0.17	3.22	1.56–6.64	3.17	0.01	2.02	0.96–4.24	1.85	0.06
SBD	56 (12.64)	11/65	53 (12.64)	4/70	51 (12.63)	4/74	2.96	0.89–9.77	1.78	0.07	3.13	0.95–10.31	1.88	0.06	1.06	0.25–4.39	0.08	0.94
DA	60 (15.52)	25/51	57 (15.48)	16/58	56 (15.54)	11/67	1.78	0.85–3.69	1.54	0.12	2.99	1.34–6.63	2.69	0.01	1.68	0.72–3.91	1.21	0.23
SWTD	64 (14.12)	29/47	58 (14.19)	16/58	52 (14.13)	11/67	2.24	1.09–4.61	2.19	0.03	3.76	1.71–8.26	3.29	0.01	1.68	0.72–3.91	1.21	0.23
DES	61 (13.77)	21/55	55 (13.76)	11/63	53 (13.78)	8/70	2.19	0.97–4.94	1.88	0.06	3.34	1.37–8.12	2.66	0.01	1.53	0.58–4.04	0.85	0.39
NH	55 (11.68)	13/63	52 (11.71)	3/71	51 (11.75)	5/73	4.88	1.33–17.93	2.39	0.02	3.01	1.02–8.92	1.9	0.05	0.62	0.14–2.68	0.64	0.52

DIMS = Disorders in initiating and maintaining sleep; SBD = sleep breathing disorders; DA = disorders of arousal; SWTD = sleep–wake transition disorder; DES = disorders of excessive somnolence; NH = nocturnal hyperhidrosis; ADHD = attention deficit hyperactivity disorder; SLD = specific learning disorder; M = mean; SD = standard deviation; c = clinical score; nc = non-clinical score.

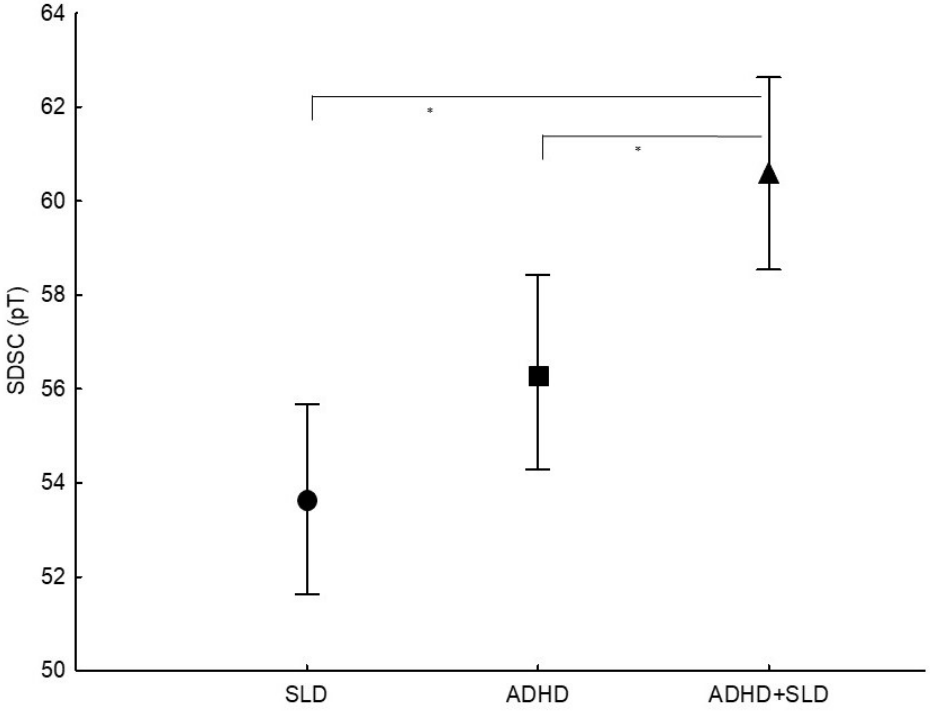

Figure 1. Comparisons of the three groups on the subscale scores of the Sleep Disturbances Scale for Children (SDSC). Children with ADHD and SLD in comorbidity had higher scores on the SDSC subscales than children with ADHD and children with SLD. * $p \leq 0.01$.

A significant main effect of the SDSC subscale was also found ($F_{5,1125} = 22.66$, $p = 0.001$, $\eta p^2 = 0.09$). As shown in Table 2, scores of the DIMS subscale were significantly higher than those obtained in the other subscales. Instead, the Group × SDSC subscale interaction was not significant ($F_{10,1125} = 1.31$, $p = 0.224$, $\eta p^2 = 0.01$).

Table 2. Means, standard deviations in SDSC subscales, and *p*-values of their comparisons.

SDSC Subscales	M (SD)	DIMS	SBD	DA	SWTD	DES
DIMS	62.76 (15.25)					
SBD	53.29 (12.78)	0.001				
DA	57.73 (15.58)	0.001	0.001			
SWTD	57.91 (14.83)	0.001	0.001	0.999		
DES	56.41 (14.11)	0.001	0.043	0.819	0.724	
NH	52.95 (11.77)	0.001	0.999	0.001	0.001	0.016

SDSC = Sleep Disturbances Scale for Children; DIMS = disorders in initiating and maintaining sleep; SBD = sleep breathing disorders; DA = disorders of arousal; SWTD = sleep–wake transition disorder; DES = disorders of excessive somnolence; NH = nocturnal hyperhidrosis; M = mean; SD = standard deviation.

Regarding differences among groups on the CBCL broadband scales scores, a significant main effect of the Group was found ($F_{2,225} = 16.25$, $p = 0.001$, $\eta p^2 = 0.13$), with lower scores (Tukey's HSD tests) in children with SLD than in children with ADHD ($p = 0.001$) and children with ADHD+SLD ($p = 0.001$), while children with ADHD and children with ADHD+SLD did not differ ($p = 0.214$). A significant main effect of the CBCL broadband scale was also found ($F_{1,225} = 13.93$, $p = 0.001$, $\eta p^2 = 0.05$) with scores (Tukey's HSD tests) of the internalizing problems subscale significantly higher than scores of the externalizing problems subscale ($p = 0.001$). In addition, the Group × CBCL broadband scale interaction was significant ($F_{2,225} = 15.89$, $p = 0.001$, $\eta p^2 = 0.012$). Post hoc analyses (Tukey's HSD tests) showed that scores of internalizing problems were significantly lower in children with SLD than in children with ADHD+SLD ($p = 0.019$), whereas scores of externalizing problems were significantly lower in children with SLD than in children with ADHD ($p = 0.001$) and with ADHD+SLD ($p = 0.001$). Children with SLD and children with ADHD did not differ on internalizing problems scores ($p = 0.989$), and children with ADHD and with ADHD+SLD did not differ in externalizing problems scores ($p = 0.998$).

The analysis of the correlation between scores of SDSC subscales and of CBCL broadband scales (see Table 3) showed that both internalizing problems and externalizing problems scores were positively correlated (after Bonferroni correction) with SDSC subscales scores with higher scores in the broadband scales corresponding to higher scores in SDSC subscales. Only the externalizing problems scores were not correlated with NH subscale scores.

Table 3. Pearson correlation coefficient (r) and *p*-values for correlation between Sleep Disturbances Scale for Children subscales and CBCL broadband scales scores.

		DIMS	SBD	DA	SWTD	DES	NH
Internalizing Problems	Pearson's r	0.362	0.246	0.378	0.369	0.447	0.215
	p-values	0.001	0.001	0.001	0.001	0.001	0.001
Externalizing Problems	Pearson's r	0.379	0.248	0.203	0.316	0.403	0.132
	p-values	0.001	0.001	0.002	0.001	0.001	0.047

DIMS = disorders in initiating and maintaining sleep; SBD = sleep breathing disorders; DA = disorders of arousal; SWTD = sleep–wake transition disorder; DES = disorders of excessive somnolence; NH = nocturnal hyperhidrosis.

In order to take into account the possible influences of emotional and behavioral symptoms in comparing the three groups on sleep disturbances, group differences in SDSC subscales were tested controlling for CBCL broadband scale scores. A significant main effect of the Group was confirmed ($F_{2,223} = 3.84$, $p = 0.023$, $\eta p^2 = 0.03$), with higher scores in children with ADHD+SLD than in children with ADHD ($p = 0.003$) and with SLD ($p = 0.001$). In addition, the main effect of SDSC Subscale was still significant ($F_{5,1115} = 2.68$, $p = 0.021$,

$\eta p^2 = 0.01$). The Group × SDSC subscale interaction was not significant ($F_{10,1115} = 0.81$, $p = 0.614$, $\eta p^2 = 0.01$), as in the previous analysis without covariates.

4. Discussion

The present study aimed to gain insight into sleep disturbances in ADHD and SLD and to better examine sleep disturbances in ADHD and SLD in comorbidity. Our results showed that sleep difficulties were more prevalent in children with ADHD and SLD in comorbidity than in children with ADHD or SLD alone. These sleep difficulties were not associated with differences in age (groups did not differ in age) or differences in behavioral and emotional problems (results were confirmed even after controlling for internalizing and externalizing symptoms).

The critical role of sleep on cognitive functioning has emerged in numerous studies. In children and adolescents who had undergone sleep education programs, improvements in sleep quality were associated with improvements in cognition and academic performance [48,49]. Indeed, high-quality sleep can promote memory consolidation and learning because during sleep, new memories are strengthened and become more resistant to interference [50,51]. On the other hand, in children [52] and adolescents [53,54], minimal but repeated sleep restrictions or sleep deprivation throughout the night have resulted in various cognitive deficits. More specifically, disturbed sleep may lead to slower responses and more variable performance during alertness, vigilance, and attention tasks [55,56]. Additionally, disturbed sleep can increase impulsive errors during executive function tasks [57]. Precisely because sleep plays this crucial role in cognitive functioning, sleep disturbances associated with neurodevelopmental disorders may exacerbate cognitive symptoms and should therefore be carefully studied.

To assess sleep disturbance in children with ADHD and SLD, we opted for the SDSC questionnaire [32]. This instrument can be easily and briefly completed by parents, has good internal consistency and test–retest stability [32], and is among the few sleep questionnaires that meet fundamental operational principles [58]. It provides a total score and six subscale scores (see the materials and methods section for details), which can be used to identify a "personal sleep disturbance profile" and indicate whether there are dysfunctional areas that require further investigation [32]. For these reasons, it has already been widely used to assess sleep difficulties in various clinical populations (e.g., children with cerebral palsy [59]; children with epilepsy [60,61]; obese adolescents [62]; youth with juvenile idiopathic arthritis [63]), including specifically ADHD and SLD [18,22,62,64–66]. One of the previous studies using the SDSC in children with ADHD showed that they had difficulty initiating and maintaining sleep, sleep–wake transition, and excessive sleepiness [18]. Recently, the SDSC was used in children with ADHD to evaluate the effect on sleep of mindfulness-oriented meditation training, with positive effects in initiating and maintaining sleep [65]. In addition, the SDSC was used in children with ADHD to assess the impact on sleep of home confinement during the COVID-19 pandemic and was found to reinforce maladaptive sleep patterns during this period [66].

In children with SLD, studies using the SDSC are very sporadic and have yielded mixed results: Some studies have documented problems with initiating and maintaining sleep, sleep breathing, and arousal [64], while others have found no difficulties [22].

According to our findings, comorbidity between ADHD and SLD exacerbates sleep disorders. Specifically, the number of children with ADHD and SLD comorbidities who had clinical levels of disorders in initiating and maintaining sleep, disorders of arousal, sleep–wake transition disorder, and disorders of excessive somnolence was higher than that of children with SLD. In addition, the number of children with ADHD and SLD comorbidity and clinical levels of sleep–wake transition disorder and nocturnal hyperhidrosis exceeded that of children with ADHD. Since comorbidity between ADHD and SLD can be as high as 76% [30], the inconsistencies between previous studies could be due to a lack of attention to this aspect.

Our findings indicate that sleep disturbances should not be overlooked, especially when there is comorbidity between ADHD and SLD. It is important to take this into account because of the role that sleep disturbances have on memory, learning, attention, or executive functioning. In children with ADHD, sleep difficulties have been found to be associated with lower attention skills, specifically the ability to remain alert and vigilant to numerous incoming stimuli [67–69], and reduced executive functioning [70]. In addition, in children with ADHD, sleep difficulties have been related to problems with working memory [71] and nighttime consolidation of declarative memories, emotional memories, and socially relevant stimuli [72–74]. In children with SLD, the effects of sleep difficulties on cognition are less well known. In a recent study [22], no relationship was found between sleep parameters such as slow-wave activity and novel word recall in children with reading difficulties, unlike in typical readers [23]. However, a relationship between reduced sleep spindles and difficulty in recall has been found in children with reading difficulties [22].

In addition, it is critical to understand how sleep disturbances interfere with the effectiveness of treatments for ADHD and SLD [75]. To date, there are preliminary data showing that in children with ADHD, the positive effect of long-acting stimulant medications on different abilities (i.e., alertness, executive functioning, working memory, and academic productivity) is limited by reduced sleep duration [76].

However, brief behavioral sleep therapy can result in wide-ranging benefits, such as reduced sleep difficulties, alongside improvement in ADHD symptoms, classroom behavior, and working memory tasks [71,77]. Similarly, melatonin treatment may result in a benefit on sleep and ADHD symptoms [78–80]. Improving children's sleep could enhance the improvements due to treatments, with benefits for children and their families, and systematic screening for sleep difficulties with its related intervention should be an integral part of the multimodal treatment plan for children with ADHD [75]. In this regard, improving children's sleep could enhance treatment-related improvements, benefiting children and their families, and systematic screening for sleep difficulties with its associated intervention should be an integral part of the multimodal treatment provided for children with ADHD [75].

Contrary to previous reports [9,26,27], sleep disturbances in ADHD may not result from emotional and behavioral symptoms alone. According to our findings, in the case of comorbidity between ADHD and SLD, sleep disturbances are not solely dependent on externalizing or internalizing problems and should be specifically treated to improve the quality of life of children and their families [81].

Our study has some limitations. The main one is the lack of a control group. Comparison with a control group could help clarify whether and how much sleep disturbance is exacerbated by the presence of a neurodevelopmental disorder.

Another limitation is the lack of objective measures to assess sleep such as polysomnography and actigraphy. Although evidence supports the validity and reliability of sleep questionnaires, particularly the SDSC [58], future studies with objective measures may be useful in supporting our findings from parent reports [82].

Another aspect that was not assessed in our study was cognitive measures, such as memory and executive functioning. This would allow us to study how any difficulties in memory, learning, and attention are associated with sleep problems in the neurodevelopmental disorders we examined.

Future studies are needed to assess the effects on sleep disturbances of other potentially crucial factors, such as drug treatment and socioeconomic status.

Finally, future longitudinal investigations would also be needed to explore how sleep disturbances may have long-term consequences for neurodevelopmental disorders.

5. Conclusions

Our results showed that ADHD and SLD are associated with sleep disturbances and that when the two disorders coexist, sleep disturbances are greater. In conclusion, this result confirms and highlights how complex the relationship between neurodevelopmental disor-

ders and sleep disorders is. Furthermore, this relationship might be bidirectional [11–13]. Neurodevelopmental disorders, especially if in comorbidity, might be considered a risk factor for sleep alterations. On the other hand, sleep alterations might lead to emotional, behavioral, and cognitive symptoms that mimic or aggravate neurodevelopmental disorders [2–4]. As a consequence, it is possible to hypothesize that similar biochemical disturbances underlie both neurodevelopmental disorders and sleep alterations; for example, a dysfunction in arousal mechanisms might be related to the etiology of both ADHD symptoms and sleep difficulties [11–13].

Understanding this relationship is important when assessing and managing patients with ADHD, SLD, and the two comorbid conditions to better understand their difficulties and develop tailored interventions while also paying attention to sleep difficulties.

Author Contributions: Conceptualization, D.M.; methodology, D.M.; formal analysis, M.S.S., L.U. and D.M.; investigation, M.S.S., L.U., S.D.V., G.L. and C.V.; data curation, M.S.S. and L.U.; writing—original draft preparation, M.S.S., L.U. and D.M.; writing—review and editing, M.S.S., L.U., S.D.V., G.L., C.V., D.M. and S.V.; supervision, D.M. and S.V.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study due to the retrospective design and the fact that the data used was anonymized.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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

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Minerva Pediatrics 2022 June;74(3):287-93
DOI: 10.23736/S2724-5276.17.04747-8

ORIGINAL ARTICLE

Disability and inclusive education in an Italian region: analysis of the data for the school year 2012-2013

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ABSTRACT

BACKGROUND: In Italy, pupils with disabilities enroll in mainstream schools and attend the ordinary classes at all educational levels. For the past twelve years, the Region Emilia Romagna has witnessed an increase in the number of children who need special support. The aim of the study was to identify the causes of disability in children attending public schools during the school year 2012-2013.

METHODS: The study was designed as a cross-sectional survey. Data were obtained from the Regional Education Department and divided into categories based on clinical diagnoses. Statistical analyses were performed to analyze the distribution of the diagnostic categories among Provinces and school grades. The most recurrent combinations of illnesses were identified.

RESULTS: Intellectual disability was the most common cause of impairment (38.5%), often associated with epilepsy and autism. Hyperkinetic disorder associated with specific disorders of scholastic skills was the most recurrent combination of diagnoses. Rare diseases were diagnosed in 4.1%, whereas 5.0% of cases were affected by psychopathological disorders.

CONCLUSIONS: Our study is the first in Italy for its focus on the causes of children's disabilities in an Italian region. Being familiar with the causes of disability affecting the children of a territory is important to allocate the available resources efficiently, and to ensure all children's effective social integration.

(*Cite this article as*: Lanzarini E, Parmeggiani A. Disability and inclusive education in an Italian region: analysis of the data for the school year 2012-2013. Minerva Pediatr 2022;74:287-93. DOI: 10.23736/S2724-5276.17.04747-8)

KEY WORDS: Mainstreaming, education; Education, special; Disabled children; Schools; Developmental disabilities.

According to Law 104/1992,[1] which states and guarantees specific rights for people with disabilities and their families, the Italian school system pursues the principle of inclusive education. Thus, pupils with disabilities generally enroll in mainstream schools and attend ordinary classes at all educational levels. Children who are identified as disabled by a medical specialist undergo mandatory disability identification procedures, to obtain the Certification for School Integration,[2] which states the type and severity of disability and the right to receive specific support. In the Region Emilia Romagna, the personal data of pupils in possession of the Certification for School Integration are collected in a database named dAbili,[3] issued by the Regional Education Department. The database contains information on the type of disability affecting the certified children and the extent of the help provided, namely the presence in class of the support teacher expressed in hours per week. Based on these data and the needs of the children, the Regional Education Department arranges and organizes the supporting staff (*i.e.*, support teach-

ers) and outlines the costs required to fulfill children's needs. Moreover, every school participating in this plan updates the database before the end of each school year. This makes the database dAbili an interface between the regional public schools and the Provincial Offices for School Inclusion, which report to the Regional Education Department. In the last years, the Region Emilia Romagna has witnessed a remarkable increase in the number of pupils who need special support, from 2.1% (8778 disabled pupils out of 420,953 pupils in total) in 2002-2003 to 2.5% (13,254 disabled pupils out of 526,571 pupils in total) in 2012-2013 of the grand totals of children attending public schools in the area.[4] This difference is statistically significant using the chi square test for independence ($P<0.01$). The reason for such an increase is not obvious. Although the lapse of time considered (twelve years) is too short to attribute this increment solely to the improvement of the diagnostic techniques, it could be hypothesized that the criteria employed for the identification of disabilities are nowadays different and broader than the ones used at the beginning of the observational period. Taking these considerations into account, we have analyzed the data concerning the pathologies involved in the release of the certificates registered in the database dAbili in the school year 2012-2013, and their distribution among the Provinces of the Region and school levels.

Materials and methods

During the school year 2012-2013, lasting from September 2012 through June 2013, 13.254 pupils enrolled in Emilia Romagna public schools received a Certification for School Integration, and were therefore listed in the database dAbili. The age range is between 3 and 28 years old (mean: 12, median: 12, mode: 11); no information about gender or nationality was given. Non-EU students accounted for 17% of the considered sample. However, no data was available to calculate the percentage of non-EU students for the school year 2002-2003. For this reason, we could not estimate the impact of this category of pupils on the increment of the number of Certifications for School Integration. For privacy reasons, children's names and surnames have been replaced with a unique numeric code. Other data provided for each child in the database include date of birth, province of residence, school level attended (preschool; primary school; first year of secondary school; second year of secondary school), description of the disease affecting the child with the matching ICD-10 code.[5] The study was designed as a cross-sectional survey. First, data have been split into macro-categories based on the medical diagnosis. Additional categories were: "ambiguous cases," which included data with missing ICD-10 codes or the disease's description, and all those cases for which it was impossible to establish the exact nature of the disability diagnosed; "miscellaneous," for medical conditions with a non-representative number of cases; "mixed disabilities," for children with multiple disabilities (Figure 1). Then, the number of pupils included in each category was expressed as percentage of the grand total, to avoid influences due to the different number of certificates generated by the various provinces. Finally, the following aims were pursued:

- to find possible significant prevalence values of the individual diagnostic categories among provinces. The percentage prevalence of each diagnostic category for every province was compared to the regional mean of prevalence, to find possible significant differences. For this purpose, we performed the chi-square test, using a 99% confidence interval. In some cases, a significant difference between the expected and the observed frequencies was found (P value <0.01, 1 degree of freedom);
- to determine which disabilities appear most often in combination. In order to obtain this information, a double-entry table was created using the ICD-10 codes grouped by the first letter and number (for example: F7 represents all codes from F70 to F79), and only the most recurrent pairs were analyzed in detail;
- moreover, an in-depth analysis of certain diagnostic categories was performed: Intellectual disability, which was the most common cause of impairment, and Rare Diseases and Mental Disorders, because of their heterogeneous composition.

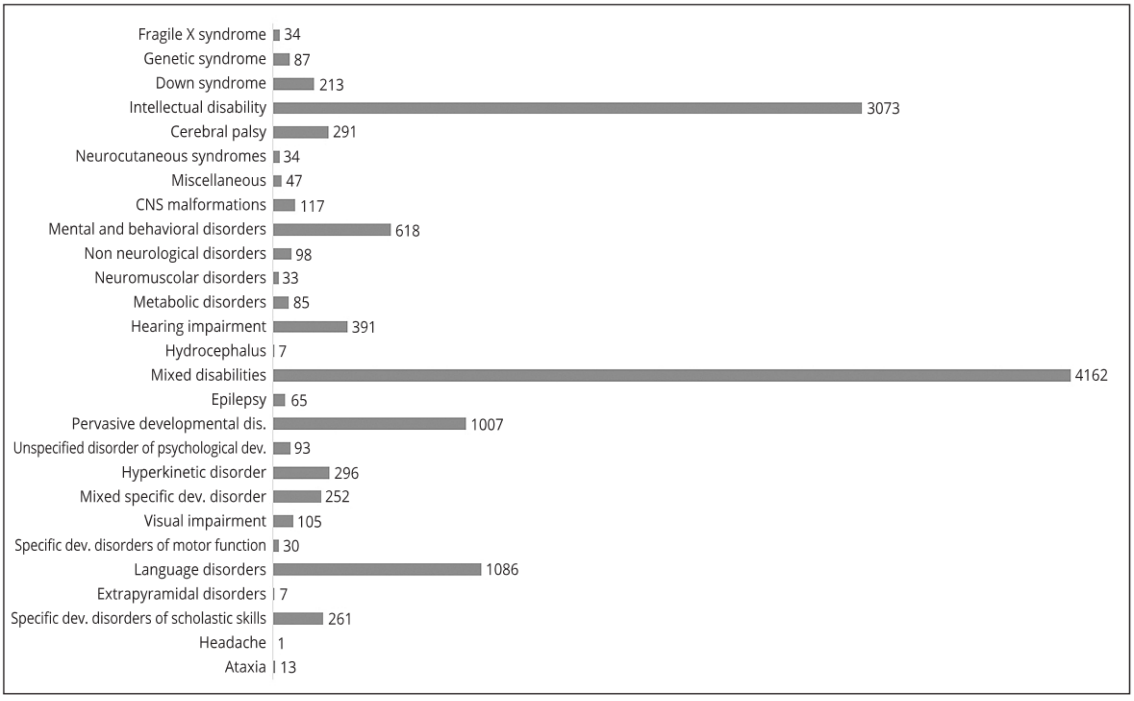

Figure 1.—The diagnostic categories into which the collected data were divided and the number of pupils included in each.

Results

After exclusion of the "ambiguous cases" (748), 12,506 subjects have been considered.

Diagnoses' distribution by Provinces and school levels

Of the 12,506 pupils considered, 785 attend preschool, 4855 attend primary school, 3365 attend the first year of secondary school, and 3501 attend the second year of secondary school. The Region Emilia Romagna has nine Provinces: the distribution of pupils by provinces counts 2649 children in Bologna, 2130 in Modena, 1950 in Reggio Emilia, 1223 in Parma, 1168 in Ferrara, 1002 in Ravenna, 824 in Rimini, 802 in Forlì and 758 in Piacenza. Among the most meaningful results, we found that the prevalence of "specific developmental disorders of scholastic skills" was remarkably higher than the regional mean in Bologna, and remarkably lower in Forlì, Modena, and Parma. Similarly, the prevalence of "Hyperkinetic disorders'" diagnosis was remarkably higher in Rimini and lower in Bologna. Moreover, the "pervasive developmental disorders" turned out to have a significantly higher prevalence in Piacenza and lower in Ravenna. These and other meaningful results are provided in Supplementary Digital Material 1 (Supplementary Table I).

"Mixed disabilities:" the most recurrent pairs of diagnoses

There are 4162 pupils in the diagnostic category of "mixed disabilities" (33% of the grand total). The most recurrent (prevalence > 1% of the grand total) combined diagnoses included: 1) "hyperkinetic disorders" associated with "specific developmental disorders of scholastic skills" (1.8%); 2) "hyperkinetic disorders" and "language disorders" (1.2%); 3) "emotional disorders with onset specific to childhood" and "specific developmental disorders of scholastic skills" (1.1%); and 4) "mixed disorders of conduct and emotions" and "specific developmental disorders of scholastic skills" (1.1%).

In-depth analysis of selected categories

Intellectual disability

The diagnosis of "intellectual disability" (ID) affects most of the pupils considered (4.819 pu-

pils), with a prevalence of 38,5% of the grand total. Down Syndrome was included in the analysis of the prevalence of this category. In fact, it is the most common chromosomal cause of intellectual disability,[6] and a discrete number of our pupils are affected by this syndrome (385, equal to a prevalence of 3.1% of the grand total). The severity of intellectual disability in the overall population of our study is represented by the associated ICD-10 code: in our sample, most of the cases are affected by a mild intellectual disability (67%), followed by moderate intellectual disability (21%), severe intellectual disability (7%), unspecified intellectual disability (3%), profound intellectual disability (1%), and "other intellectual disability" (1%). Among the 5204 pupils with Intellectual disability or Down syndrome, we found 1390 pupils with an associated diagnosis (26.7% of the ID category). "Epilepsy" is the most common comorbid illness (4.9%), followed by "pervasive developmental disorders" (2.7%). "Hyperkinetic disorders" and "cerebral palsy" have the same prevalence (1.5% for each diagnosis), whereas other diagnoses account for a lower prevalence (1.1-0.7% of the pupils with ID). The distribution of the diagnosis by provinces is irregular, with the highest prevalence in Bologna (20% of cases) and the lowest in Ferrara, Forlì, Piacenza, and Rimini (less than 8%). The distribution of diagnoses of "Intellectual disability" by school levels, instead, is homogeneous, except for preschool, where the number of cases is remarkably low (118 pupils in preschool, 1535 in primary school, 1470 in the first year of secondary school, 1696 in the second year of secondary school).

Rare diseases

Due to the lack of a specific ICD 10 code, pupils displaying the name of a rare disease in the disability description were included in this category. They accounted for the 4,1% of the grand total. The most recurrent rare disease that we found is neurofibromatosis (57 pupils; this group encompasses both neurofibromatosis type I and neurofibromatosis II). The other rare diseases that we found among the pupils of our region are listed in Table I. The prevalence of these diagnoses by Provinces is irregular, with the highest values in Bologna and the lowest in Piacenza. The same applies to the distribution by school levels, with a low prevalence in preschool and higher prevalence in the first year and second year of secondary schools.

Mental and behavioral disorders

Pupils included in this category display an ICD 10 code referring to a mental and behavioral disorder that is not associated with an organic illness. They account for the 5% of the grand total. The most common mental and behavioral disorders are "Behavioral and emotional disorders with onset usually occurring in childhood and adolescence" (494 pupils, 4% of the grand total). This and other recurrent mental and behavioral disorders are listed in Table II. Similarly to other diagnostic categories, the distribution of the diagnoses by provinces is irregular, with the highest prevalence in Bologna (148 pupils) and Parma (109 pupils), and the lowest in Rimini and Piacenza (22 and 21 pupils, respectively). On

TABLE I.—*Rare diseases represented in our sample.*

Achondroplasia	1.2%	Noonan Syndrome	1.0%
Albinism	1.6%	Osteogenesis imperfecta	1.6%
Angelman Syndrome	2.4%	Prader Willi Syndrome	1.4%
Chiari malformation	3.6%	Rett Syndrome	9.3%
Cornelia De Lange Syndrome	1.2%	Sotos Syndrome	1.0%
DiGeorge Syndrome	2.6%	Spinal muscular atrophy	4.3%
Duchenne muscular dystrophy	3.4%	Steinert dystrophy	1.2%
Fragile X syndrome	5.1%	Sturge Weber Syndrome	1.2%
Goldenhar Syndrome	2.2%	Tuberous sclerosis complex	5.3%
Klinefelter Syndrome	2.0%	Turner Syndrome	1.2%
Lissencephaly	1.0%	West Syndrome	1.8%
Mucopolysaccharidoses	1.2%	Others	27.8%
Neurofibromatoses	11.2%		

"Others" refers to diseases with a prevalence of less than 1% of rare diseases category.

TABLE II.—*Mental and behavioral disorders found in the considered sample and corresponding number of pupil diagnosed.*

ICD 10 code	Category name	Number of pupils diagnosed
F07	Personality changes due to known physiological condition	1
F20-F29	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	12
F30-F39	Mood [affective] disorders	30
F40-F48	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	37
F50	Eating disorders	1
F60-F69	Disorders of adult personality and behavior	40
F88	Other disorders of psychological development	3
F90-F98	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	494
Total		618

the contrary, the prevalence among school level is quite homogeneous (199 cases in primary school, 203 in the first year of secondary school and 208 in the second year of secondary school), except for preschool where only 8 pupils are affected by a mental or behavioral disorder.

Discussion

This study has several strengths. To the best of our knowledge, this is the first research that focuses on all the causes of disability affecting the scholastic population of a geographical region. Moreover, the size sample considered is large and up to date; therefore, the statistical analyses that we conducted are reliable. The diagnoses that we considered are made by clinical specialists, in contrast to several published studies that relied on the direct observation of the pupils made by school staff or parents.[7-9] Furthermore, no questionnaires have been employed. A study similar to ours, published at the end of the 1960s, listed the main causes of children's disabilities in England and Wales[10] in comparison to the data from the beginning of the 20th century. The authors divided the causes of disability into categories which reflected the scientific knowledge available at that time: "physically handicapped children," mainly constituted by pupils affected with cerebral palsy, spina bifida, congenital heart diseases and muscular dystrophy, but also hemophilia and diabetes; "epilepsy;" "blind and deaf children;" "speech and language disorders;" "educationally retarded and educationally subnormal children;" "children with emotional and behaviour difficulties;" "psychotic or autistic children;" "brain damaged children;" and "delinquent children." However, the authors underline the fact that many children had multiple disabilities, making it difficult to divide them into clear-cut categories. A more recent work investigated the causes of severe disability among children between 8- and 17-years old living in three French regions[11] by using the data gathered by the *Commission Dèpartementale de l'Éducation Spèciale* (CDES), which provides help for minors with disabilities and their families who live in France. However, by admission of the authors of this research themselves, only severe causes of disability were considered, and not all the disabled children of the examined regions were included in the study. Several studies calculate the prevalence of disability among the pupils of a region without investigating the causes of the disability itself.[12, 13] Our study offers particularly relevant insights and data because intellectual disability is often overshadowed by other illnesses that draw greater media attention, whereas it is important to consider how widely spread and recurrent this condition is, with a global estimated prevalence of 1%.[14] Pupils with intellectual disability require a complex management, which takes into consideration the frequent association of this condition with physical and mental diseases as well as the discrimination that they often experience.[15] Thus, it is important that teachers and school staff are adequately educated about this condition. The analysis of the "mixed disabilities" can provide information about the most recurrent associations of pathologies that can be encountered in the school setting. Given the complexity of managing and

supervising these children, there is the need to focus on special measures, which can differ from those ones applied to children with isolated disabilities. The association between "hyperkinetic disorders" and "intellectual disability" is one of the most recurrent associations, in agreement with the published literature on the subject. It is well established that the typical symptoms of hyperkinetic disorders have a higher prevalence among individuals with intellectual disability than among individuals with a normal cognitive level,[16] even if the disorder is often under-diagnosed, especially when the cognitive impairment is severe or profound. This phenomenon is described as "diagnostic overshadowing."[17, 18] In our study, the prevalence of this association was 1.7% among pupils with intellectual disability, excluding those with a Down syndrome. Several published studies, which have defined the prevalence of the hyperkinetic disorders among individuals with intellectual disability, offer, however, conflicting results, with minimal values of 6.8%.[16] The association between mental and behavioral disorders (*e.g.*, hyperkinetic disorders, emotional disorders with onset specific to childhood, mixed disorders of conduct and emotions) and "specific developmental disorders of scholastic skills" is frequently encountered in our sample. This finding can be explained by considering emotional issues because of scholastic difficulties or, vice versa, by considering emotional and behavioral disorders as an additional factor that may impact scholastic performances negatively. Therefore, teachers should consider the frequent co-morbidity of these conditions to help obtain an early recognition of critical situations and guarantee an appropriate referral. Furthermore, specific educational strategies can be applied in class to promote an adequate integration of pupils with emotional and behavioral disorders. Regarding the non-homogeneous distribution of the diagnostic categories considered in our study, this could be the consequence of a non-standardized use by the provinces' medical commissions of the criteria for the identification of pupils' disabilities. This use brings relevant consequences in terms of guaranteeing the right of an equal education. Another interesting point is that the number of students in need of special assistance is higher in the second year of secondary school than in the first year of secondary school. In fact, these students tend to drop out of school generally sooner. Such difference could be explained with the fact that the total of the pupils attending the second year of secondary school is higher (172,517 *versus* 113,151 total pupils). A possible explanation for this result could be a lower birth rate or a greater enrollment in non-public schools, which were not included in our study.

Limitations of the study

However, our study is not devoid of limitations. Therefore, possible limitations of the study are: 1) mistakes made by the school staff while entering the data about disabled pupils into the database dAbili can sometimes generate "ambiguous cases;" however, the number of "ambiguous cases" was scarce and did not influence the reliability of the statistical analyses; 2) the database includes neither pupils attending the private schools of the region, who accounted for the 4% of the school population of the period under consideration, nor those children whose disability is severe enough to prevent them from attending school; 3) the prevalence of rare diseases is likely underestimated due to the lack of a specific ICD 10 code; 4) only data from one school year were examined; therefore, we were not able to evaluate variation of the values over time; 5) each province has its own medical commission and this may explain some of the differences that we observed in the distribution of diagnoses; and 6) only the ICD-10 classification was utilized in the diagnosis of the sampled students. The ICF classification could also be employed in future studies.

Conclusions

In conclusion, our paper describes for the first time both the diseases and their prevalence that cause disability in almost all the pediatric population of an Italian Region. Further research is necessary to monitor the changes in term of prevalence year by year, and to obtain a deeper knowledge by considering other variables such as sex and nationality.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Evamaria Lanzarini has given substantial contributions to the study design, and to data acquisition, analysis, and interpretation; all authors equally contributed to the study conception and to the manuscript draft, Antonia Parmeggiani revised it critically. Both authors read and approved the final version of the manuscript.

Acknowledgements.—The authors acknowledge Graziella Roda of the Department of Regional Education for the data availability, Maria S. Borgia, and Ada Dormi for the statistical analysis.

History.—Article first published online: February 17, 2017. - Manuscript accepted: February 2, 2017. - Manuscript revised: January 3, 2017. - Manuscript received: July 20, 2016.

Supplementary data.—For supplementary materials, please see the HTML version of this article at www.minervamedica.it

Online version at https://www.minervamedica.it
Minerva Pediatrics 2022 June;74(3):373-4
DOI: 10.23736/S2724-5276.19.05529-4

Sleep paralysis in two children with attention deficit hyperactivity disorder

Sleep paralysis (SP) is a brief inability to perform voluntary movements at sleep onset, upon awakening during the night, or in the morning. SP may last for a few minutes and is often finally interrupted by noise or other external stimuli. The symptom is frequent in narcoleptic subjects associated with frightening hallucinations but may occur as an isolated phenomenon, affecting 5–40% of the general adult population.[1] SP is such a vivid experience that it has been incorporated into popular folklore in many parts of the world, and may be interpreted as a supernatural experience, a nocturnal visitation of demons and devils, in a culturally distinct manner. Isolated SP might be precipitated by stress, anxiety, panic disorder, sleep deprivation or irregular or disturbed sleep-wake rhythm. The consequences of disrupted sleep or sleep deprivation are strikingly similar to the core symptoms of attention deficit hyperactivity disorder (ADHD).[2] It has been reported that a specific hypo-arousal phenotype of ADHD might be linked to a dysfunction in arousal mechanisms, similar to narcolepsy[3] and the motor hyperactivity is considered a reaction to counteract somnolence. We reported here two cases of school-age children with ADHD experiencing hypnagogic hallucinations associated with SP. The first case is represented by a male, aged 9 years and 10 months, suffering from tensive headache and with divorced parents. Neurological examination and sleep and awake EEG were normal. No history of seizures was reported. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) PL 1.0 Psychiatric Interview, ADHD rating scale and psychiatric examination revealed a diagnosis of ADHD associated with Generalized Anxiety Disorder. Intelligent quotient was normal. The sleep schedule of the child was regular, and no symptoms related to sleep disturbances were reported. Laboratory examinations were normal. No polysomnographic study was performed. The child was drug free since parents refused pharmacological intervention. The child reported SP onset at 8 years of age, the episodes lasted for approximately 5 minutes, occurring when falling asleep or at awakening, with a frequency 1-2 times per week. The child described that he suddenly feels the impossibility to move, and he attempted to speak or shout without success. SP sometimes were preceded by the feeling of sudden falling. All SP episodes were associated with a typical hallucination of a black monster that touched him, hearing voices and step noises. The child lived with intense fear of the reoccurrence of the episodes and this condition generated anxiety symptoms. The descriptions reported by the child were identical after 45 days and confirmed by the mother. The child showed no specific symptoms related to narcolepsy even at 2 years follow-up. The first case is represented by a male, aged 10 years and 1 month, suffering from migraine and with divorced parents. Sleep and awake EEG and neurological examination were normal. Intelligence quotient was normal. K-SADS PL 1.0 Psychiatric Interview disclosed a diagnosis of ADHD, Oppositional Defiant Disorder, Generalized Anxiety Disorder. The child was reported as a restless sleeper; however, the sleep questionnaire showed no symptoms related to sleep disturbances. No history of seizures. Laboratory examinations were normal. No polysomnographic study was performed. The child was drug free since parents refused pharmacological intervention. SP started at 9 years and 8 months; the episode duration was 1 to 5 minutes, presenting mainly at falling asleep, with a frequency 1-2 times per month. The child suddenly had the impossibility to move, and he attempted to speak or shout without success. Sometimes he experienced a feeling of sudden falling down. During the episodes, he cannot speak or move any muscles but the eyes and reported several kinds of hallucinations, mainly consisting in a shadow with a dark man appearance and red eyes. The shadow had a malignant feature and tried to enter in the body. He reported to see globes of light and to hear noises of open windows. All the episodes are lived with intense fear with an impact on his well-being. The diagnosis of SP was performed by a direct interview with the child repeated after 45 days to test the reliability of the reported symptomatology. No clinical symptoms related to narcolepsy, have been reported by parents even at 2 years follow-up. We described for the first time the presence of SP in two children with ADHD that was associated with the presence of a sinister shadowy "bedroom intruder" that sometimes attacked the sleeper. The "creature" was lurking in the distant dark, slowly approaching and appearing as a dark shadow, similar to the human size and shape.[4] The pathophysiology of SP and the associated hypnagogic hallucinations might be related to a dysfunctional overlap of the REM and waking stages and polysomnographic studies found that individuals who experience SP have shorter REM sleep latencies along with shortened NREM and REM sleep cycles, and frag-

mentation of REM sleep.[5] Since SP is a common symptom of narcolepsy, we hypothesized that there may be common underlying pathophysiological mechanisms linking narcolepsy and ADHD that might be linked to a dysfunction in the arousal mechanisms present in narcolepsy and in a specific hypo-arousal phenotype of ADHD.[3] We may assume that in some children with the hypo-arousal phenotype of ADHD determined a sort of REM rebound facilitating the appearance of SP and hypnagogic hallucinations. Unfortunately, no polysomnographic evaluation has been carried out due to parent refusal; however, our observation suggests a comorbidity between ADHD and SP, especially in those children with ADHD narcolepsy-like sleep phenotype.[3]

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Renato Donfrancesco has given substantial contributions to the patients' diagnosis; all authors equally contributed to the manuscript preparation and to the study discussion. All authors read and approved the final version of the manuscript.

History.—Article first published online: July 2, 2019. - Manuscript accepted: June 28, 2019. - Manuscript revised: June 12, 2019. - Manuscript received: February 22, 2019.

(*Cite this article as*: Donfrancesco R, Melegari MG, Di Trani M, Borrelli E, Ferri R, Bruni O. Sleep paralysis in two children with attention deficit hyperactivity disorder. Minerva Pediatr 2022;74:373-4. DOI: 10.23736/S2724-5276.19.05529-4)

Online version at https://www.minervamedica.it
Minerva Pediatrics 2022 June;74(3):374-5
DOI: 10.23736/S2724-5276.19.05534-8

Apnea induced by respiratory syncytial virus infection: an inappropriate immune response requiring long-term follow-up for adult-onset progressive neurodegenerative diseases?

Respiratory syncytial virus (RSV) represents a major respiratory pathogen of infants and young children.[1] It has been written that RSV infection triggers a wide spectrum of diseases, including apnea, and this may be a result, in part, of differences in biological properties of the infecting virus.[1] During each seasonal epidemic, numerous strains of both subgroup A and B of RSV have been reported to circulate in the community.[1] RSV strains have been revealed not to be homogeneous with regard to pathogenesis or virulence.[1] The inflammatory response to RSV infection has emerged to play an important role in the disease pathogenesis.[1] RSV has been shown to stimulate the production of a variety of cytokines during and after infection.[1] Among all the proinflammatory cytokines, there is a significant amount of evidence showing that interleukin-6 (IL-6) is a key component of the response of the host to RSV infection.[1, 2] IL-6 represents a pleiotropic, proinflammatory cytokine that can promote both innate and adaptive immune responses being implicated both in protection and pathology.[2] In humans suffering from by RSV infections, increased concentrations of IL-6 have related to more severe disease.[2] It has been indicated that induction of IL-6 in human respiratory epithelial cells by clinical isolates of RSV is strain specific.[1] It has been supposed that genetic polymorphisms of clinical isolates of RSV may contribute to the severity of infection by variations in IL-6 induction.[1] Apnea represents one of the neurologic conditions described in hospitalized children affected by RSV infection.[3] Nowadays, the mechanisms connected with neurological complications due to human RSV-infection (hRSV) is still unclear.[4, 5] It has been reported that infection by hRSV reaches Central Nervous System (CNS), causing the production of high levels of IL-6 in the zone.[5] Increased levels of IL-6 during hRSV infection have been advised to be involved in the pathogenesis of CNS conditions.[6] It has been proposed that hRSV spreads from the lungs

Neuropsychiatrie de l'enfance et de l'adolescence xxx (xxxx) xxx–xxx

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Review

ADHD and obesity: A narrative review from the perspective of a child psychiatrist

TDAH et obésité : une revue narrative du point de vue d'un pédopsychiatre

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ARTICLE INFO

Keywords:
Obesity
ADHD
Pediatric psychiatry

ABSTRACT

Purpose. – This narrative review is aimed at presenting recent evidence on the association between two widespread, chronic, and growing diseases in childhood: attention-deficit/hyperactivity disorder (ADHD) and obesity. Several hypotheses have been put forward about the correlations between the two conditions, concerning prenatal, perinatal and postnatal factors.
Method. – We approached this topic through a search of recent literature on this subject, from the perspective of a child psychiatrist, a specialist in child development with an integrative view of the various factors involved in the onset, development and maintenance of a pathological condition, as well as a clinical approach, directed at addressing these factors in a combined manner.
Conclusion. – The most important point that emerged from our research and to be considered, as a child mental health specialist, seems to maintain an integrated view of the etiology and the management of mental disorders, through an integrative approach.

Mots clés :
Obésité
TDAH
Psychiatrie pédiatrique

RÉSUMÉ

But de l'étude. – Cette revue narrative a pour but de présenter les données récentes sur l'association entre deux maladies répandues, chroniques et en augmentation dans l'enfance : le trouble du déficit de l'attention/hyperactivité (TDAH) et l'obésité.
Méthode. – Nous avons abordé ce sujet par le biais d'une revue de la littérature récente sur le sujet du point de vue d'un pédopsychiatre, un spécialiste du développement de l'enfant ayant une vision intégrative des différents facteurs impliqués dans l'apparition, le développement et le maintien d'une condition pathologique ainsi qu'une approche clinique visant à aborder ces facteurs de manière combinée.
Conclusion. – Plusieurs hypothèses ont été émises sur les corrélations entre ces deux pathologies, concernant les facteurs prénataux, périnataux et postnataux. Le point le plus important, qui ressort de nos recherches et à considérer en tant que spécialiste de la santé mentale de l'enfant, semble être de maintenir une vision intégrée de l'étiologie et de la gestion des troubles mentaux, à travers une approche intégrative.

1. Introduction

Because obesity and ADHD are common conditions, establishing whether and to what extent obesity and ADHD are associated is significantly relevant from a clinical and public health point of view and could have treatment implications. Besides, the COVID-19 pandemic impacted both symptomatology of Youths with attention-deficit/hyperactivity disorder (ADHD) [1] and the prevalence of overweight and obesity [2]. The review is informed by previous relevant systematic reviews and a search in Pubmed up to 23rd November 2021.

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https://doi.org/10.1016/j.neurenf.2022.05.004
0222-9617/

Please cite this article as: Rossi L, Isnard P, ADHD and obesity: A narrative review from the perspective of a child psychiatrist, Neuropsychiatr Enfance Adolesc, https://doi.org/10.1016/j.neurenf.2022.05.004

2. ADHD and obesity

Childhood obesity and overweight have increased from <1% globally in 1975 to 6% of girls and 8% of boys in 2016 and this trend could be exacerbated by the COVID-19 pandemic response. This trend is significantly influenced by psychosocial determinants since children from more disadvantaged backgrounds are significantly more at risk of excess weight [2].

ADHD is a prevalent and impairing condition which affects around 5% school-age children worldwide and literature pointed to a significant association between attention-deficit/hyperactivity disorder (ADHD) and obesity [3]. An increasing trend in the prevalence of unhealthy weight was observed from children aged 6 to 12 years to adults with ADHD (obesity: from 13.5% to 19.3%, overweight: from 18.8% to 31.2%) [4] and both meta-analyses carried on this subject confirmed that the ADHD-obesity association was stronger in adults, showing that the risk of obesity increases in people with ADHD from childhood to adulthood [5,6]. However, this association is controversial and there is research that revealed no reliable association of ADHD and body mass index at any age or time point. Sex and racial/ethnic differences had been found in the association between the ADHD subtypes and higher BMI. A recent study carried out on an American population, pointed that ADHD predominantly hyperactive/impulsive is associated with higher BMI among European males and females whereas ADHD predominantly inattentive is associated with higher BMI only among females. Combined ADHD was found to be associated with higher BMI in Hispanic Americans whereas no evidence of an association was found in African American [7].

Specifically, ADHD was associated with obesity only in adolescent girls but not in children or boys [5]. A recent study confirmed that girls with ADHD increased in BMI at a significantly faster rate than comparison girls across development, even when adjusting for covariates such as stimulant medication [8].

A recent large-scale longitudinal study indicated that ADHD status was not associated with BMI when other child and parental factors were adjusted for, explaining this association by a variety of psychosocial factors [9]. Nevertheless, the meta-analysis carried in 2016 pointed to a significant association of the two conditions even when odds ratios were adjusted for possible confounders including socio- economic status and comorbid psychiatric conditions [6].

2.1. Prenatal factors: genetic and epigenetic

Genome-wide association studies were carried on investigating if ADHD has a causal effect on BMI in childhood: one study results suggested that higher BMI increases the risk of developing ADHD but not the other way around [10] whereas more recent research found consistent evidence for a bidirectional causal association [11].

One study confirmed the familiar coaggregation of the two conditions, giving evidence that full siblings of index males with overweight/obesity are at higher risk of attention-deficit/hyperactivity disorder (ADHD) compared to full siblings of index males with normal weight [12].

Overweight in boys with ADHD might be associated with SNPs of three candidate genes: DRD4 rs1800955, SNAP25 rs363039, rs363043, and 5HTR2A rs17288723. This association is not explained through conditioning of deficits in cool executive functions, in laboratory situations but might be connected to a lower level of hot executive functions, related to self-regulation under emotional and motivational arousal in "real world" conditions [13].

Both obesity and ADHD conditions may be considered in the light of the fetal programming hypothesis, since low birth weight was pointed as both one of the risk factors for obesity [14] and ADHD [15].

In one study published in 1947, it appeared that maternal malnutrition during early gestation was associated with higher Body Mass Index and waist circumference in 50-year-old women but not in men. Exposure to maternal obesity at the start of pregnancy was first reported as a risk factor for ADHD symptoms in the child in 2008 [16] and confirmed by a recent systematic review and meta-analysis [17]. Potential underlying biological mechanisms include oxidative stress and inflammation or dysregulation of hormone signaling in the developing brain by maternal obesity prior to pregnancy. According to a recent review published in 2020 maternal pre-pregnancy obesity and overweight, pre-eclampsia, hypertension, acetaminophen exposure, smoking during pregnancy and childhood atopic diseases were strongly associated with ADHD [18]. Interesting original research published in 2021 indicated that grandmother underweight prior to pregnancy is associated with an increased risk of ADHD among grandchildren, independent of grandmother gestational weight gain and independent of maternal pre-pregnancy weight status. The association was observed even after adjustments for socioeconomic status variables and epigenetic modifications, such as DNA methylation patterns, may underlie the observed association [19].

Epigenetic mechanisms may be involved in durable alterations of the hypothalamus-pituitary- adrenergic axis and preliminary findings in humans show that prenatal stress or maternal depression may influence the development of the child [20].

2.2. Early postnatal factors: attachment and emotional dysregulation

The role of perinatal factors seems to be decisive in the constitution of a vulnerability for the development of unsecure attachment and ADHD, with certain risk factors identified, such as prenatal smoking and prematurity [20].

A child's first years of life are of fundamental importance for his or her physical, cognitive and emotional development and research linked early attachment relationships to a wide range of long-term outcomes, including children's cognitive and language development and BMI [21].

Emotional dysregulation, which is an important feature in reactive attachment disorder as well as in ADHD, is highly related to attachment security in young children and could play a part in the development of early attention processes. [20]. Insecure attachment in early childhood, linked to child's stress responses and emotional regulation in the early stages of brain development, may also be a risk factor for obesity [22].

There is growing evidence linking the stress response to obesity and metabolic syndrome, since high levels of stress and therefore cortisol level can disrupt the functioning of the physiology of systems that affect energy balance and body weight.

The importance of the relationship between the caregiver and the child for the development of ADHD and obesity is highlighted also by one study that clearly showed that the duration of breastfeeding had negative predictor effects on overweight/obesity in the ADHD subjects [23].

2.3. Late postnatal factors: lifestyle and brain pathways

A robust association of ADHD with a less healthy lifestyle was confirmed, as defined by the children following fewer healthy lifestyle behaviors than control children of the same age. These results held even after adjustment for multiple confounding factors, including age, sex, IQ, ADHD medication, comorbid psychiatric conditions, and household income [24]. Healthy behaviors may influence one another and children with one unhealthy behavior are likely to have unhealthy behaviors in other areas as well [5].

Undesirable lifestyle factors could contribute directly to inattention and/or hyperactivity symptoms, could lead to other long-term health issues, and could affect scholastic outcomes. Numerous mechanisms exist that could mediate such effects, such as secondary effects on energy level, immune function, and epigenetic change [5].

ADHD may lead to obesity through impulsivity, less attention to internal hunger and satiety cues and research of immediate reward through junk food, bulimic patterns, and more screen time [25]. The importance of this concept is also confirmed by studies investigating the neuropsychological mechanisms that correlate the two phenomena: a pilot study found that not obesity alone but obesity with binge eating was specifically associated with a mechanism often reported in ADHD, namely delay discounting, which is the tendency to place less value on rewards that are delayed in time [26,27]. Seeking immediate rewards rather than planning and rewarding later in time may also lead to reduced physical activity.

Physical activity is important for attention, mood, and ADHD symptoms and could be identified as the main factor responsible for the association between ADHD and obesity [28]. Exercise appears to be particularly important for the normal development of executive function, a key driver of symptoms of inattention and disorganization in ADHD. Children with ADHD may also avoid sports participation due to negative social interactions in the team environment [5].

Some research focused on common brain pathways (hypothalamic, executive, and reward centers) with pathophysiology in these areas manifesting in partial or complete expression of these diseases, highlighting the fact that sleep dysfunction, binge-eating disorder and anxiety share similar pathways and are associated with ADHD and obesity [29]. Both genetic and neuroimaging ADHD research lead to the dopamine (DA) dysfunction hypothesis of the disorder and significant results support the hypothesis that elevated DA in the ventral striatum, representative of a greater reward response, contribute to the ADHD symptom and obesity relationship [30].

But other studies suggested that obesity may also lead to ADHD: in particular it is possible that factors associated with obesity, such as sleep-disordered breathing, shorter or later sleep, and systemic chronic inflammation could lead to ADHD-like symptoms [31]. Chronic systemic inflammation and neuroinflammation triggered by obesity could play a potential role in the pathophysiology of ADHD both in prenatal exposure and in life exposure [32].

Sleep disorders can impact the presentation of both obesity and ADHD and obese children are more predisposed to them. Disorders such as obstructed sleep apnea and sleep disordered breathing share neural pathophysiology with obesity and ADHD and can exacerbate ADHD symptoms of inattention, impulsivity, and poor executive function [29]. A biological link involving leptin and sleep dysfunction was described in patients with obesity and ADHD [33].

Considering others hormonal pathways, a possible correlation linked to thyroid hormones has been ruled out [34], whereas another hormonal mechanism related to ADHD and obesity is the chronic increase in cortisol, the "stress hormone" already mentioned between the prenatal and early postnatal factors, which can increase the intake of high-caloric and high- fat food and the accumulation of body fat [25].

Besides, multiple conditions are associated with obesity and ADHD with potential interactions still to be determined. Of the disorders associated with ADHD, the greatest modulating impact on the relationship between obesity and ADHD was found to be oppositional defiant disorder, conduct disorder and emotional overeating. Consumption of food in response to emotions can be linked to emotion regulation difficulties and the hypothesis of a mediating role of emotion dysregulation in the association between ADHD and disordered eating is strongly supported by the association between emotion dysregulation and eating disorders [35].

Sex differences in associated comorbidities might also explain why the etiology of the association between ADHD symptoms and BMI is different for males and females [36].

3. Conclusion

In conclusion, considering these mixed findings, it seems that a simple dichotomy between gene and environment should be avoided and that the link between obesity and ADHD is likely explained by genetic and epigenetic alterations which contribute to an obesogenic environment, as well as by traits that lead to weight gain such as unsecure attachment and emotional dysregulation.

Although this concept may seem counter-intuitive, given that this disorder has a variant associated with hyperactivity and therefore greater energy expenditure, ADHD could lead to an increased risk of obesity through various mechanisms during lifetime (particularly impulsivity and reduced physical activity) and especially in females. Conversely, obesity could also lead to an increased risk of ADHD, through neuroinflammation and sleep disorders. A third hypothesis argues for a common pathophysiological substratum between the two disorders, with evidence provided by the study of genetic, prenatal, and early life factors that could explain this association. A key element of this association could be related to emotional dysregulation. Although first-line treatments for ADHD often help to resolve emotional dysregulation symptoms as well, the response to treatment is variable. We are particularly interested in the hypotheses concerning prenatal factors and infantile attachment as an important preventive or risk factor for child emotional dysregulation, which we can influence with our intervention as pediatric psychiatrists. Our work consists in creating opportunities and means for families to develop their skills and competencies and acquire resources which meet their children's needs, to allow them to develop appropriate skills in the face of conflicts and help them better regulate and express their feelings [21]. Family-based behavioral treatments based on improving the parent-child relationship, communication, and more cooperative behavior (such as praise and reward systems) have been widely employed and studied in the treatment of disruptive behavior problems and large effect sizes for child behavioral improvement have been reported. Other psychosocial treatments that engage processes underlying emotional dysregulation are in development, such as adaptations of dialectical behavior therapy [37].

The most important point that emerges from research and to be considered as a child mental health specialist seems to maintain an integrated view of the etiology and the management of mental disorders, through an integrative approach. Lifestyle factors are usually inter-related: healthy behaviors may influence one another; and children with one unhealthy behavior often have unhealthy behaviors in other areas as well. For example, physical activity can reduce screen time, and improve sleep, while reading can replace screen time and help sleep hygiene rituals [24]. Thereby, an integrated healthy behavior picture should be the base of any clinical and therapeutic program. At a practical level, since too many recommendations can overwhelm parents, it is necessary to balance the idea of one step at a time change which may have cascade effects versus the cases where it is easier to put a new schedule of activity in place with multiple changes at once. The importance of evaluating potential benefits of lifestyle intervention on ADHD and obesity continues to grow.

Addressing sleep may resolve attentional symptoms as well as improve obesity management goals.

To reduce sleep alterations, sleep health education and sleep hygiene should be the priority to prevent long-term adverse

outcomes and the Cognitive and Behavioral Therapy for Insomnia (CBT-I), the first-line treatment for insomnia, showing promising effects also for children and adolescents, should be made more widely available [38,39]. Mindfulness, the practice of paying attention to the present moment, purposefully and nonjudgmentally, has been gaining popularity as adjunct treatment for adults and adolescents with a range of physical and mental health problems. Mindfulness-based interventions show promising results in various areas including the treatment of sleep disorders in adolescence and, according to recent meta-analysis, could also mitigate both ADHD symptoms [40] and assist weight loss among obese children and adolescents [41].

Disclosure of interest

The authors declare that they have no competing interest.

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Review

A Systematic Review on Feature Extraction in Electroencephalography-Based Diagnostics and Therapy in Attention Deficit Hyperactivity Disorder

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Abstract: A systematic review on electroencephalographic (EEG)-based feature extraction strategies to diagnosis and therapy of attention deficit hyperactivity disorder (ADHD) in children is presented. The analysis is realized at an executive function level to improve the research of neurocorrelates of heterogeneous disorders such as ADHD. The Quality Assessment Tool for Quantitative Studies (QATQS) and field-weighted citation impact metric (Scopus) were used to assess the methodological rigor of the studies and their impact on the scientific community, respectively. One hundred and one articles, concerning the diagnostics and therapy of ADHD children aged from 8 to 14, were collected. Event-related potential components were mainly exploited for executive functions related to the cluster *inhibition*, whereas band power spectral density is the most considered EEG feature for executive functions related to the cluster *working memory*. This review identifies the most used (also by rigorous and relevant articles) EEG signal processing strategies for executive function assessment in ADHD.

Keywords: ADHD; executive function; ERP; P300; children

Citation: Arpaia, P.; Covino, A.; Cristaldi, L.; Frosolone, M.; Gargiulo, L.; Mancino, F.; Mantile, F.; Moccaldi, N. A Systematic Review on Feature Extraction in Electroencephalography-Based Diagnostics and Therapy in Attention Deficit Hyperactivity Disorder. *Sensors* **2022**, *22*, 4934. https://doi.org/10.3390/s22134934

Academic Editor: Andrea Facchinetti

Received: 16 May 2022
Accepted: 27 June 2022
Published: 29 June 2022

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and/or hyperactivity–impulsivity. According to the fifth edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5), inattention and/or hyperactivity–impulsivity symptoms must be present before age 12, in two or more contests, such as school and home. Impairment contributes to academic, professional, or social dysfunction. These symptoms must be present for at least 6 months and do not occur exclusively during schizophrenia or another psychotic disorder and must not be better explained by another mental disorder (mood disorder, anxiety disorder, dissociative disorder, and personality disorder). The DSM-5 lists nine symptoms related to inattention and hyperactivity–impulsivity, respectively. If the subject exhibits at least 6 of the 9 symptoms of inattention, predominantly inattentive type (ADHD-I) is diagnosed; predominantly hyperactive–impulsive type (ADHD-PH) includes at least 6 of the 9 symptoms of hyperactivity–impulsivity; the combined type (ADHD-C) involves inattention and hyperactivity–impulsivity symptoms [1].

The diagnostic criteria of DSM V are based on subjective assessments of perceived behavior. There is no mention of the use of biomarkers. Nonetheless, for 75 years, the EEG has been used for the study of ADHD [2]. EEG is recognized in the literature as one of the main candidates to provide support for the diagnosis and treatment of ADHD on a biological basis [3]. The first studies based on EEG and ADHD hypothesized a hypoarousal condition [4] of the subjects revealed by a polarisation of the EEG signal power at low frequencies. This hypothesis was confirmed by the U.S. Food and Drug Administration, which authorised the use of a device based on the ratio between power at high and low frequencies for diagnostic purposes [5]. Subsequently, further studies have not always confirmed the statistical significance of this electroencephalographic phenomenon in ADHD. Further approaches are therefore being considered for the study of such a heterogeneous phenomenon. For example, inattentive sub-types are characterized by deficits in stimuli processing speed. Therefore, ERPs assessment is particularly useful. The main advantage of ERPs is that they are able to capture the evolution of brain activity following a specific event with high temporal accuracy and thus can be used to detect sensory processing deficits [3].

In the literature, numerous studies consider the use of EEG both for diagnostics [3] and therapy [6]. To date, however, generalizable electroencephalographic patterns of ADHD have not yet been identified. According to [3], there can be no generally valid electroencephalographic features for an extremely heterogeneous phenomenon such as ADHD. DSM 5, compared with DSM 4, has increased the articulation of ADHD into subtypes. In doing so, it has also indicated a direction to go in to achieve a greater EEG-based understanding of the disorder. Anchoring EEG features to elementary cognitive functions allows the heterogeneity of ADHD-related disorders to be mapped more effectively. The correspondence between the ADHD subtype and the impairment of one or more EFs is discussed in [7]. In fact, EFs are elementary constructs that can be combined into more complex systems. The EEG features of the different executive functions can also be combined for a more targeted assessment of the different ADHD subtypes [8]. Executive functions (EF) are a set of neurocognitive processes involved in goal-oriented problem-solving [9]. According to Miyake et al., the basic EFs are *inhibition, working memory*, and *flexibility* [10]. In particular, inhibition is linked to the activation of networks involving bilateral frontal, upper right temporal occipital gyrus, and lower left, right thalamic structures and midbrain [11]. Working memory involves the dorsolateral prefrontal cortex [12], while flexibility relates to the prefrontal and posterior parietal cortex [10]. The combination of basic EF gives rise to higher-order EFs, i.e., *reasoning, problem-solving*, and *planning* [13–15]. In the early 2000s, Baddeley proposed the sub-articulation of the basic EFs in components (sub-functions) [16]. In particular, as an example, working memory is divided into (i) phonological loop; (ii) visuospatial sketchpad; and (iii) episodic buffer. However, a few years later, Friedman and Miyake (2004) did not consider this distinction. In recent years, an emerging trend has focused on analyzing executive sub-functions. Stahl et al. (2014) focused on two sub-EFs of inhibition, namely, *interference inhibition* and *inhibiting prepotent responses*. Rey-Mermet et al. (2017) also demonstrated how a two-component inhibition model best explained the data observed in young and older adults. A further articulation of the inhibition sub-functions was proposed by Diamond et al., in 2013. They broke down the response inhibition into *continuous response* and *response to temptations*, and they broke down interference inhibition into *selective attention* and *cognitive inhibition*.

Feature extraction is a pillar step of digital signal processing and can be summarized in (i) choosing a suitable analysis domain (e.g., time, frequency, and space); (ii) eventually, focusing on a portion of the domain (sub-domain); and (iii) applying proper mathematical functions to obtain synthetic and highly informative values of the input signals. Sometimes features extracted in this way undergo further transformation and/or calibration to improve the detection or classification process [17,18]. Currently, the relationship between EFs and EEG features is not uniquely defined. Moreover, many studies examine the EEG signal of the ADHD subject without clarifying which particular EF is being investigated. In other

studies, the investigated EF is related to non-specific EEG features (i.e., those already associated with other EFs in the literature).

This review aims to improve the EEG-based approaches to the ADHD by focusing on the EEG feature of EFs. The EEG can offer a multivariate approach to the study of a heterogeneous syndrome such as ADHD, by measuring executive functions and sub-functions. Consequently, as far as EEG-based studies associating ADHD with EFs deficit are concerned, the key points of the research are reported below:

- Identifing EFs evaluated in EEG-based ADHD studies and their resolution level among high order-, basic-, sub-, and components of sub-EFs;
- Counting the articles that studied each specific relationship between an EEG feature and an EF;
- Reporting wether the relationships between EEG features and EFs are statistically relevant or not;
- Analyzing the methodological rigor of the articles and their impact within the reference scientific community.

The review is structured as follows: in Section 2, the procedures for the selection and analysis of the articles are presented. Section 3 reports the results of the quantitative and qualitative analysis. Finally, the results are discussed in Section 4.

2. Methods

The method consists of two steps: (i) the article selection process (Figure 1) and (ii) the article analysis (Figure 2). The article analysis identifies the relationship between EEG features and EFs and evaluates the rigor and scientific impact of the studies.

2.1. Article Selection Process

In this Section, the inclusion and exclusion criteria, and the database search, are presented.

2.1.1. Inclusion and Exclusion Criteria

The present study was carried out in compliance with the PRISMA recommendations [19] (including the Kitchenham's guide [20]). All the articles were selected according to the following inclusion/exclusion criteria:

- The age of the experimental sample: only articles recruiting six fourteen-year-old participants were included; the choice of the age range of the experimental sample was due to (i) the maturation of basic EFs; (ii) the stimulation of higher order EFs in the school environment; (iii) the greater understanding and adherence to the various tasks; and (iv) the better exclusion of other pathologies diagnosable from the age of six.
- The participants' conditions during EEG signal recording: studies focused on resting state were excluded. Indeed, EFs selective activation requires specific task execution;
- Comorbidities: articles with the concurrent presence of other pathologies in participants were excluded to avoid these sources of interference on the EEG signals;
- Drug therapy: articles with participants under pharmacological treatment were excluded. Nevertheless, articles were included in case of the interruption of drug assumption at least six months before the execution of the experimental sessions. Articles were excluded if information about pharmacological therapy was not specified.
- The type of article: journal and conference articles were included, while reviews, commentaries, and editorials were excluded because they do not report directly on field studies.

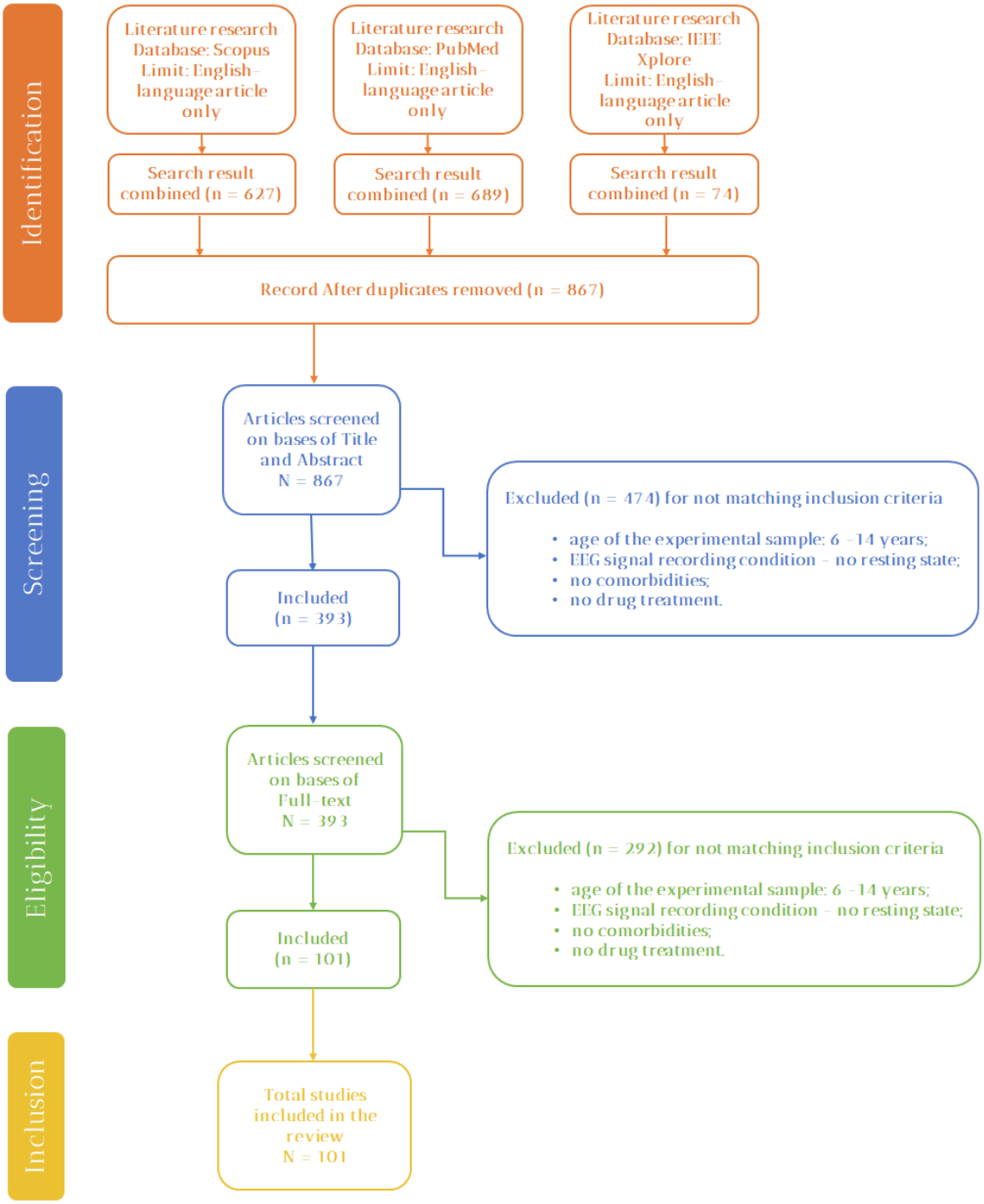

Figure 1. PRISMA-flow of the articles selection process.

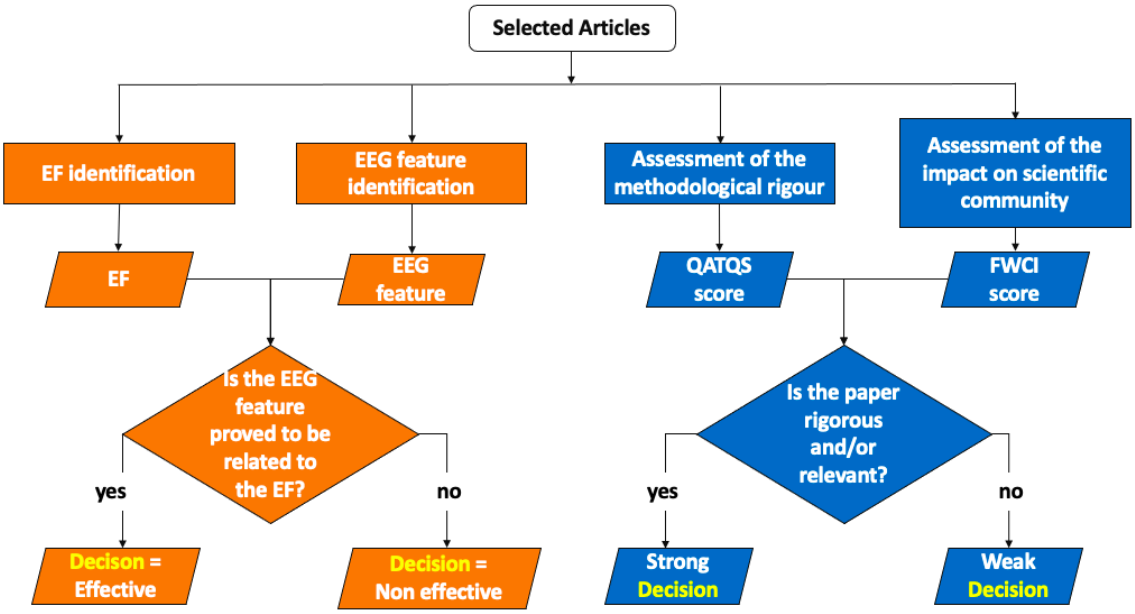

Figure 2. The flow-chart of the article analysis. Each article is subjected to two types of analysis in parallel: (i) the analysis to extract relationships between EEG features and executive functions (in orange) and (ii) the analysis to assess the rigor and scientific impact of the study (in blue).

2.1.2. Database Searches

A flow diagram representation of the database search is shown in Figure 1. The identification, the screening, the eligibility, and the inclusion phases are reported. The articles were collected from Pubmed, Scopus, and IEEEXplore databases by using the query "ADHD AND EEG AND NOT Adult". Only English results published from January 1996 to March 2021 were considered. An initial search led to 1390 articles: 689 from Pubmed, 74 from IEEEXplore, and 637 from Scopus, and 867 articles were the output of the identification phase, after removing duplicates. The full-text abstracts were analyzed in the screening phase, and 474 articles were excluded based on the selection criteria reported in Section 2.1.1. In the eligibility phase, the full text of the remaining 393 articles was screened according to the aforementioned criteria. At the end of the process, 101 articles were included: 86 from Scopus and 15 from PubMed.

2.2. Article Analysis Procedure

In this Section, the procedures for the executive function identification, the EEG feature identification, and the assessment of the methodological rigor and scientific impact of the articles are presented.

2.2.1. Executive Function Identification

Each article was labeled by the main focused EFs. When the authors did not specify the EFs under investigation, the links between the EFs and the articles were based on the performed experimental test. In the literature and clinical practice, several tests are administered to assess the impairments of EFs. Nevertheless, an exclusive link between a test and an EF cannot be guaranteed [21,22]. However, for each test, prevalent activated EFs can be assumed in many cases [13]. Below, a description of the EFs and the main tests used for their evaluation is reported.

In ADHD studies, researchers are mainly interested in basic and sub-EF levels [8]. Inhibition is defined as the ability "to control one's behavior, thoughts, and/or emotions to override a strong internal predisposition or external lure, and instead do what's more appropriate or needed" [13]. This function is usually tested in an *oddball framework* [13]. The two components of inhibition, i.e., interference and response, are defined, respectively, as the ability to "filter out irrelevant information in the environment" and " inhibit inap-

propriate but prepotent responses", respectively [23]. Paradigms implemented to test these components include tasks in which subjects must ignore irrelevant stimuli [24] and inhibit prepotent response inclinations [25,26].

The working memory keeps in mind information during the execution of complex tasks [16]. This function is assessed by asking the participants to recall information previously received through multi-sensorial channels [27]. Working memory resources are separated into verbal and visuospatial constructs based on the type of information held in memory [28]. Namely, the phonological loop deals with the phonetic and phonological therapy ensuring the time properties preservation. At the same time, the visuospatial sketchpad maintains and processes the visual-spatial information and can generate mental images. The paradigms use auditory or visual contents to test these components [29,30]. Finally, cognitive flexibility represents a creative and adaptive mindset to rapid circumstance variations. In the experimental setup, the subject is required to shift among different cognitive schemes in response to a dynamic task [31]. Links among EFs and some of the main used tests are shown in Table 1.

The proposed method to identify links among EFs and articles is articulated in mutually-exclusive successive steps as follows: (i) standard tests are implemented: therefore, articles are labeled based on the test-related EFs; (ii) the article employed custom tests, but the authors clarified the investigated Efs: therefore, articles are labeled based on the declared EFs; (iii) custom tests are used, and the authors did not declare to focus on specific EFs: therefore, articles are tagged based on EFs related to the most similar standard test.

Table 1. FE investigated mainly in children with ADHD and the main tests for their analysis.

Basic Executive Function	Sub-Executive Function	Main Related Test
Inhibition	Response Inhibition Interference Inhibition	Go/No Go Task [24] Flanker Test [26]
Cognitive Flexibility	-	Wisconsin Card Sorting Task [31]
Working Memory	Verbal Working Memory Visual Spatial Working Memory	N-Back Task [29] Corsi Block Test [30]

2.2.2. EEG Features Identification

Once the EFs mainly investigated for each article are identified, the individuation of the link between EEG features and EFs is almost automatic. All the features collected from the articles are organized according to a multi-level pattern (Figure 3). The first level is the domain of definition: spatio-time, spatio-frequency, or spatio-time-frequency domain. In all cases, the spatial domain can be considered once the distributed mode of recording the EEG signal is given: it is acquired in a specific scalp region depending on the chosen headset.

At this level, the signal is treated by referring to peculiar pre-processing (averaging) or transformation (Fourier, Welch, and so on). As far as the second level is concerned, the sub-domains are adopted, namely, the time sub-domains and the bands (alpha, beta, theta, and so on). Finally, in third level, the identification of the features is completed by means of a synthetic value extracted after a specific operation (mean, peak, power spectral density, and so on).

In the case of articles focused on therapy, only the features subjected to experimental validation are considered.

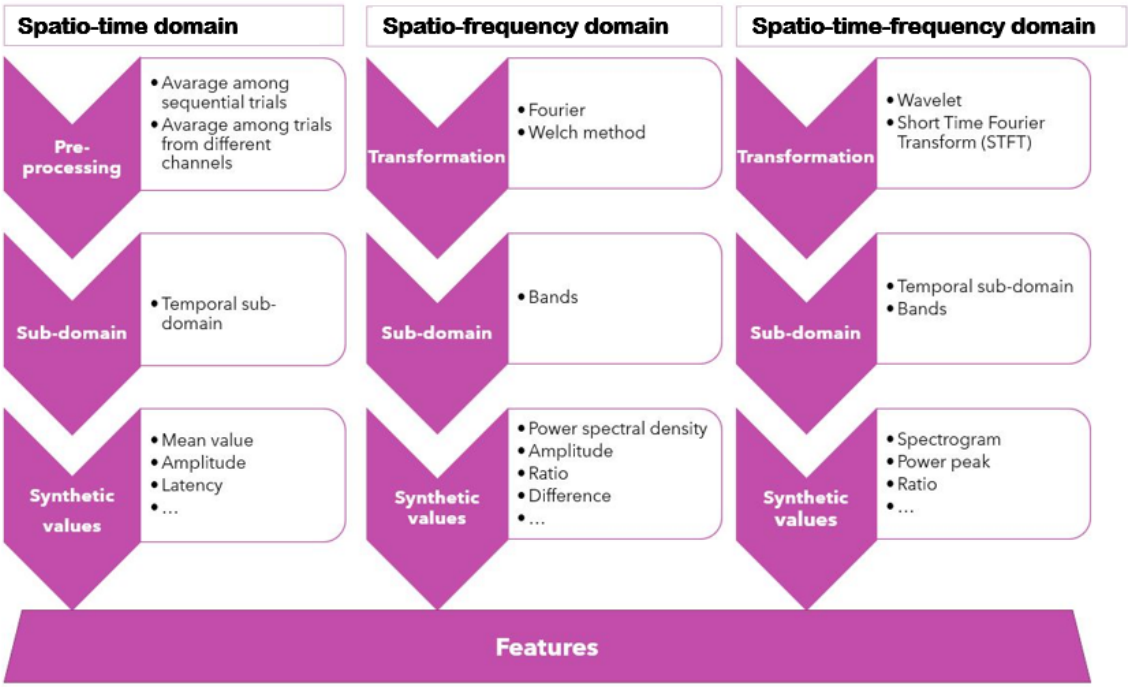

Figure 3. EEG features classification pattern.

2.2.3. Assessment of the Methodological Rigor and Scientific Impact of the Articles

The quality of the collected articles was evaluated according to the PRISMA guidelines [32,33]. Namely, the Quality Assessment Tool for Quantitative Studies (QATQS) [34], a method created by researchers from Canada's Efficient Public Health Practice Project (EPHPP), was used.

All the studies were classified according to the six components of QATQS: (1) selection bias, (2) study design, (3) confounders, (4) blinding, (5) data collection methods, and (6) withdrawal and dropouts. These components embed the criteria indicated in the Cochrane Collaboration and PRISMA declaration guidelines relating to the bias issues [19,35].

The blinding method was strictly developed in the framework of therapy effectiveness assessment, and, therefore, the blinding component was not considered for diagnostic articles.

The quality of each paper was assessed by assigning a score from 1 (high) to 3 (low) to each component. Firstly, the score was assigned by the sixth author of this review. Then, the evaluation was made by the fifth author. In case of disagreement, all the authors discussed and sought convergence.

After evaluating the rating of the components, the global rating was calculated for each article. Therefore, if no components scored 3, the article was labeled as *strong*; if only one component scored 3, the article was labeled as *moderate*; and finally, if more than one component scored 3, it was labeled as *weak*.

Finally, a further analysis based on Scopus's *field-weighted citation impact* metric was conducted to highlight the impact of the articles on the reference scientific community. The field-weighted citation impact metric is useful to benchmark regardless of differences in disciplinary profile, age, and publication type composition, and it provides a useful way to evaluate the article's citation performance. A value grater than 1 means that the article is more cited than the average of articles published in the same year and in the same field of interest. For example, 1.21 means 21% more cited than expected.

3. Results

In Table 2 EFs, EEG features, quality assessment output, and field-weighted citation impact are reported for each article. As far as quality assessment output is concerned, the normalised QATQS score (the smaller the score, the higher the quality of the article), the quality label (weak, strong, or moderate), the size of the experimental sample (N), and the use of other bio-markers (beside the EEG signal) are reported. In Section 3.1, the relationship between EEG features and EFs is focused on, while in Section 3.2, quality results are detailed.

Table 2. List of articles and related executive functions. EEG features and quality scores. FWCI: field-weighted citation impact; N: the size of the experimental sample; LZC: Lempel–Ziv Complexity; EEGVR: electroencephalogram valid rate; MSE: multi-scale entropy; SCP: slow cortical potentials; TBR: theta–beta ratio; TAR: theta–alpha ratio; TBAR: theta–beta–alpha ratio; SMR: sensomotor rhythm; WPLI: weighted phase lag tndex; ERN: error-related negativity; FD: fractal dimension; BP: bereitschaftspotential; LRP: lateralised readiness potential; CNV: contingent negative variation; ERP: event-related potential; PSD: power spectral density; MI: modulation index; CI: consistency index; ERD: event-related desynchronization; ERS: event-related synchronization; and ITC: inter-trial coherence. See the Appendix for more information about some of the EEG features considered. ERP components are evaluated in terms of amplitude or latency. n.a.: not available.

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Computer-based inhibitory control training in children with Attention-Deficit/Hyperactivity Disorder (ADHD): evidence for behavioral and neural impact [36]	Meyer, K.N.; Santillana, R.; Miller, B.; Clapp, W.; Way, M.; Bridgman-Goines, K.; Sheridan, M.A.	inhibition	ERP-N2	Global QATQS Rating: moderate (score = 1.67); No additional bio-markers; N = 40	0.41
Executive dysfunction in medication-naïve children with ADHD: a multi-modal fNIRS and EEG study [37]	Kaga, Y.; Ueda, R.; Tanaka, M.; Kita, Y.; Suzuki, K.; Okumura, Y.; Egashira, Y.; Shirakawa, Y.; Mitsuhashi, S.; Kitamura, Y.; et al.	inhibition	ERP-N2, ERP-P3	Global QATQS Rating: moderate (score = 1.60); Additional bio-markers; N = 20	0.93
Effect of combined neurofeedback and game-based cognitive training on the treatment of ADHD: a randomized controlled study [38]	Rajabi, S.; Pakize, A.; Moradi, N.	working memory	PSD-TBR, PSD-SMR	Global QATQS Rating: strong (score = 1.67); No additional bio-markers; N = 32	0.58
Individualized neurofeedback training may help achieve long-term improvement of working memory in children with ADHD [39]	Dobrakowski, P.; Łebecka, G.	working memory	PSD-Beta, PSD-Theta	Global QATQS Rating: strong (score = 1.83); No additional bio-markers; N = 48	4.17
Increased mirror overflow movements in ADHD are associated with altered EEG alpha/beta band desynchronization [40]	McAuliffe, D.; Hirabayashi, K.; Adamek, J.H.; Luo, Y.; Crocetti, D.; Pillai, A.S.; Zhao, Y.; Crone, N.E.; Mostofsky, S.H.; Ewen, J.B.	inhibition	PSD-Alpha, PSD-Beta	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 50	0.77
Event-related potentials (ERPs) and other EEG based methods for extracting biomarkers of brain dysfunction: examples from pediatric attention deficit/hyperactivity disorder (ADHD) [41]	Ogrim, G.; Kropotov, J.D.	inhibition	ERP	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 128	0.00

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Alpha modulation during working memory encoding predicts neurocognitive impairment in ADHD [42]	Lenartowicz, A.; Truong, H.; Salgari, G.C.; Bilder, R.M.; McGough, J.; McCracken, J.T.; Loo, S.K.	working memory	PSD-alpha, PSD-Theta, ERP-P2	Global QATQS Rating: moderate (score = 1.40); No additional bio-markers; N = 119	2.24
Bereitschaftspotential and lateralized readiness potential in children with attention deficit hyperactivity disorder: altered motor system activation and effects of methylphenidate [43]	Jarczok, T.A.; Haase, R.; Bluschke, A.; Thiemann, U.; Bender, S.	inhibition	LRP, BP	Global QATQS Rating: moderate (score = 1.67); Additional bio-markers; N = 33	0.55
Oscillatory neural networks underlying resting-state, attentional control and social cognition task conditions in children with ASD, ADHD and ASD+ ADHD [44]	Shephard, E.; Tye, C.; Ashwood, K.L.; Azadi, B.; Johnson, M.H.; Charman, T.; Asherson, P.; McLoughlin, G.; Bolton, P.F.	inhibition, working memory	CNV	Global QATQS Rating: moderate (score = 1.40); No additional bio-markers; N = 92	0.41
Evidence for an altered architecture and a hierarchical modulation of inhibitory control processes in ADHD [45]	Chmielewski, W.; Bluschke, A.; Bodmer, B.; Wolff, N.; Roessner, V.; Beste, C.	inhibition	ERP-P3, ERP-N2	Global QATQS Rating: moderate (score = 1.40); Additional bio-markers; N = 50	0.80
Diagnosis of attention deficit hyperactivity disorder with combined time and frequency features [46]	Altınkaynak, M.; Dolu, N.; Güven, A.; Pektaş, F.; Özmen, S.; Demirci, E.; İzzetoğlu, M.	inhibition	ERP-P3	Global QATQS Rating: moderate (score = 1.80); Additional bio-markers; N = 46	0.76
Lateral prefrontal theta oscillations reflect proactive cognitive control impairment in males with attention deficit hyperactivity disorder [47]	Zamorano, F.; Kausel, L.; Albornoz, C.; Lavin, C.; Figueroa-Vargas, A.; Stecher, X.; Aragón-Caqueo, D.; Carrasco, X.; Aboitiz, F.; Billeke, P.	inhibition	ERP-P3	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 54	0.42
Refining the picture of reduced alerting responses in ADHD–A single-trial analysis of event-related potentials [48]	Heinrich, H.; Busch, K.; Studer, P.; Erbe, K.; Moll, G.H.; Kratz, O.	inhibition	ERP-P3	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 43	0.21
A brain–computer interface based attention training program for treating attention deficit hyperactivity disorder [49]	Lim, C.G.; Lee, T.S.; Guan, C.; Fung, D.S.S.; Zhao, Y.; Teng, S.S.W.; Zhang, H.; Krishnan, K.R.R.	inhibition	PSD-sum of all bands	Global QATQS Rating: strong (score = 1.80); No additional bio-markers; N = 20	1.21
Frontal alpha asymmetry predicts inhibitory processing in youth with attention deficit/hyperactivity disorder [50]	Ellis, A.J.; Kinzel, C.; Salgari, G.C.; Loo, S.K.	inhibition	ERP	Global QATQS Rating: moderate (score = 1.80); No additional bio-markers; N = 50	0.58
Different cortical source activation patterns in children with attention deficit hyperactivity disorder during a time reproduction task [51]	Khoshnoud, S.; Shamsi, M.; Nazari, M.A.; Makeig, S.	working memory, inhibition	CNV, ERP-P3, ERP-P5	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 34	1.21

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
On the efficiency of individualized theta/beta ratio neurofeedback combined with forehead EMG training in ADHD children [52]	Bazanova, O.M.; Auer, T.; Sapina, E.A.	inhibition	PSD-beta, PSD-theta	Global QATQS Rating: strong (score = 2.00); Additional bio-markers; N = 117	1.64
Complexity analysis of brain activity in attention-deficit/hyperactivity disorder: a multiscale entropy analysis [53]	Chenxi, L.; Chen, Y.; Li, Y.; Wang, J.; Liu, T.	inhibition	PSD-beta, PSD-theta, PSD-alpha, PSD-beta, PSD-delta, MSE	Global QATQS Rating: strong (score = 2.40); No additional bio-markers; N = 26	0.78
A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD [54]	Janssen, T.W.; Bink, M.; Geladé, K.; van Mourik, R.; Maras, A.; Oosterlaan, J.	inhibition	PSD-TBR	Global QATQS Rating: moderate (score = 1.67); No additional bio-markers; N = 112	2.75
Effect of EEG biofeedback on cognitive flexibility in children with attention deficit hyperactivity disorder with and without epilepsy [55]	Bakhtadze, S.; Beridze, M.; Geladze, N.; Khachapuridze, N.; Bornstein, N.	flexibility	PSD-SMR, PSD-beta, PSD-gamma	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 69	0.76
Electroencephalogram complexity analysis in children with attention-deficit/hyperactivity disorder during a visual cognitive task [56]	Zarafshan, H.; Khaleghi, A.; Mohammadi, M.R.; Moeini, M.; Malmir, N.	working memory	LZC	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 64	0.58
Electroencephalogram valid rate in simple reaction time task as an easy index of children's attention functions [57]	Liao, Y.C.; Guo, N.W.; Lei, S.H.; Fang, J.H.; Chen, J.J.; Su, B.Y.; Chen, S.J.; Tsai, H.F.	inhibition	EEGVR	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 50	0.17
Development and evaluation of an interactive electroencephalogram-based neurofeedback system for training attention and attention defects in children [58]	Israsena, P.; Hemrungrojn, S.; Sukwattanasinit, N.; Maes, M.	reasoning	PSD-beta/a, lpha ratio	Global QATQS Rating: strong (score = 2.60); No additional bio-markers; N = 28	0.11
Use of EEG beta-1 power and theta/beta ratio over Broca's area to confirm diagnosis of attention deficit/hyperactivity disorder in children [59]	Sangal, R.B.; Sangal, J.M.	inhibition	PSD-beta, PSD-theta, PSD-TBR	Global QATQS Rating: strong (score = 1.83); No additional bio-markers; N = 86	0.68
Neurofeedback, pharmacological treatment and behavioral therapy in hyperactivity: multilevel analysis of treatment effects on electroencephalography [60]	Moreno-García, I.; Delgado-Pardo, G.; De Rey, C.C.V.; Meneres-Sancho, S.; Servera-Barceló, M.	inhibition. working memory	PSD-beta, PSD-theta	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 57	1.06

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Neurofeedback training intervention for enhancing working memory function in attention deficit and hyperactivity disorder (ADHD) Chinese students [61]	Wang, Z.	working memory	PSD-alpha	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 24	0.77
EEG differences in ADHD-combined type during baseline and cognitive tasks [62]	Swartwood, J.N.; Swartwood, M.O.; Lubar, J.F.; Timmermann, D.L.	working memory, inhibition, planning, problem solving	PSD-beta, PSD-alpha, PSD-theta, PSD-delta	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 56	0.39
Children with ADHD shown different alpha, beta and SMR EEG bands during habil motor tasks with high attention demand [63]	Silva, V.F.d.; Calomeni, M.R.; Borges, C.J.; Militão, A.G.; Freire, I.d.A.; Simões, K.M.; Arêas, N.T.; Silva, P.B.d.; Cabral, P.U.L.; Valentim-Silva, J.R.	flexibility	PSD-beta, PSD-alpha, PSD-SMR	Global QATQS Rating: strong (score = 2.67); No additional bio-markers; N = 14	0.00
Frequency bands in seeing and remembering: comparing ADHD and typically developing children [64]	Fabio, R.A.; Tindara, C.; Nasrin, M.; Antonio, G.; Gagliano, A.; Gabriella, M.	working memory	PSD-beta, PSD-alpha, PSD-theta	Global QATQS Rating: strong (score = 2.20); Additional bio-markers; N = 46	3.25
Decision support algorithm for diagnosis of ADHD using electroencephalograms [65]	Abibullaev, B.; An, J.	working memory	PSD-alpha, PSD-theta, PSD-theta, PSD-theta/alpha ratio, PSD-TBR, PSD-relative delta, PSD-relative beta	Global QATQS Rating: strong (score = 2.40); No additional bio-markers; N = 10	0.89
Dynamic changes in quantitative electroencephalogram during continuous performance test in children with attention-deficit/hyperactivity disorder [66]	Nazari, M.A.; Wallois, F.; Aarabi, A.; Berquin, P.	working memory	PSD-relative beta, PSD-relative alpha, PSD-relative theta, PSD-relative delta, PSD-relative TBR	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 32	1.26
Designing a brain-computer interface device for neurofeedback using virtual environments [67]	Yan, N.; Wang, J.; Liu, M.; Zong, L.; Jiao, Y.; Yue, J.; Lv, Y.; Yang, Q.; Lan, H.; Liu, Z.	working memory	PSD-relative TBR, PSD-relative SMR	Global QATQS Rating: strong (score = 3.00); No additional bio-markers; N = 12	0.27
Changes in cognitive evoked potentials during non pharmacological treatment in children with attention deficit/hyperactivity disorder [68]	Bakhtadze, S.; Dzhanelidze, M.; Khachapuridze, N.	inhibition	PSD-relative TBR, PSD-relative SMR, PSD-alpha	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 93	0.51

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
EEG spectral analysis of attention in ADHD: implications for neurofeedback training? [69]	Heinrich, H.; Busch, K.; Studer, P.; Erbe, K.; Moll, G.H.; Kratz, O.	inhibition	PSD-alpha, PSD-beta, PSD-theta	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 43	1.79
The effects of individual upper alpha neurofeedback in ADHD: an open-label pilot study [70]	Escolano, C.; Navarro-Gil, M.; Garcia-Campayo, J.; Congedo, M.; Minguez, J.	inhibition	PSD-alpha	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 17	1.20
A proposed multisite double-blind randomized clinical trial of neurofeedback for ADHD: need, rationale, and strategy [71]	Kerson, C.; Group, C.N.	inhibition, working memory	PSD-TBR	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 180	2.41
Functional disconnection of frontal cortex and visual cortex in attention-deficit/hyperactivity disorder [72]	Mazaheri, A.; Coffey-Corina, S.; Mangun, G.R.; Bekker, E.M.; Berry, A.S.; Corbett, B.A.	inhibition	PSD-alpha, PSD- theta	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 25	2.29
Quantative EEG during baseline and various cognitive tasks in children with attention deficit/hyperactivity disorder [73]	Bakhtadze, S.; Janelidze, M.	inhibition, working memory	PSD-alpha, PSD-delta	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 32	0.26
Frontal theta/beta ratio changes during TOVA in Egyptian ADHD children [74].	Halawa, I.F.; El Sayed, B.B.; Amin, O.R.; Meguid, N.A.; Kader, A.A.A.	inhibition	PSD-TBR	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 104	0.21
Desynchronization of theta-phase gamma-amplitude coupling during a mental arithmetic task in children with attention deficit/hyperactivity disorder [75]	Kim, J.W.; Kim, B.N.; Lee, J.; Na, C.; Kee, B.S.; Min, K.J.; Han, D.H.; Kim, J.I.; Lee, Y.S.	working memory	PSD-alpha-PSD-delta, PSD- theta, PSD- synchro-nization index (SI))-theta-gamma	Global QATQS Rating: strong (score = 1.80); No additional bio-markers; N = 97	0.66
Near-infrared spectroscopy (NIRS) neurofeedback as a treatment for children with attention deficit hyperactivity disorder (ADHD)—a pilot study [76]	Marx, A.M.; Ehlis, A.C.; Furdea, A.; Holtmann, M.; Banaschewski, T.; Brandeis, D.; Rothenberger, A.; Gevensleben, H.; Freitag, C.M.; Fuchsenberger, Y.; et al.	inhibition, flexibility	SCP	Global QATQS Rating: strong (score = 2.17); Additional bio-markers; N = 27	2.73
Children with ADHD show impairments in multiple stages of information processing in a Stroop task: an ERP study [77]	Kóbor, A.; Takács, Á.; Bryce, D.; Szucs, D.; Honbolygó, F.; Nagy, P.; Csépe, V.	inhibition	ERP-N1, ERP-P1, ERP-N450, LRP, SCP	Global QATQS Rating: strong (score = 2.00); Additional bio-markers; N = 24	0.61

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Increased reaction time variability in attention-deficit hyperactivity disorder as a response-related phenomenon: evidence from single-trial event-related potentials [78]	Saville, C.W.; Feige, B.; Kluckert, C.; Bender, S.; Biscaldi, M.; Berger, A.; Fleischhaker, C.; Henighausen, K.; Klein, C.	working memory	LRP, ERP-P3	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 45	2.70
Small-world brain functional networks in children with attention-deficit/hyperactivity disorder revealed by EEG synchrony [79]	Liu, T.; Chen, Y.; Lin, P.; Wang, J.	inhibition	cluster coefficient C, and character-istic path length L-alpha, beta, theta, delta	Global QATQS Rating: strong (score = 2.40); No additional bio-markers; N = 26	1.56
Electroencephalography correlates of spatial working memory deficits in attention-deficit/hyperactivity disorder: vigilance, encoding, and maintenance [80]	Lenartowicz, A.; Delorme, A.; Walshaw, P.D.; Cho, A.L.; Bilder, R.M.; McGough, J.J.; McCracken, J.T.; Makeig, S.; Loo, S.K.	working memory	ERP-P2, PSD-TBR	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 99	2.66
First clinical trial of tomographic neurofeedback in attention-deficit/hyperactivity disorder: evaluation of voluntary cortical control [81]	Liechti, M.D.; Maurizio, S.; Heinrich, H.; Jäncke, L.; Meier, L.; Steinhausen, H.C.;Walitza, S.; Drechsler, R.; Brandeis, D.	inhibition	SCP	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 13	2.12
Visual sensory processing deficit in the occipital region in children with attention-deficit/hyperactivity disorder as revealed by event-related potentials during cued continuous performance test [82]	Nazari, M.; Berquin, P.; Missonnier, P.; Aarabi, A.; Debatisse, D.; De Broca, A.; Wallois, F.	inhibition	ERP-N2, ERP-P1	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 30	0.72
Do children with ADHD and/or PDD-NOS differ in reactivity of alpha/theta ERD/ERS to manipulations of cognitive load and stimulus relevance? [83]	Gomarus, H.K.; Wijers, A.A.; Minderaa, R.B.; Althaus, M.	working memory, inhibition	ERS, ERD	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 60	0.09
Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? [84]	Doehnert, M.; Brandeis, D.; Straub, M.; Steinhausen, H.C.; Drechsler, R.	inhibition	CNV	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 26	2.13
Longitudinal change of ERP during cued continuous performance test in child with attention-deficit/hyperactivity disorder [85]	Okazaki, S.; Ozaki, H.; Maekawa, H.; Futakami, S.	inhibition	ERP-P3, ERP-N2, ERP-P2	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 1	0.00

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Exogenous orienting of visual-spatial attention in ADHD children [86]	Ortega, R.; López, V.; Carrasco, X.; Anllo-Vento, L.; Aboitiz, F.	inhibition	ERP-N1, ERP-P3, ERP-P2, ERP-CNV	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 60	0.92
EEG classification of ADHD and normal children using non-linear features and neural network [87]	Mohammadi, M.R.; Khaleghi, A.; Nasrabadi, A.M.; Rafieivand, S.; Begol, M.; Zarafshan, H.	working memory	ApEn, LE, FD	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 60	3.06
Diagnose ADHD disorder in children using convolutional neural network based on continuous mental task EEG [88]	Moghaddari, M.; Lighvan, M.Z.; Danishvar, S.	working memory	Amplitude of alpha, theta, beta+low gamma frequency bands	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 61	0.64
Combining functional near-infrared spectroscopy and EEG measurements for the diagnosis of attention-deficit hyperactivity disorder [89]	Güven, A.; Altınkaynak, M.; Dolu, N.; İzzetoğlu, M.; Pektaş, F.; Özmen, S.; Demirci, E.; Batbat, T.	inhibition	ERP-P3, LZC, FD	Global QATQS Rating: weak (score = 1.60); Additional bio-markers; N = 44	1.20
Methodology proposal of ADHD classification of children based on cross recurrence plots [90]	Aceves-Fernandez, M.	working memory	Recurrence rate, Determinism, Entropy, Laminarity, Trapping Time, Trend	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 121	0.00
Improved neuronal regulation in ADHD: an application of 15 sessions of photic-driven EEG neurotherapy [91]	Patrick, G.J.	inhibition	PSD-theta, PSD-SMR	Global QATQS Rating: strong (score = 2.67); No additional bio-markers; N = 25	0.57
Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD [92]	M. A. Nazari, F. Wallois, A. Aarabi, P. Berquin,	inhibition	ERP-N1, ERP-P1, ERP-P3	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 32	4.16
Neuroelectric mapping reveals precursor of stop failures in children with attention deficits [93]	Brandeis, D.; van Leeuwen, T.H.; Rubia, K.; Vitacco, D.; Steger, J.; Pascual-Marqui, R.D.; Steinhausen, H.C.	inhibition	ERP-N1, ERP-P1, ERP-P2, ERP-P460, ERP-P550, ERP-P640	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 15	3.76
Electroencephalographic and psychometric differences between boys with and without attention-deficit/hyperactivity disorder (ADHD): a pilot study [94]	Cox, D.J.; Kovatchev, B.P.; Morris, J.B.; Phillips, C.; Hill, R.J.; Merkel, L.	inhibition	PSD-theta, PSD-alpha, PSD-theta	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 8	1.06
Audio-visual entrainment program as a treatment for behavior disorders in a school setting [95]	Joyce, M.; Siever, D.	inhibition	PSD-alpha,PSD-beta, PSD-SMR	Global QATQS Rating: strong (score = 2.67); No additional bio-markers; N = 34	0.21

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
EEG biofeedback training and attention-deficit/hyperactivity disorder in an elementary school setting [96]	Carmody, D.P.; Radvanski, D.C.; Wadhwani, S.; Sabo, M.J.; Vergara, L.	inhibition	PSD-beta, PSD-delta, PSD-SMR	Global QATQS Rating: strong (score = 2.67); No additional bio-markers; N = 16	0.00
A psychophysiological marker of attention deficit/hyperactivity disorder (ADHD)—defining the EEG consistency index [97]	Kovatchev, B.; Cox, D.; Hill, R.; Reeve, R.; Robeva, R.; Loboschefski, T.	inhibition	CI	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 35	0.61
A potential electroencephalography and cognitive biosignature for the child behavior checklist–dysregulation profile [98]	McGough, J.J.; McCracken, J.T.; Cho, A.L.; Castelo, E.; Sturm, A.; Cowen, J.; Piacentini, J.; Loo, S.K.	inhibition	PSD-alpha, PSD-beta, PSD-theta, PSD-delta	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 2	0.36
The effects of neurofeedback training on concentration in children with attention deficit/hyperactivity disorder [99]	Kim, S.K.; Yoo, E.Y.; Lee, J.S.; Jung, M.Y.; Park, S.H.; Park, J.H.	inhibition	EEG concentration index	Global QATQS Rating: strong (score = 2.83); No additional bio-markers; N = 3	0.31
EEG dynamics of a go/nogo task in children with ADHD [100]	Baijot, S.; Cevallos, C.; Zarka, D.; Leroy, A.; Slama, H.; Colin, C.; Deconinck, N.; Dan, B.; Cheron, G.	inhibition	ERP, ITC	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 14	0.68
Electroencephalographic activity before and after cognitive effort in children with attention deficit/hyperactivity disorder [101]	Buyck, I.; Wiersema, J.R.	working memory	PSD-alpha, PSD-beta, PSD-theta, PSD-TBR	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 43	0.48
A randomized controlled trial of a brain-computer interface based attention training program for ADHD [102]	Lim, C.G.; Poh, X.W.W.; Fung, S.S.D.; Guan, C.; Bautista, D.; Cheung, Y.B.; Zhang, H.; Yeo, S.N.; Krishnan, R.; Lee, T.S.Buchmann, J.; Gierow, W.; Reis, O.; Haessler, F.	inhibition	PSD-alpha, PSD-beta, PSD-theta,	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 172	1.27
Intelligence moderates impulsivity and attention in ADHD children: an ERP study using a go/nogo paradigm [103]	Buchmann, J.; Gierow, W.; Reis, O.; Haessler, F.	inhibition	ERP-P3	Global QATQS Rating: strong (score = 2.40); No additional bio-markers; N = 15	0.90
Motor cortical inhibition in ADHD: modulation of the transcranial magnetic stimulation-evoked N100 in a response control task [104]	D'Agati, E.; Hoegl, T.; Dippel, G.; Curatolo, P.; Bender, S.; Kratz, O.; Moll, G.H.; Heinrich, H.	inhibition	ERP-N1	Global QATQS Rating: strong (score = 2.17); No additional bio-markers; N = 37	0.85
ERP correlates of selective attention and working memory 654 capacities in children with ADHD and/or PDD-NOS [105]	Gomarus, H.K.; Wijers, A.A.; Minderaa, R.B.; Althaus, M.	inhibition, working memory	ERP	Global QATQS Rating: moderate (score = 1.60); No additional bio-markers; N = 60	0.59

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Error and feedback processing in children with ADHD and children with autistic spectrum disorder: an EEG event-related potential study [106]	Groen, Y.; Wijers, A.A.; Mulder, L.J.; Waggeveld, B.; Minderaa, R.B.; Althaus, M.	working memory	ERP-P3, ERP-P2, ERP-Pe	Global QATQS Rating: moderate (score = 2.00); No additional bio-markers; N = 72	2.33
Changes in EEG spectrograms, event-related potentials, and event-related desynchronization induced by relative beta training in ADHD children [107]	Kropotov, J.D.; Grin-Yatsenko, V.A.; Ponomarev, V.A.; Chutko, L.S.; Yakovenko, E.A.; Nikishena, I.S.	inhibition	PSD-relative beta	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 86	0.43
Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence [108]	Murias, M.; Swanson, J.M.; Srinivasan, R.	working memory	PSD, Coherence Power	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 63	1.46
Case study: improvements in IQ score and maintenance of gains following EEG biofeedback with mildly developmentally delayed twins [109]	Fleischman, M.J.; Othmer, S.	inhibition	PSD-SMR	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 2	0.00
A controlled study of the effectiveness of EEG biofeedback training on children with attention deficit hyperactivity disorder [110]	Zhonggui, X.; Shuhua, S.; Haiqing, X.	working memory, inhibition	PSD-SMR, PSD-theta	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 60	0.10
ERPs correlates of EEG relative beta training in ADHD children [111]	Kropotov, J.D.; Grin-Yatsenko, V.A.; Ponomarev, V.A.; Chutko, L.S.; Yakoveuhua,E.A.; Nikishena, I.S.	inhibition	ERP-N1, ERP-P2, late ERP	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 86	1.14
Event-related potentials in attention-deficit/hyperactivity disorder of the predominantly inattentive type: an investigation of EEG-defined subtypes [112]	Brown, C.R.; Clarke, A.R.; Barry, R.J.; McCarthy, R.; Selikowitz, M.; Magee, C.	inhibition	ERP-N2, ERP-P3, ERP-N1, ERP-P1, ERP-P2	Global QATQS Rating: moderate (score = 1.80); Additional bio-markers; N = 81	0.17
Lateralized modulation of posterior alpha oscillations in children [113]	Vollebregt, M.A.; Zumer, J.M.; Ter Huurne, N.; Castricum, J.; Buitelaar, J.K.; Jensen, O.	inhibition	MI-alpha	Global QATQS Rating: moderate (score = 1.80); Additional bio-markers; N = 21	0.49
Posterior alpha oscillations reflect attentional problems in boys with attention deficit hyperactivity disorder [114]	Vollebregt, M.A.; Zumer, J.M.; Ter Huurne, N.; Buitelaar, J.K.; Jensen, O.	inhibition	MI-alpha	Global QATQS Rating: moderate (score = 1.40); Additional bio-markers; N = 26	1.04
Intact stimulus–response conflict processing in ADHD—multilevel evidence and theoretical implications [115]	Bluschke, A.; Mückschel, M.; Roessner, V.; Beste, C.	inhibition	ERP-N1, ERP-P3, ERP-N2, ERP-P1	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 69	0.36

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Topographical analyses of attention disorders of childhood [116]	DeFrance, J.; Smith, S.; Schweitzer, F.; Ginsberg, L.; Sands, S.	inhibition	PSD-beta, PSD-alpha, PSD-theta, ERP-P3, ERP-P2, ERP-P5	Global QATQS Rating: strong (score = 1.80); Additional bio-markers; N = 71	0.53
Varying required effort during interference control in children with AD/HD: task performance and ERPs [117]	Johnstone, S.J.; Watt, A.J.; Dimoska, A.	inhibition	ERP-N2, ERP-P3, ERP-P4	Global QATQS Rating: weak (score = 1.20); Additional bio-markers; N = 52	0.69
Response inhibition and interference control in children with AD/HD: a visual ERP investigation [118]	Johnstone, S.J.; Barry, R.J.; Markovska, V.; Dimoska, A.; Clarke, A.R.	inhibition	ERP-N1, ERP-N2, ERP-P3, ERP-P2	Global QATQS Rating: strong (score = 1.83); Additional bio-markers; N = 40	1.58
A comparative study on the neurophysiological mechanisms underlying effects of methylphenidate and neurofeedback on inhibitory control in attention deficit hyperactivity disorder [119]	Bluschke, A.; Friedrich, J.; Schreiter, M.L.; Roessner, V.; Beste, C.	inhibition	ERP-N1, ERP-N2, ERP-P3, ERP-P2	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 20	1.30
A pilot study of combined working memory and inhibition training for children with AD/HD [120]	Johnstone, S.J.; Roodenrys, S.; Phillips, E.;Watt, A.J.; Mantz, S.	inhibition, working memory	ERP-N1, ERP-N2, ERP-P3	Global QATQS Rating: weak (score = 1.17); Additional bio-markers; N = 40	1.91
Abnormal alpha modulation in response to human eye gaze predicts inattention severity in children with ADHD [121]	Guo, J.; Luo, X.; Wang, E.; Li, B.; Chang, Q.; Sun, L.; Song, Y.	inhibition	ERP	Global QATQS Rating: moderate (score = 1.60); No additional bio-markers; N = 108	0.13
Aiding diagnosis of childhood attention-deficit/hyperactivity disorder of the inattentive presentation: discriminant function analysis of multi-domain measures including EEG [122]	Johnstone, S.J.; Parrish, L.; Jiang, H.; Zhang, D.W.; Williams, V.; Li, S.	inhibition	PSD-alpha, PSD-beta, PSD-theta, PSD-delta, PSD-TBR	Global QATQS Rating: strong (score = 2.00); No additional bio-markers; N = 214	0.00
Behavioural and ERP indices of response inhibition during a stop-signal task in children with two subtypes of attention-deficit hyperactivity Disorder [123]	Johnstone, S.J.; Barry, R.J.; Clarke, A.R.	inhibition	ERP-N1, ERP-N2, ERP-P3, ERP-P2	Global QATQS Rating: moderate (score = 1.80); No additional bio-markers; N = 38	0.79
Virtual reality therapy in prolonging attention spans for ADHD [124]	Sushmitha, S.; Devi, B.T.; Mahesh, V.; Geethanjali, B.; Kumar, K.A.; Pavithran, P.	inhibition, planning	PSD-alpha, PSD-beta, PSD-theta, PSD-delta, PSD-TBR	Global QATQS Rating: strong (score = 2.33); Additional bio-markers; N = 20	0.00

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Quantifying brain activity state: EEG analysis of background music in a serious game on attention of children [125]	Soysal, Ö.M.; Kiran, F.; Chen, J.	inhibition, planning	PSD-alpha, PSD-beta	Global QATQS Rating: strong (score = 2.50); No additional bio-markers; N = 6	0.79
Source-based multifractal detrended fluctuation analysis for discrimination of ADHD children in a time reproduction paradigm [126]	Khoshnoud, S.; Nazari, M.A.; Shamsi, M.	inhibition	ERP-P3- multifractality	Global QATQS Rating: moderate (score = 2.00); Additional bio-markers; N = 34	0.00
Virtual classroom: an ADHD assessment and diagnosis system based on virtual reality [127]	Tan, Y.; Zhu, D.; Gao, H.; Lin, T.W.; Wu, H.K.; Yeh, S.C.; Hsu, T.Y.	working memory	PSD-TBR, PSD-alpha, PSD-beta, PSD-theta, PSD-deta	Global QATQS Rating: weak (score = 1.20); Additional bio-markers; N = 100	1.45
Acquisition and analysis of cognitive evoked potentials using an emotiv headset for ADHD evaluation in children [128]	Mercado-Aguirre, I.M.; Gutiérrez-Ruiz, K.; Contreras-Ortiz, S.H.	working memory	ERP-P3	Global QATQS Rating: strong (score = 2.83); No additional bio-markers; N = 19	0.50
Personalized features for attention detection in children with attention deficit hyperactivity disorder [129]	Fahimi, F.; Guan, C.; Goh,W.B.; Ang, K.K.; Lim, C.G.; Lee, T.S.	inhibition	PSD, PSD-TAR, PSD-TBAR	Global QATQS Rating: strong (score = 2.33); No additional bio-markers; N = 120	1.19
Identification of ADHD cognitive pattern disturbances using EEG and wavelets Analysis [130]	Gabriel, R.; Spindola, M.M.; Mesquita, A.; Neto, A.Z.	inhibition, working memory	Morlet Wavelet Transform - delta, theta, alpha, and beta-power spectrum and amplitude	Global QATQS Rating: strong (score = 2.20); No additional bio-markers; N = 19	0.00
Neurofeedback based attention training for children with ADHD [131]	Chen, C.L.; Tang, Y.W.; Zhang, N.Q.; Shin, J.	inhibition, working memory	PSD-alpha, PSD-beta, PSD-theta, PSD-deta	Global QATQS Rating: strong (score = 2.50); Additional bio-markers; N = 10	n.a.
Influence of a BCI neurofeedback videogame in children with ADHD. Quantifying the brain activity through an EEG signal processing dedicated toolbox [132]	Blandón, D.Z.; Muñoz, J.E.; Lopez, D.S.; Gallo, O.H.	inhibition	PSD-alpha, PSD-beta, PSD-delta, PSD-gamma, PSD-TBR	Global QATQS Rating: strong (score = 2.83); No additional bio-markers; N = 9	2.64
Neurofeedback treatment experimental study for adhd by using the brain–computer interface neurofeedback system [133]	Liu, T.; Wang, J.; Chen, Y.; Wang, R.; Song, M.	inhibition	PSD-beta, PSD-theta, PSD-TBR, PSD- SMR	Global QATQS Rating: moderate (score = 1.83); Additional bio-markers; N = 22	2.63
Analysis of attention deficit hyperactivity disorder in EEG using wavelet transform and self organizing maps [134]	Lee, S.H.; Abibullaev, B.; Kang, W.S.; Shin, Y.; An, J.	working memory	Wavelet Transform- alpha, theta, beta power spectrum	Global QATQS Rating: strong (score = 2.60); No additional bio-markers; N = 39	1.09

Table 2. *Cont.*

Articles	Authors	Executive Functions	EEG-Features	Quality Assessment	FWCI
Classification of ADHD and non-ADHD using AR models [135]	Marcano, J.L.L.; Bell, M.A.; Beex, A.L.	inhibition	PSD-TBR	Global QATQS Rating: weak (score = 3.00); No additional bio-markers; N = 4	1.19
Deep learning based on event-related EEG differentiates children with ADHD from healthy controls [136]	Vahid, A.; Bluschke, A.; Roessner, V.; Stober, S.; Beste, C.	inhibition	ERP-P3	Global QATQS Rating: strong (score = 1.20); Additional bio-markers; N = 28	3.44

3.1. Executive Functions and EEG Features

As far as the investigation level of EFs focused by the articles is concerned, the sub-EFs level is predominant (68 articles), followed by that of basic EFs (31 articles), and, lastly, that of high-order EFs (5 articles). In particular, as the sub-function level is concerned, interference inhibition is absolutely the most investigated (47 articles), with about twice as many articles on response inhibition (26 articles) and visual-spatial memory (17 articles). There are very few studies on verbal working memory (3 articles). Considering basic EFs, working memory and inhibition (16 and 13 articles, respectively) are investigated more than flexibility (3 articles). As far as high-level FEs are concerned, only planning is considered more than once (four articles) (Figure 4).

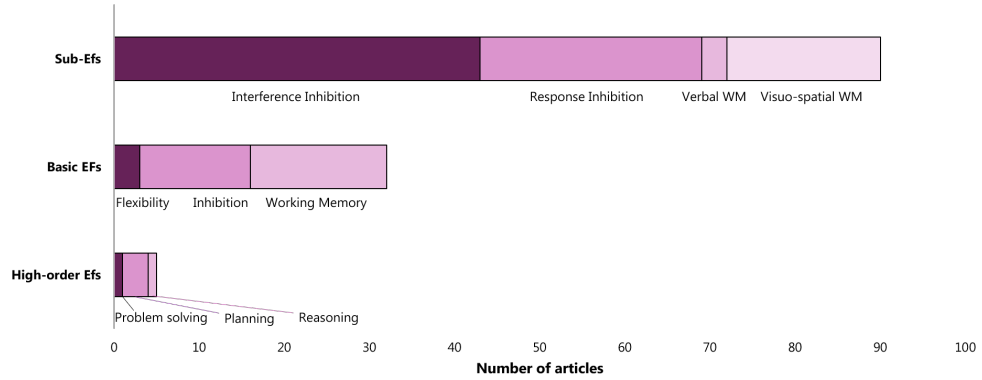

Figure 4. Number of articles per executive function considering the level of details in analysis of executive functions.

Considering that sub-functions are an articulation of basic EFs, 64 of the articles investigate the cluster *inhibition* (inhibition and its sub-functions) and the 30% the cluster *working memory* (working memory and its sub-functions). The relationship between EF clusters and EEG features was analyzed starting from their domains of definition. In particular, the feature was defined *effective* when it assumed different levels (with statistical relevance) in the group with ADHD (target group) compared to the control group (or to the pre-treatment condition if the comparison is made within the same group). Otherwise, the feature is defined as *not effective*.

The features related to the cluster inhibition are extracted at 52% in the time domain, at 45% in the frequency domain, and at 2% in the time-frequency domain. In the time domain, 13 articles consider the amplitude of P3 (See the Appendix A for details) and 9 amplitude of N1 (See the Appendix A for details) (Figure 5). In the frequency domain, 15%, 17%, and 18% analyzed the power spectrum density in alpha, beta, and theta bands, respectively (Figure 6). The WM-cluster features are mainly proposed by referring to the frequency domain (71%) (Figure 7), 28% of articles focus on time domain (Figure 8), and only

1% focus on time-frequency domain. In the frequency domain, the most considered features are the power spectrum density in alpha (16%), beta (14%), and theta (7%) bands. In the time domain, 20% of the articles considered the P3 amplitude.

As far as sub-functions are concerned, the interference inhibition features are mainly extracted from the frequency domain (65%). In particular, almost half of the articles evaluate the power spectrum density in alpha, beta, and theta bands (Figure 9). For response inhibition, the time domain is the most investigated (73%), with particular attention paid to the N1 and N2 (See the Appendix A for details) amplitudes (Figure 10). Most of the articles concerning the visuospatial WM features are centred on frequency domain (66%), but no clear trends emerged (Figure 11). As aforementioned, only three articles focus on verbal WM; therefore, any statistic on the features would be inconsistent.

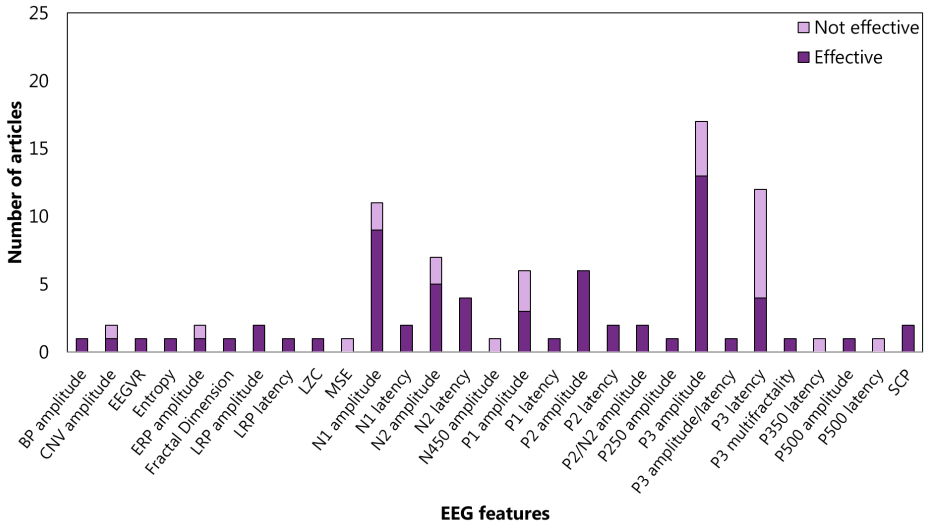

Figure 5. Articles focusing on the relationship between EFs from cluster *inhibition* and EEG features from time domain. P300 amplitude is the feature most studied: 12 articles verified (effective) the relationship, and 3 articles did not (not effective). LZC: Lempel–Ziv complexity; EEGVR: electroencephalogram valid rate. MSE: multi-scale entropy. SCP: slow cortical potentials; and ERP: event-related potential.

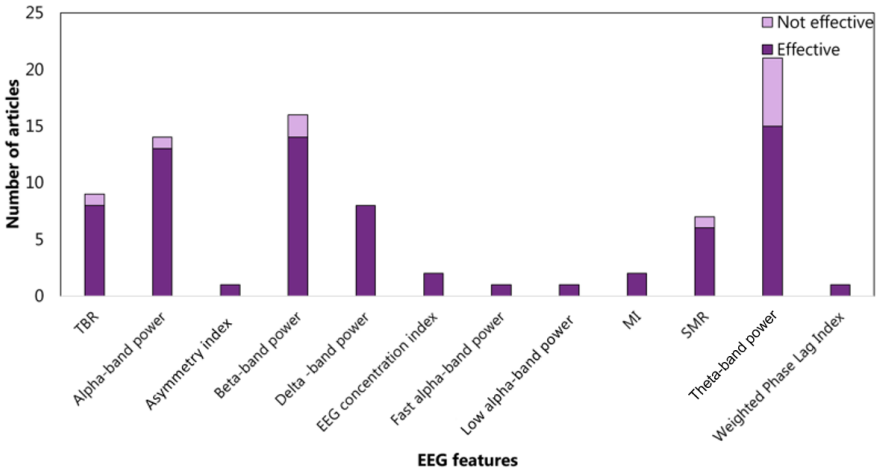

Figure 6. Articles focusing on the relationship between EFs from cluster *inhibition* and EEG features from frequency domain. Theta-band power is the feature most studied: 15 articles verified (effective) the relationship, and 6 articles did not (not effective). MI: modulation index. SMR: senso-motor rhythm.

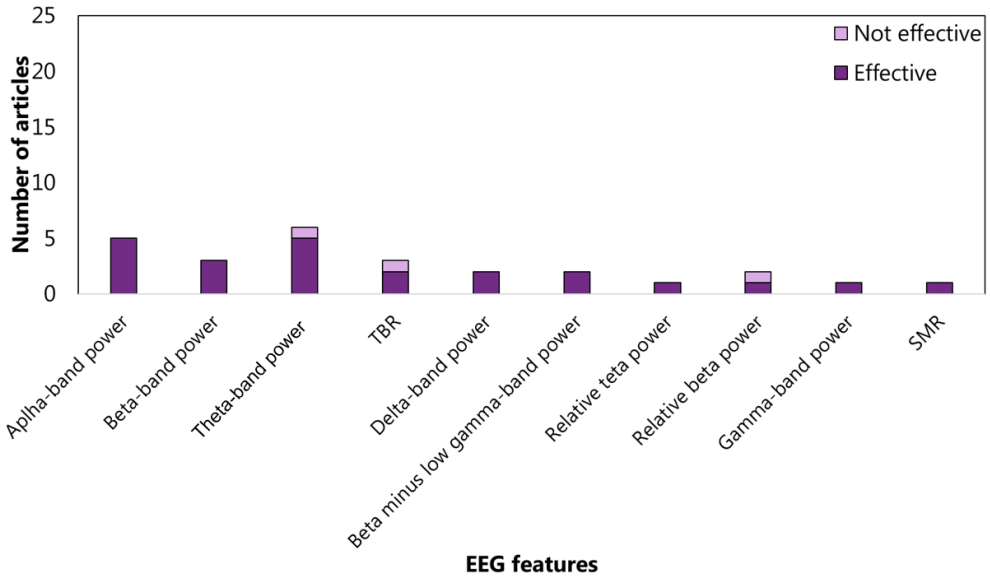

Figure 7. Articles focusing on the relationship between EFs from *cluster working memory* and EEG features from frequency domain. Theta-band power is the feature most studied: five articles verified (effective) the relationship. TBR: theta–beta ratio; SMR: senso-motor rhythm.

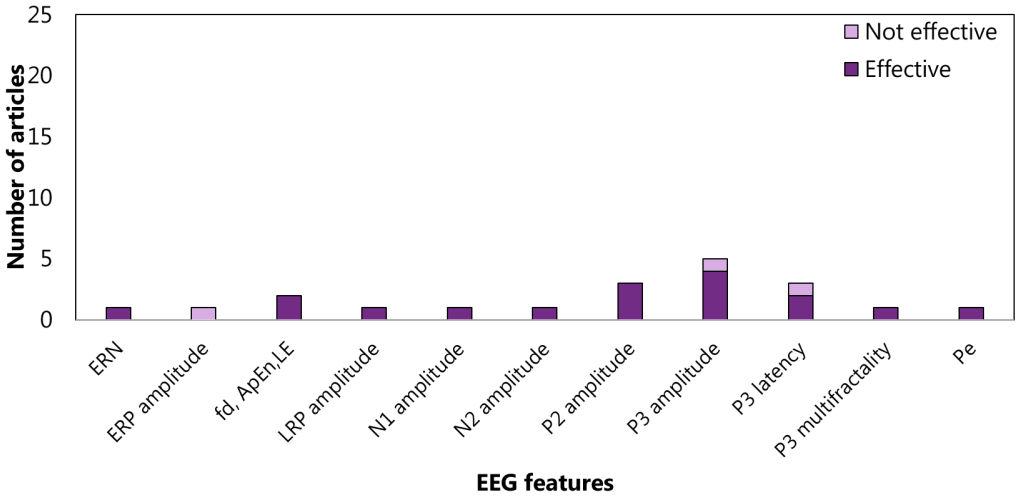

Figure 8. Articles focusing on the relationship between EFs from *cluster working memory* and EEG features from time domain. P300 amplitude is the feature most studied: four articles verified (effective) the relationship, and 1 article did not (was not effective). fd: fractal dimension; ApEn: Approximate Entropy; LRP: lateralised readiness potential; LE: Lyapunov Exponent ; ERN: error-related negativity; and Pe: error positivity.

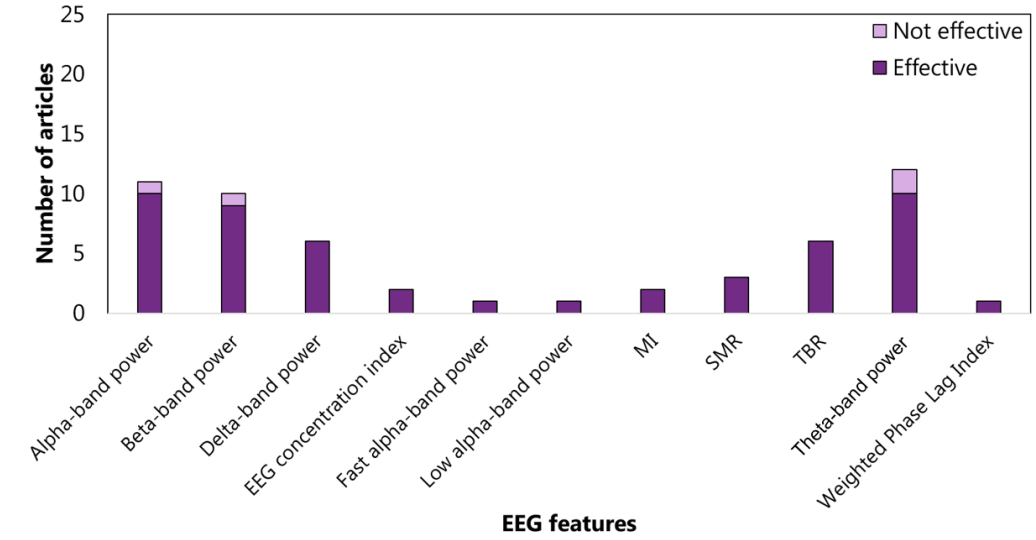

Figure 9. Articles focusing on the relationship between *interference inhibition* and EEG features from frequency domain. Theta-band power is the feature most studied: 10 articles verified (effective) the relationship, and 2 articles did not (not effective). TBR: theta-beta ratio; MI: modulation index; SMR: senso-motor rhythm; and CI: EEG consistency index.

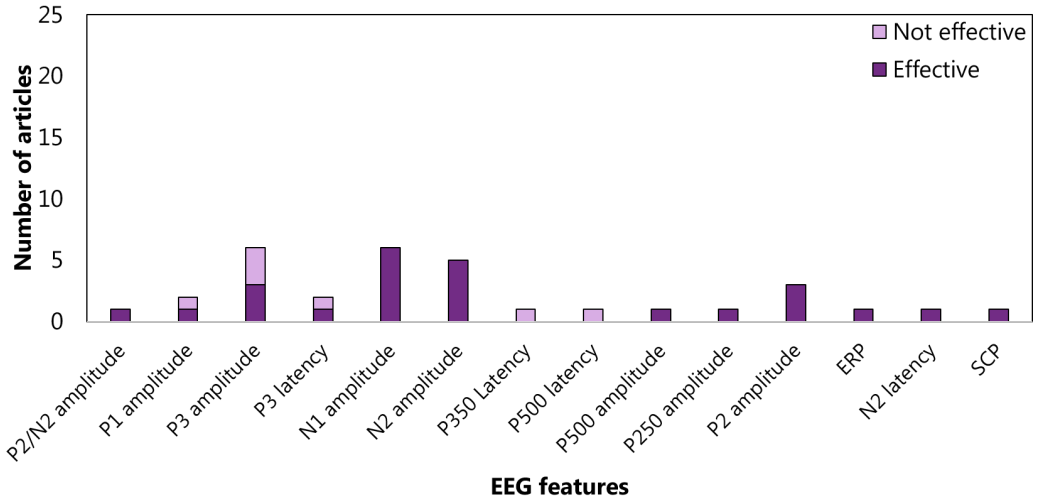

Figure 10. Articles focusing on the relationship between *response inhibition* and EEG features from time domain. P300 and N100 amplitudes are the features most studied. As far as P300 is concerned, three articles verified (effective) the relationship, and three articles did not (not effective), while all six articles considered verified the effectiveness of N100. ERP: event-related potential; SCP: slow cortical potentials.

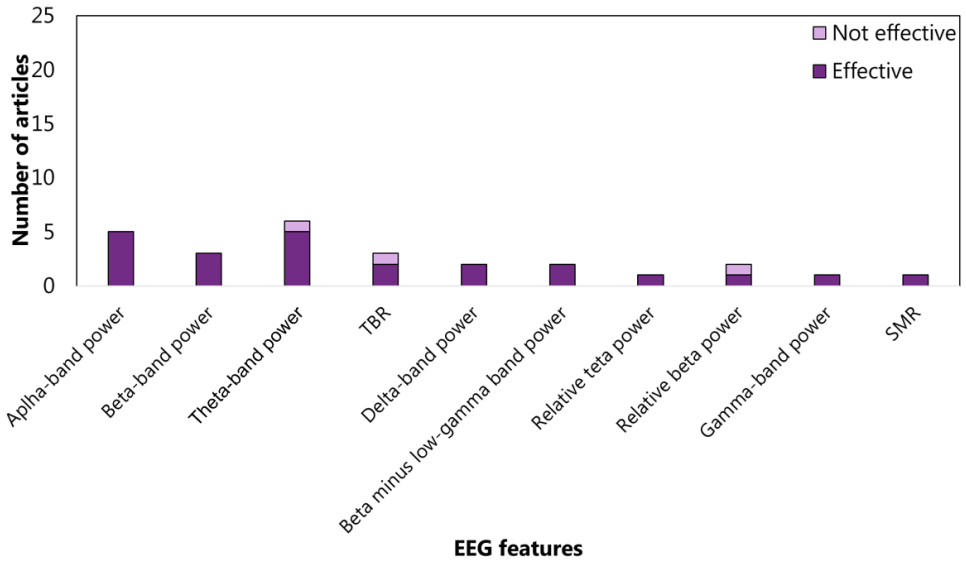

Figure 11. Articles focusing on the relationship between *visuo-spatial working memory* and EEG features from frequency domain. Theta-band power is the feature most studied: five articles verified (effective) the relationship, and one article did not (not effective). TBR: theta–beta ratio; SMR: sensorimotor rhythm.

3.2. Quality Assessment Output

The analysis results were carried out separately on the diagnostic and therapeutic articles due to the different numbers of QATQS components considered for the two type of articles, as stated in Section 2.2.3. Articles on diagnostics were grouped into 4 strong, 14 moderate, and 29 weak, following the application of the above criteria, as shown in Figure 12. Regarding the articles on therapy, 1 strong, 4 moderate, and 49 weak articles arose, as shown in Figure 13.

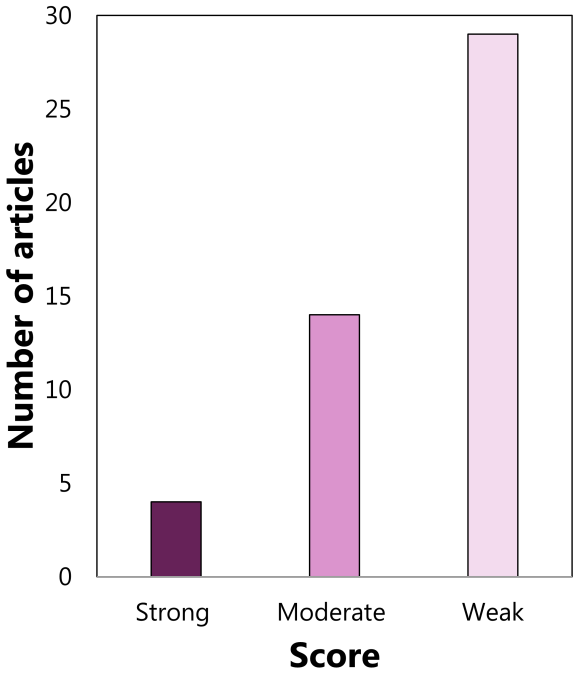

Figure 12. Global rating of articles on diagnostics.

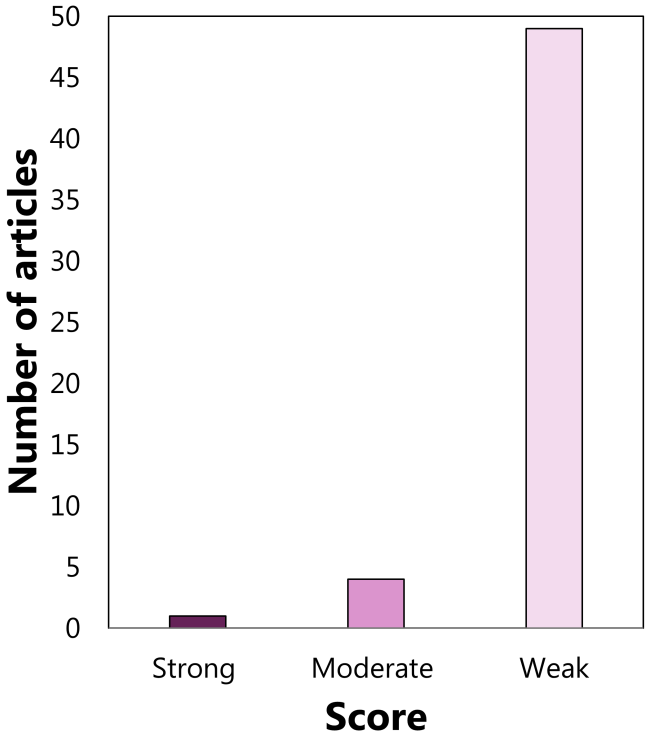

Figure 13. Global Rating of articles on therapy.

Moreover, each component was analyzed to evaluate some relevant trends. Regarding articles on therapy, (i) 72% of authors included a control group in addition to the target one, (ii) 9% performed a double-blinded study, (iii) 2% supported the subjective data acquired through the administration of questionnaires or with the quantitative data from other biosignal sensors besides the EEG, and (iv) 9% comprehensively described the causes of the withdrawal and dropouts.

Regarding articles on diagnostics, (i) 92% of authors included a control group in addition to the target one, (ii) 10% supported the subjective data acquired through the administration of questionnaires or with quantitative data from other biosignal sensors besides the EEG, and (iii) 23% comprehensively described the causes of the withdrawal and dropouts. Therefore, even if the most of the studies considered a control group, the prevalence of a weak score emerged due to the partial respect for the other components proposed by the QATQS.

4. Discussion

ADHD has been investigated at a higher level of detail in the last decades: firstly, from a clinical point of view, DSM-V identified ADHD sub-types (2013); secondly, from a scientific point of view, impaired EFs in ADHD have been studied at the level of sub-components since the early 2000s. The review results confirmed that ADHD analysis is increasingly converging on the study of the sub-EFs. Indeed, the majority of articles (65%) analyzed the sub-components of inhibition and working memory. Only 30% evaluated the basic EFs, while 5% dwelled on high-order EFs (i.e., reasoning, planning, and problem solving). In particular, the interference inhibition and visual-spatial working memory are the mainly studied sub-functions of inhibition and working memory basic EFs, respectively. A poorly studied sub-function is the verbal working memory.

Concerning cluster *inhibition* , studies are mainly centred on the EEG features extracted from time domain (53%) with respect to the frequency domain (45%) and the time-frequency domain (2%). In particular, the most investigated time-domain features are the ERP components. Several authors studied the P3 and N1 amplitudes during inhibition tasks in

ADHD subjects and controls; 13 vs. 4 and 9 vs. 2 articles found a significant statistical difference for P3 and N1 amplitudes, respectively. As stated in Section 2.2.3, in the case of features from the frequency domain, the focus was on the power spectral density in the alpha, beta, and theta bands. These studies almost agreed to identify a higher alpha and beta activity in the ADHD group than in the controls group during inhibition tasks. Conversely, concerning the power spectral density in the theta bands, six articles among 21 did not confirm this EEG feature effective in discriminating or treating ADHD patients. As far as inhibition sub-functions are concerned, a slight link was found between interference inhibition and spectral density in alpha, beta, and theta bands. Among articles concerning cluster *inhibition*, ERP components were not focused only on studies on interference inhibition. The last consideration may be due to the fact that more articles on therapy fell into this category than ones on diagnostics. Indeed, ERP components are rarely used in neurofeedback due to the high latency required for their computation. In fact, by restricting the analysis to articles on diagnostics, a prevalence in considering the amplitude of the P3 component emerged.

Working memory (WM) is another EF mainly considered in ADHD. The WM-related features were evaluated at 28% in the time domain, 71% in the frequency domain, and 1% in the time-frequency domain. A trend emerged in the frequency domain between working memory and power spectral density in alpha (9 articles), beta (8 articles), and theta (11 articles) bands. Studies on working memory sub-functions focused mainly on the visuospatial component and investigated frequency EEG features, but no significant trends prevailed. The results showed that identifying clear relationships between EFs and EEG features is still challenging. However, within some fragmentation, ERP components were particularly studied. In particular, P3 amplitude emerged as the most focused EEG feature for the diagnostics and therapy of ADHD.

So in summary, power spectral density in alpha, beta, and theta bands are the most attentioned EEG features concerning interference inhibition. Instead, N1 and N2 amplitude are the most used features with regard to response inhibition. Visuospatial working memory is mainly linked to alpha and theta band power spectral density. On the other hand, studies on cognitive flexibility and verbal working memory are few and poorly convergent.

The quality of articles was analyzed to reinforce the emerged quantitative trends. The quality evaluation was conducted according to QATQS' guidelines. The therapeutic articles on diagnostics were classified separately because the blinding component was only analyzed for the articles on therapy, as explained in Section 2.2.3. The application of QATQS criteria to the articles on diagnostics led to the identification of 9% strong articles, 30% moderate articles, and 61% weak articles, whereas it was apparent from the analysis of the articles on therapy that 2% of the articles had a strong score, 7% had a moderate score, and 91% reported a weak score. Within the moderate scoring categories, articles showing high scores on at least half of the components of the QATQS were identified as *higher quality articles*, along with articles with strong scores. In total, there are 15 higher-quality articles; 20% studied the working memory and 80% analyzed inhibition and/or its sub-functions.

As reported in Figures 14 and 15, the articles focused on inhibition confirmed the effectiveness of the ERP components for diagnostics and therapy of ADHD patients. Finally, a further analysis based on Scopus's *Field-Weighted Citation Impact* metric was conducted. Specifically, a comparison was performed focusing on the five best performing articles according to the Scopus metric (Table 3) and the five articles found to be of higher quality with the application of the QATQS (Table 4). In both the cases, the comparison between the two scores, namely, Scopus and QATQS, was realized.

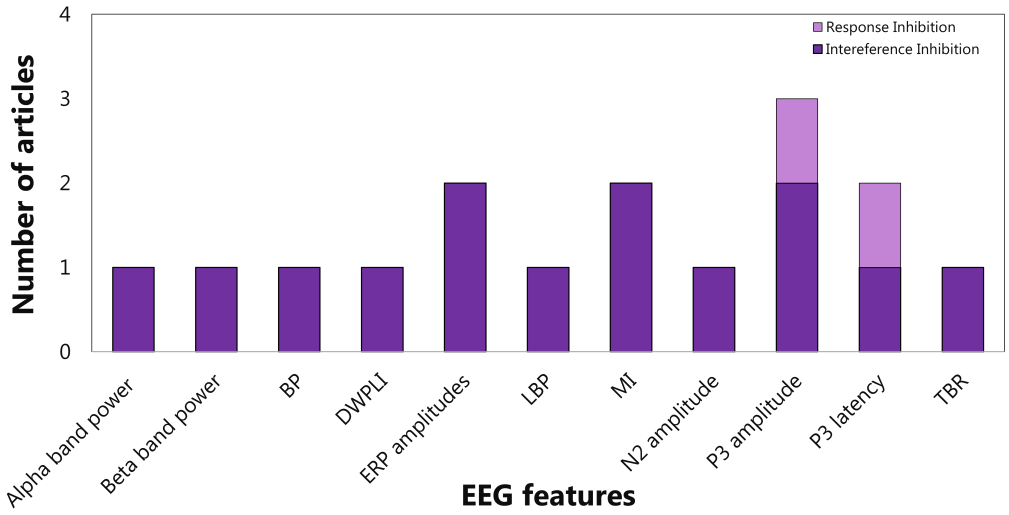

Figure 14. EEG features for inhibition's sub-function emerged from highest quality articles.

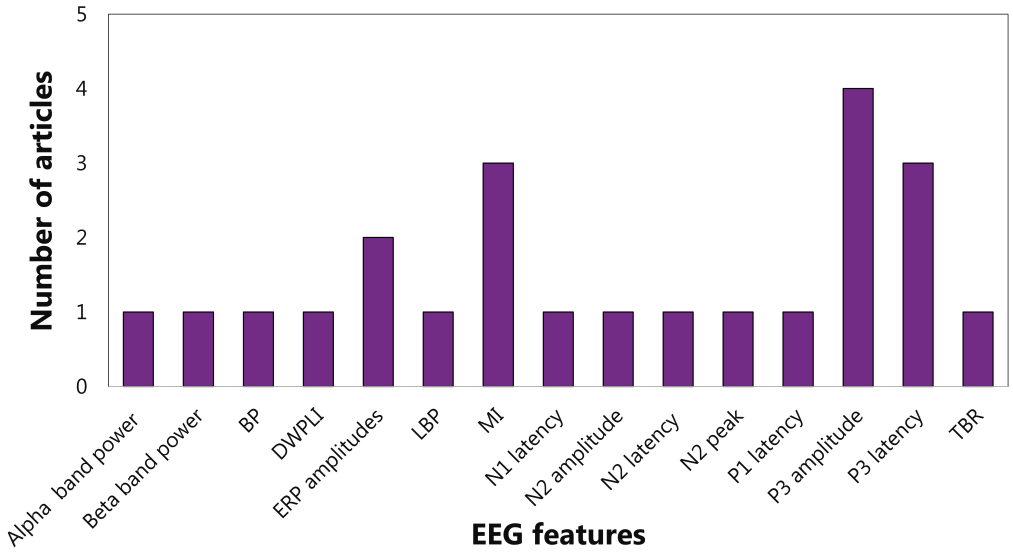

Figure 15. EEG features for inhibition emerged from highest quality articles.

Table 3. The five top scored articles according to the field-weighted citation impact metric by Scopus (the higher, the best). For each article, the normalized QATQS Score is also reported (the lower, the better). The normalized QATQS Score is computed as the ratio between the global quality score of the article and the number of quality components considered. FWCI: field-weighted citation impact.

Article	FWCI Range [0.00–4.17]; Median = 0.77	Normalized QATQS Score Range [1.17–3.00]; Median = 2.17
[39]	4.17	1.83
[92]	4.16	2.00
[93]	3.66	2.00
[136]	3.44	1.20
[64]	3.25	2.20

Table 4. The five top scored articles according to the normalized QATQS Score. For each article, the field-weighted citation impact metric by Scopus is also reported (the higher, the best). The normalized QATQS score is computed as the ratio between the global quality score of the article and the number of quality components considered (the lower, the better). FWCI: field-weighted citation impact.

Article	Normalized QATQS Score Range [1.17–3.00]; Median = 2.17	FWCI Range [0.00–4.17]; Median = 0.77
[120]	1.17	1.91
[127]	1.20	1.45
[136]	1.20	3.44
[117]	1.20	0.69
[89]	1.60	1.20

In Table 3, the articles were sorted according to the field-weighted citation impact. The table includes the top five articles with the associated standardized QAQTS score.

The normalized QATQS score is computed as the ratio between the global quality score of the article and the number of quality components considered. Analyzing the five articles with the highest FWCI, only 20% of the articles report a higher quality score than the quality score median. In Table 4, the articles were sorted according to the normalized QAQTS. In particular, the five articles with the highest score are reported with the corresponding FWCI obtained. From the analysis of these articles, it emerged that 80% of the articles report a higher FWCI than the FWCI median. Finally, only one article appears in both tables, as shown in Tables 3 and 4. However, the results obtained by means of the two metrics appear to be compatible. Indeed, four of the five articles performed better according to one criterion scored higher than the median value with respect to the other criterion.

Articles with higher scores according to the two metrics confirmed the results of the quantitative analysis. As far as the article that scored 4.17 according to Scopus parameters (highest score), visuospatial working memory is the investigated executive function. The authors identified power spectral density in theta and beta bands as the most representative features for diagnostics and therapy. The highest QATQS scored article (1.17 scored) considered both inhibition and working memory and highlighted the role of ERP components (in particular, N1, N2, and P3 latencies). Finally, the only article, highly scored according to both the metrics is focused on interference inhibition and the related EEG features are P1, P2, and N1 amplitudes. These last considerations also confirmed the centrality of the ERP components in the diagnostics and therapy of ADHD based on inhibition and the role of power spectral density for the visuospatial working memory, which already emerged from the quantitative study. This review encourages further investigation into the use of EEG in the diagnosis and therapy of ADHD based on EFs assessment.

5. Conclusions

A systematic review of feature extraction strategies in electroencephalographic (EEG) studies concerning the diagnosis and therapy of attention deficit hyperactivity disorder (ADHD) in children is presented. The analysis was realized at the executive function level to manage the effort of finding neurocorrelates of an heterogeneous disorders such as ADHD. One hundred and one articles, concerning the diagnostics and therapy of ADHD children aged 8 to 14, were collected. Each article was subjected to two types of analysis in parallel: (i) the analysis to extract relationships between EEG features and executive functions and (ii) the analysis to assess the rigor and scientific impact of the study (quality analysis). Event-related potential components resulted mainly exploited for executive functions related to the cluster *inhibition*, whereas band power spectral density is the most considered EEG feature for executive functions related to the cluster *working memory*. The quality analysis confirmed the quantitative results regarding the significance of the band power spectral density and event-related potential components for the analysis of executive functions in ADHD. This review identifies the most promising EEG features for the study of executive functions in ADHD. Anchoring EEG features to elementary cognitive functions

allows the heterogeneity of ADHD-related disorders to be electroencephalographically analyzed more effectively.

Author Contributions: Conceptualization, P.A., L.C., M.F., L.G., F.M. (Francesca Mancino) and N.M.; methodology, P.A., A.C., L.C., M.F., L.G., F.M. (Francesca Mancino), F.M. (Federico Mantile) and N.M.; articles search and analysis L.G., F.M. (Federico Mantile) and N.M.; writing—original draft preparation, L.G., F.M. (Francesca Mancino) and N.M.; review and editing, all authors; supervision, P.A. and L.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors thank *Villa delle Ginestre* Rehabilitation Center (Volla, Na, Italy) for the scientific collaboration. The authors also thank Paola Lanteri for her helpful suggestions.

Conflicts of Interest: The authors declare no competing interest.

Appendix A. Most Used EEG Features in EF Analysis

Appendix A.1. Event-Related Potential

Event-related potential (ERP) waveforms are composed of a sequence of positive and negative voltage deflections, defined as ERP components. Most ERP components are named by a letter and a number. In particular, the letter refers to the positivity (P) or negativity (N) of the wave's amplitude, while the number indicates either the latency in milliseconds or the component's ordinal position in the waveform.

Some of the main ERP components are shown in Figure A1 and are summarized in the following sections.

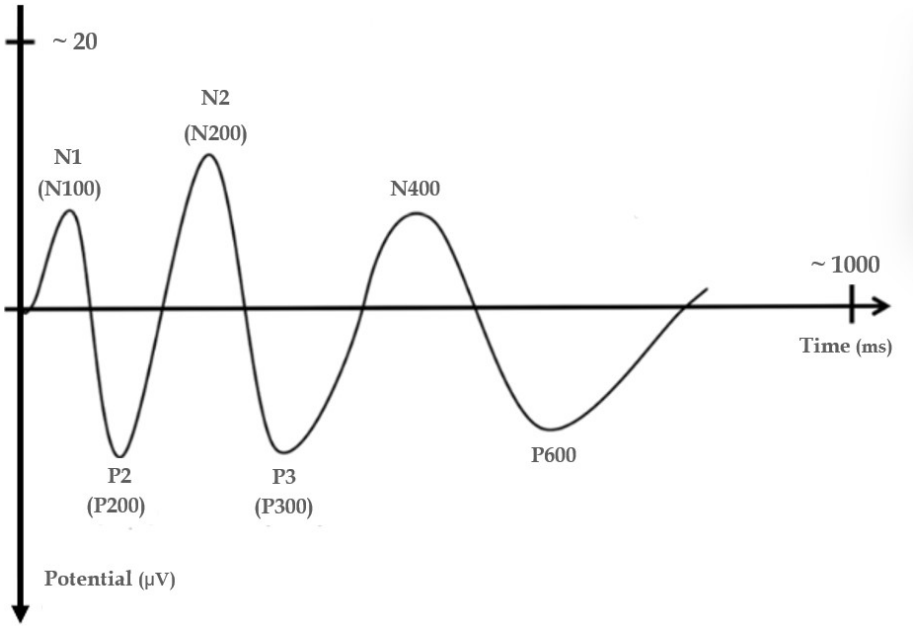

Figure A1. ERP waveform.

Appendix A.1.1. N1

The N1 or N100 component of ERP is a negative-going peak, the first substantial peak in the waveform, and often occurs between 90 and 200 msec after a stimulus is presented.

Appendix A.1.2. N2

The N2 or N200 ERP component is the second negative peak and occurs 200 ms after the stimulus.

Appendix A.1.3. P2

P2 or P200 ERP component is the second positive peak and occurs around 100–250 msec after the stimulus.

Appendix A.1.4. P3

The P3 or P300 ERP component is the third positive peak and has a quite variable latency. Particularly, the peak of the P300 component may occur between 250 ms and 700 ms.

Appendix A.1.5. N400

It is the fourth negative peak and peaks around 400 milliseconds post-stimulus onset.

Appendix A.1.6. P600

P600 is characterized as a positive-going deflection with an onset around 500–600 milliseconds after the stimulus and lasts several hundred milliseconds.

Appendix A.1.7. Error-Related Negativity

Error-related negativity (ERN) is a negative component of the ERP occurring after a wrong answer during sensorimotor tasks. The peak of these components is around 150 msec after response onset.

Appendix A.1.8. Contingent Negative Variation

The contingent negative variation (CNV) is the negative portion of the wave between the presentation of the warning and imperative stimuli.

Appendix A.1.9. Lateralised Readiness Potential

The lateralised readiness potential (LRP) is an event-related potential associated with preparing of motor activity in contralateral motor areas.

Appendix A.1.10. Bereitschaftspotential

The bereitschaftspotential (BP) is an event-related potential reflecting cortical activity associated with the initiation and preparation of voluntary motor actions. BP is a slow negative EEG-shift starting about 1 s before the onset of a self-paced movement.

Appendix A.2. Slow Cortical Potential

Slow cortical potentials (SCPs) are negative deviations in electrical activity that last from several hundred milliseconds to several seconds. SCPs can be induced by the subject himself or activated by external factors.

Appendix A.3. Fractal Dimension

Fractal dimension (FD) is a measure of the complexity of a time series. Different complexity estimators such as Higuchi, Katz, box-counting, and Petrosian are used to calculate FD. In particular, according to Higuchi's algorithm, FD is computed as follows. Given a one-dimensional EEG discrete time series $x = \{x_1, \dots x_N\}$ and the scale factor k, a new time series y_j^k is calculated as

$$y_j^k = \{x(m), x(m+k), x(m+2k), \dots, x(m+[\frac{N-m}{k}]k)\}$$

for m = 1, 2, 3, . . . , k, where [.] indicates the integer part of the series. The length L_m^k is computed for y_j^k as

$$L_m^k = \frac{\sum |y(m+ik) - y(m+(i-1)k|(N-1)}{[\frac{(N-m)}{k}]k}$$

where N is the number of samples. FD is calculated as the total average length, $L(k)$, for k_1 to k_{max}.

Appendix A.4. Power Spectral Density/Relative Power Spectral Density

The power spectral density (PSD) represents the power distribution of EEG series in the frequency domain. The power spectral density (PSD) of the EEG signal can be calculated into six EEG sub-bands: delta (0.5–4 Hz), theta (4–7 Hz), low alpha (8–10 Hz), high alpha (10–12 Hz), beta (13–30 Hz), and gamma (30–40 Hz)). Welch's, FFT, and Burg's methods are the three most generally used algorithms for PSD computation within a frequency band in EEG. The relative PSD is the ratio of the PSD to one frequency band and the total frequency signal.

Appendix A.5. Modulation Index

The alpha modulation index (*MI*) is calculated as the difference between the alpha power of each electrode's right-cued trials and left-cued trials.

This subtraction was then normalized by dividing by half of the sum of these values:

$$MI = \frac{(\alpha_{leftcuedtrials} - \alpha_{rightcuedtrials})}{(\frac{1}{2}\alpha_{leftcuedtrials} + \alpha_{rightcuedtrials})}$$

Appendix A.6. Consistency Index

The first step to obtain the EEG consistency index (*CI*) consists in calculating discrete spectra for all EEG channels. Then, for each EEG band and channel, the power change distances (PCD) between two contiguous tasks are calculated and filtered to remove changes below a 'noise threshold'. This threshold works as follows: the PCDs that are larger by an absolute value than the threshold are marked by 1 or -1 depending on their direction, whereas all PCDs below threshold are marked by zero. This filtering transforms the PCD into a sequence of 1, 0, and -1 that indicates whether a significant power change was observed for each EEG band and channel while the person shifted from one task to another. Finally, filtered PCD below and above the treshold value are summed. The EEG consistency index (*CI*) is defined as

$$CI = 100|\frac{1}{2}(\sum_{belowcutoff} \delta_i - \sum_{abovecutoff} \delta_j)|\%$$

where δ_i, δ_j= -1,0,1

Appendix A.7. Asymmetry Index

The asymmetry index (*AI*) of alpha ERD definition is

$$AI = \frac{Alpha(RightHemisphere) - Alpha(LeftHemisphere)}{Alpha(RightHemisphere) + Alpha(LeftHemisphere)}$$

Appendix A.8. Multiscale Entropy

The multiscale entropy (MSE) method has been used to quantify the complexity of signal by calculating the sample entropy (SampEn) over multiple time scales, which was realized by the coarse-grained procedure [137]. Given a one-dimensional EEG discrete time

series $x = \{x_1, \ldots x_N\}$ and the scale factor τ, the time series is calculated into consecutive and nonoverlapping time series y_j^τ as

$$y_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i; 1 \leq j \leq \frac{N}{\tau}$$

It then calculates the SampEn of each series y_j^τ as

$$SampEn(m, r, N) = -\ln \frac{C^{m+1}}{C^m};$$
$$C^m = numberofpairs(i, j), i \neq j; |y_i^m - y_j^m| < r$$

where $|y_i^m - x_y^m|$ denotes the distance between vectors y_i^m and y_j^m, m is the dimension of vectors y_i^m and y_j^m, r is the tolerable distance between the two vectors, and N represents the time series length.

Appendix A.9. Lempel–Ziv Complexity

Lempel–Ziv complexity (LZC) is a popular measure for characterizing the complexity of biomedical signals [138]. To compute the LZC, the oscillations of a time series have to be transformed into a binary sequence. The simplest approach is to convert the time series $x(k)$, $k = 1, \ldots n$ into a 0–1 sequence by comparison with a threshold T_d, as follows:

$$s(i) = \begin{cases} 1 & \text{if } x(i) < T_d \\ 0 & \text{if } x(i) \geq T_d \end{cases}$$

A good choice for T_d is the median value of the signal in each electrode because it is robust to outliers [139]. Then, a complexity counter, *c(n)*, is increased by one unit each time a new subsequence of successive characters is found in the scanning process of the p sequence. Finally, normalized LZC is defined by

$$C_{LZ} = \frac{\log_2 nc(n)}{n}$$

Appendix A.10. EEG Valid Rate

The EEG valid rate (EEGVR) is the ratio of artifact-free EEG epochs divided by total epochs.

Appendix A.11. WPLI

The weighted phase-lag index (WPLI) is a measure of phase-synchronization. It is defined as

$$\Phi = \frac{|E\{J(X)\}|}{E\{J(X)\}}$$

where $J(X)$ denotes the imaginary component of the cross-spectrum.

Appendix A.12. Theta Beta Ratio

The theta beta ratio (TBR) is the ratio between the power spectral density in theta band and the power spectra density in beta band.

Appendix A.13. Sensorimotor Rhythms

Sensorimotor rhythms (SMR) are brain signals associated with motor activities, e.g., limb movements. They consist of EEG oscillations measurable in the μ and β bands, typically corresponding to the 8 Hz to 13 Hz and 13 Hz to 30 Hz ranges.

Appendix A.14. The EEG Concentration Index

The EEG concentration index is defined as the sum of the sensory motor rhythm and the beta/theta wave ratio.

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"MATTI DA MORIRE": TRE COMMENTI AUTOREVOLI

IL GRANDE COCOMERO

Ancora una volta Medico e Bambino si caratterizza per l'unicità nel panorama italiano, tra chi si prende cura dei bambini e degli adolescenti, di porre l'attenzione su un problema largamente inevaso aprendo un dibattito sulla salute mentale in età evolutiva. Una riflessione su quali e come attivare appropriati interventi e da parte di chi. Una ragione quarantennale per uno strumento di formazione e aggiornamento, in particolare per i giovani e per tutti coloro che fanno (anche) advocacy per una migliore salute dei bambini, degli adolescenti e delle loro famiglie. Il tema sintetizzato in "Matti" da morire rilancia un'attenzione che perdura "ormai da molti anni sulle pagine di Medico e Bambino".

Difendere e promuovere la salute anche mentale (advocacy) [1] in età evolutiva è un'azione a garanzia di un diritto ancora largamente inevaso[2].

I diritti sono complessi perché i bisogni sono associati, interdipendenti e sequenziali; ne consegue che l'operare in modo appropriato a garanzia del diritto di salute non può che essere collaborativo, condiviso e basato sulle evidenze. Il lavoro in "équipe multidisciplinari e multiprofessionali" non è esclusivo di una disciplina, ma l'approccio consolidato della moderna Medicina (di tutte le sue aree), un indicatore del processo assistenziale. Lavorare in équipe, in sinergia, investendo attitudini personali e professionali per migliorare lo stato di salute di un paziente affetto da un disturbo grave, cronico o raro non è esclusivo di alcuna area medica, ma è elemento essenziale del processo di cura: lo è per i disturbi della nutrizione e dell'alimentazione come per la sindrome metabolica, lo è per la sindrome di Rett come per la fibrosi cistica; lo è per il disturbo bipolare come per la leucemia mieloide. Interventi multidisciplinari, multiprofessionali, multimodali non solo per ragioni di aggiornamento dell'epistemologia medica con il superamento del parere dell'esperto o della supervisione, ma perché la complessità della domanda (dei singoli disturbi) per una risposta scientifica e basata sulle evidenze lo impone. Perché la complessità non è determinata dal sistema organico preso in considerazione ("il cervello è per sua definizione un sistema complesso"), ma dal continuo sviluppo di conoscenze in ambito diagnostico e terapeutico di cui disponiamo, produciamo e dobbiamo districarci con capacità. Perché la complessità è determinata anche dalle comorbilità che per alcuni disturbi come quelli psichiatrici sono un'essenza nosografica[3].

Parafrasando un motto dell'Antipsichiatria americana di ispirazione basagliana: la salute mentale (anche) in età evolutiva è una cosa troppo seria per lasciarla solo ai neuropsichiatri, che devono esserci, ed esserci in un certo modo, non abbandonati dalle Istituzioni e a perseguire modelli teorici e organizzativi non sempre validati e valutati nella pratica italiana. Bisogna costruire un'alleanza di saperi e professioni, ma anche di reti e relazioni di solidarietà per curare la sofferenza mentale sia dei piccoli che dei grandi[4]. Serve un "cambio di passo" per un percorso di cura che deve essere condiviso e partecipato: iniziative in questa direzione sono in corso[5].

"Servono risorse e risposte di sistema, integrate e coordinate" per contrastare la cronica disattenzione istituzionale. L'organizzazione dei Servizi di cura e riabilitazione neuropsichiatrica per l'età evolutiva scontano ritardi nell'allocazione di risorse, ma solo la qualità e l'uso appropriato di queste ultime può caratterizzare "la ricchezza dei nostri Servizi". Gli indicatori strutturali, tecnologici, organizzativi e professionali sono necessari, ma non sufficienti a garantire equità e qualità delle cure[6]. Così come fare di più non significa fare meglio (choosing wisely) fin tanto che l'alleanza tra professionisti e l'assunzione di responsabilità dei percorsi di cura non è condivisa e partecipata, anche con i pazienti e le loro famiglie[7]. "Fare meglio con meno" è possibile come dimostrato da una parte della Pediatria[8] e dall'origine della Neuropsichiatria[9]. Promuovere la salute (anche) mentale in età evolutiva implica attuare anche strategie preventive e non solo di cura dove le comunità (operatori, pazienti, famiglie) siano protagoniste.

La speranza in un cambiamento positivo rappresentata con la metafora de "Il grande cocomero"[10] non si attenua a distanza di anni. La speranza in quel cambio di passo che superi lo spezzettamento del percorso di cura tra prestazioni pediatriche, psichiatriche, neurologiche, psicologiche… come viene insegnato dall'Accademia e come sono strutturati i Servizi. Più che un "graffio" è un grido la riflessione lanciata da Medico e Bambino che sottolinea la inderogabilità di un cambiamento per prevenire il progressivo affievolimento delle ancor poche "ricchezze"[11].

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MALATTIE RARE: URGENZA DI NUOVI MODELLI FORMATIVI

Caro prof Ventura, provo a dare un contributo al dibattito sollevato dal Graffio "Matti da morire" e lo faccio da operatore sul campo, per scelta e per cammino assai vicino alle tematiche della neurodisabilità. I temi sollevati dall'articolo erano sostanzialmente due: la dichiarazione di "stato nazionale di emergenza" in ambito neuropsichiatrico annunciato da AAP, AACAP e CHA negli USA e la riproposta di un dibattito tra modelli di approccio formativi assistenziali in questo ambito specialistico

Dal campo il primo tema è quello che mi tocca maggiormente e quotidianamente. Secondo la Treccani nel linguaggio giornalistico emergenza è definita una "situazione di estrema pericolosità pubblica, tale da richiedere l'adozione di interventi eccezionali" oppure "particolare condizione di cose, momento critico, che richiede un intervento immediato, soprattutto nella locuzione stato di emergenza".

Come viene giustamente riportato la "fatica" a dare risposte efficaci e tempestive alle mille sfaccettature delle condizioni che afferiscono all'area neuropsichiatrica infantile è sotto gli occhi di chiunque lavori quotidianamente sul campo. Tale consapevolezza è ben presente anche tra i colleghi neuropsichiatri. Già nel 2016 la SINPIA aveva elaborato un documento denuncia della situazione e, ancora più recentemente, aprile 2021 la stessa Società scientifica aveva mandato una lettera molto esplicita al presidente Draghi e ai Ministri della Salute, dell'Istruzione, della Famiglia, della Disabilità e dell'Economia. In questo documento venivano sintetizzati dati molto chiari:

- raddoppio degli utenti seguiti dai servizi di Neuropsichiatria infantile negli ultimi 10 anni;
- 200 bambini/ragazzi su 1000 lamentano un disturbo neuropsichico;
- solo 60 su 200 di loro ha accesso a Servizi territoriali;
- solo 30 su 200 ottiene risposte terapeutico riabilitative adeguate;
- andamento in aumento dei ricoveri per problemi psichiatrici (+22% tra il 2017 e il 2018);
- solo 1 paziente su 5 riesce a essere ricoverato in un reparto di NPIA;
- 4 pazienti su 5 sono ricoverati in reparti non appropriati.

Come ben stigmatizzato dalla dott.ssa Costantino a una Tavola rotonda di Policlinico Kids a Milano, ancora in epoca pre-pandemica: "se i tempi di attesa di una presa in carico NPI fossero applicati a una condizione oncologica scoppierebbe il finimondo". Ma sebbene la situazione sia da tempo sotto gli occhi di tutti e sia stata documentata in modo molto chiaro, il finimondo non scoppia mai.

Se ritorniamo alla definizione di emergenza ("situazione di estrema pericolosità pubblica, tale da richiedere l'adozione di interventi eccezionali") comprendiamo che il nocciolo del (nostro) problema sta proprio lì. Nonostante ciò che viviamo quotidianamente questi dati assolutamente imbarazzanti non vengono ancora considerati espressione di una situazione di "pericolosità pubblica" dimenticando che una riabilitazione precoce ed efficiente per un paziente sindromico con disabilità intellettiva ha un significato sovrapponibile a quello della terapia genica per un paziente SMA, facendo finta di non capire che una presa in carico tempestiva e olistica di una paziente con un disturbo della condotta alimentare o con comportamenti autolesivi ha un impatto sulla prognosi non molto lontano dall'inizio precoce di un trattamento chemioterapico in ambito oncologico.

Il vero nodo cruciale è smettere di pensare e di agire come se alcuni bambini, alcune famiglie e alcuni problemi fossero persone e tematiche di serie B rispetto alla alta Medicina personalizzata basata sulle più recenti evidenze biologiche molecolari. Così come non transigiamo nello sforzo di offrire le terapie più innovative, affascinanti, promettenti e costose a un bambino con una malattia metabolica ereditaria, così come sosteniamo con forza la necessità di uno screening neonatale generalizzato della SMA per poter essere tempestivi nell'inizio della terapia mirata, dovremmo essere altrettanto intransigenti e determinati nel pretendere che il bambino con sospetto DSA, individuato precocemente tramite ciò che oggi abbiamo imparato, abbia lo stesso diritto di accedere alle "semplici e meno roboanti" terapie necessarie, garantite da Servizi con organici adeguati in termini quantitativi e qualitativi. E tutto ciò senza voler minimamente entrare nel pericoloso e complesso dibattito dei costi e dell'allocazione dei fondi

I primi quindi a dover chiamare le cose con il proprio nome (emergenza), a porre i problemi con la necessaria urgenza e determinazione (situazione di estrema pericolosità pubblica, necessità di provvedimenti eccezionali), dobbiamo essere proprio noi, pediatri e neuropsichiatri, forti dei dati citati che dobbiamo con coraggio portare insistentemente all'attenzione dei decisori e dei programmatori dei servizi pubblici. La necessità di questo sforzo condiviso trova fondamento nella responsabilità che abbiamo nei confronti dei nostri pazienti che con fiducia si affidano alle nostre cure e devono trovare in noi degli alleati, dei compagni di strada, fidati e affidabili.

Da un'ottica di grande pragmatismo ed efficienza, deriva qualche considerazione anche sul secondo tema del dibattito. Abbiamo imparato negli anni che le patologie pediatriche croniche e complesse sono ormai diventate sia ambiti fortemente specialistici che terreno privilegiato di un approccio multidisciplinare. Oggi nessuno di noi accetterebbe di affidare un paziente affetto da una problematica nefrologica pediatrica seria alla gestione di un gastroenterologo o di un epatologo. Allo stesso modo troverei poco efficiente che il NPI esperto di epilettologia o di terapie innovative di malattie neuromuscolari debba essere considerato lo specialista adeguato per coordinare la riabilitazione del bambino con PCI o il trattamento lungo, complesso e faticoso dell'adolescente con disturbo della condotta alimentare. Sebbene in ambito formale la figura dello specialista pediatra (cardiologo pediatra, nefrologo pediatra ecc.) sia ben lungi dall'essere definita, in ambito sostanziale assistenziale la tendenza è sempre quella di attivare, ove possibile, un invio specialistico. Di fatto, nella pratica clinica quotidiana, questo avviene anche per l'area neuropsichiatrica dove ben conosciamo e apprezziamo le competenze specifiche dei vari poli ospedalieri e dei vari centri di terzo livello. Sostenere la necessità di definire e valorizzare l'esistenza di varie aree complementari del sapere neuropsichiatrico non significa, quindi, mettere in discussione l'unitarietà concettuale delle funzioni neuromotorie, cognitive, psichiche e relazionali del bambino ma, semmai, ha il solo scopo di valorizzarne le varie sfaccettature in modo che più competenze possano concorrere a un esito terapeutico più completo ed efficiente.

In sostanza siamo solamente chiamati ad adeguare i nostri modelli formativi e assistenziali (ad esempio identificando e

definendo delle sub-specialità in ambito NPI) a ciò che la realtà quotidiana e l'evoluzione vorticosa delle conoscenze ci pone sotto gli occhi in modo sempre più chiaro ed evidente.

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IL TELEFONO A GETTONI

Il graffio del numero di aprile di *Medico e Bambino* ha dato il via a uno scambio di lettere che riflette il rapporto sempre molto intenso, talvolta intricato, tra pediatri e neuropsichiatri dell'infanzia e dell'adolescenza e l'attenzione di entrambi alla tutela della salute dei bambini e degli adolescenti italiani.
Alle criticità assistenziali (ahimè presenti in diverse realtà nazionali) rilevate da Alessandro Ventura ha risposto il Consiglio Direttivo della SINPIA (Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza), riprendendo una serie di principi generali indispensabili (il "neurosviluppo"), ma anche descrivendo le molte buone pratiche messe in atto in altrettante realtà nazionali.
Facendo seguito al confronto scaturito dallo scambio di lettere, vorremmo continuare a condividere con i lettori di Medico e Bambino alcune brevi considerazioni.

Il sistema nervoso come sede dei disturbi sia neurologici che psichiatrici

Vorremmo ripartire dal concetto di neurosviluppo come fenomeno di maturazione sia anatomica che funzionale del sistema nervoso centrale e conseguentemente delle funzioni motorie, sensoriali, cognitive affettive e sociali, modulato da come gli assetti genici e genomici dei singoli individui interagiscono con svariati fattori ambientali: durante lo sviluppo tali funzioni interagiscono costantemente rendendo spesso impossibile, o comunque estremamente complesso e talvolta poco utile, parcellizzarne l'analisi. Per restare nell'ambito dei disturbi psicopatologici, si è assistito a una vera rivoluzione copernicana, passando dal considerare bambini e adolescenti come "adulti in piccolo" all'interpretare tutta la psicopatologia come alterazioni delle traiettorie di sviluppo del sistema nervoso centrale e delle sue funzioni: in non pochi casi tali alterazioni biologiche molto precoci si manifestano clinicamente diversi decenni dopo. La diagnosi e la terapia di tutti i disturbi neuropsichici dovrebbe basarsi sulla conoscenza e sulla gestione clinica di tutti questi fattori *(Figura 1)*.

Aspetti comuni e oggettiva differenziazione delle prassi cliniche

Negli scorsi decenni le prassi cliniche (es. definire come assetti genici e fattori ambientali specifici possano modulare le diverse presentazioni cliniche e, conseguentemente, le specifiche strategie terapeutiche) nella gestione dei disturbi del neurosviluppo si sono significativamente evolute e spesso differenziate. Tali differenze non giustificano però la divisione dei percorsi formativi di base: per rimanere in ambito pediatrico, risulta in genere impossibile chiedere a un neonatologo ospedaliero di essere allo stesso tempo un valido oncologo pediatra: per un pediatra di famiglia è però necessario saper gestire clinicamente sia un neonato patologico che un minore con patologia oncologica. Può sembrare estremamente difficile formare, in quattro anni di Scuola di Specializzazione, un giovane collega nella gestione di pazienti a elevata complessità, sia neurologica che psichiatrica: a differenza di quanto spesso accade con gli adulti, in un'ottica di neurosviluppo, non avere sufficienti conoscenze scientifiche e abilità

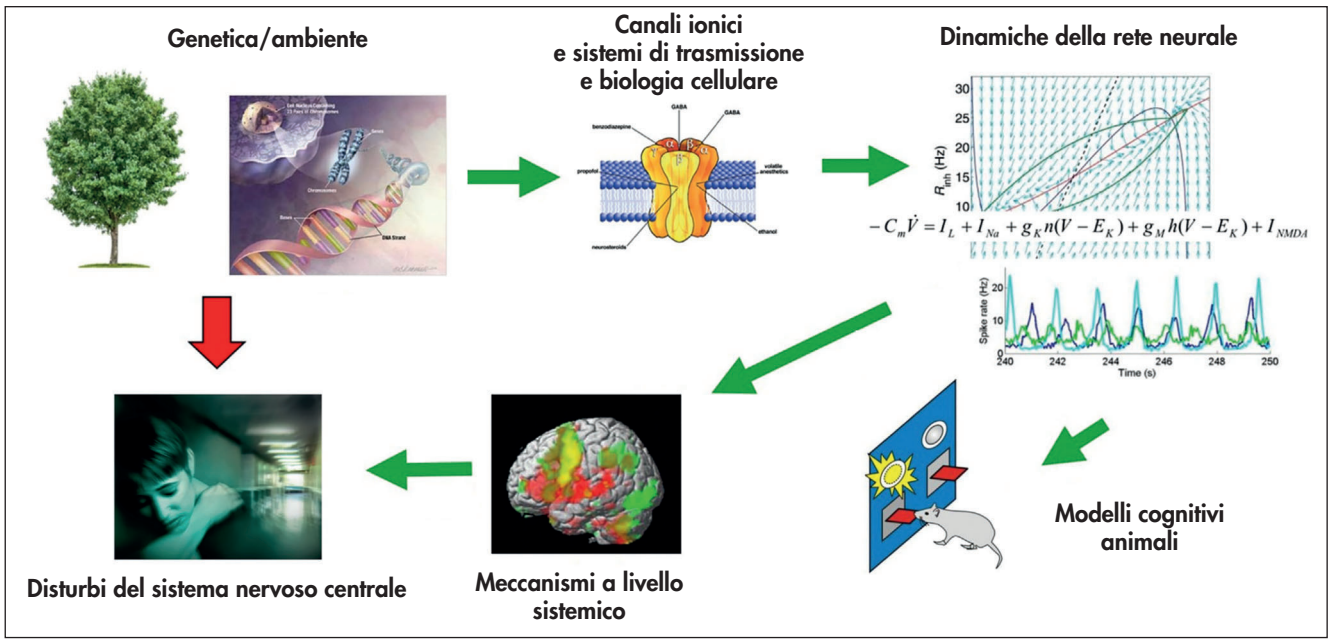

Figura 1. *Dai fattori di rischio genetici e ambientali ai disturbi del sistema nervoso centrale (da: Meyer-Lindenberg A, et al. Prospects for improved prevention and treatment of neuropsychiatric disorders. Neuroscience Applied 2022;1:100103. doi: 10.1016/j.nsa.2022.100103, modificata).*

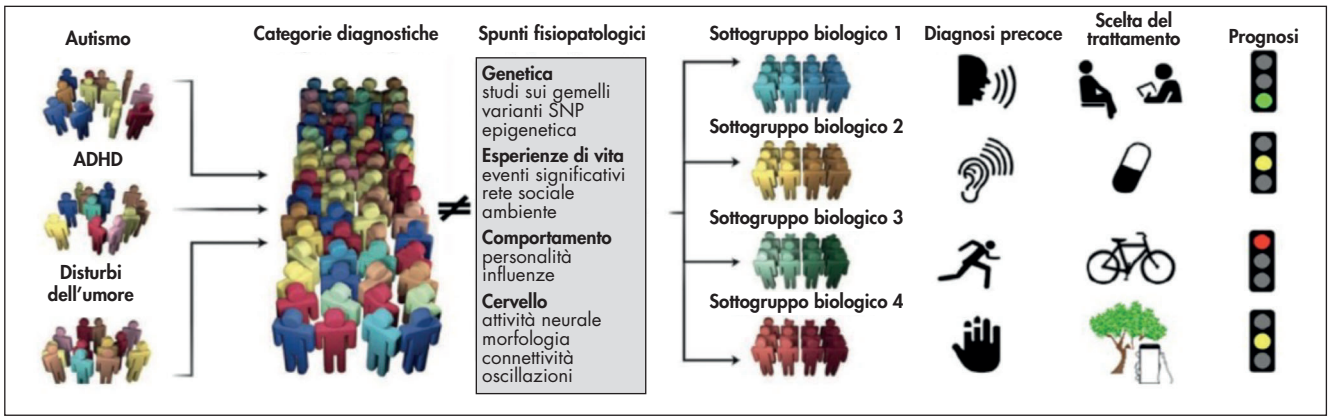

Figura 2. *Dalla diagnosi categoriale agli interventi di precisione (da: Meyer-Lindenberg A, et al. Prospects for improved prevention and treatment of neuropsychiatric disorders. Neuroscience Applied 2022;1:100103. doi: 10.1016/j.nsa.2022.100103, modificata).*

clinica in entrambi i campi rende impossibile gestire sia le patologie psichiatriche che neurologiche. Come per i pediatri, le differenze tra le diverse prassi cliniche vanno declinate in articolazioni e differenziazioni di specifici servizi, non nella formazione di base degli specialisti.

Eterogeneità dei Servizi

Molte delle criticità riportate da Alessandro Ventura sono fortemente correlate alla significativa eterogeneità e soprattutto al drammatico sottodimensionamento dei Servizi di Neuropsichiatria dell'Infanzia e dell'Adolescenza nelle diverse Regioni italiane. Servizi che, come SINPIA da tempo sottolinea, non sono monoprofessionali ma multiprofessionali integrati e con una specifica struttura organizzativa per poter mettere in campo risposte appropriate ai bisogni.

In importanti realtà come Trieste NON esistono i Servizi territoriali specialistici di NPIA; in Veneto si sta programmando di smantellarli: non è pensabile che una presa in carico che preveda l'integrazione tra Sevizi sanitari a intensità assistenziale diversificata, Servizi educativi formali e informali, Servizi sociali e talvolta anche giudiziari possa essere effettuata in ospedale o da singoli professionisti isolati e "dispersi" nel distretto o nella casa di comunità, e in assenza di risorse adeguate nello specifico territorio!

D'altra parte, in diverse Regioni italiane NON esistono posti letto di degenza ordinaria di NPIA, e i pazienti gravi vengono incongruamente ricoverati in reparti di Pediatria o Psichiatria dell'Adulto.

Simili disparità esistono però anche in campo pediatrico: in diverse realtà (in Sardegna, ma anche in diverse realtà lombarde e in importanti IRCCS nazionali) l'assistenza pediatrica, anche ospedaliera, termina a 14 anni. Le Cliniche di cui siamo responsabili assistono i pazienti fino al compimento del 18° anno di età: a essa afferiscono sia pazienti del Pronto Soccorso pediatrico, che appunto termina a 14 anni, che da quello "generale", con modalità assistenziali, protocolli e aspetti amministrativi significativamente differenti.

È certo difficile ricoverare in stanze vicine un lattante epilettico e un diciasettenne delirante; l'organizzazione di un ricovero richiede appropriate competenze, spazi e risorse sufficienti: non può essere improvvisata. Con approccio ultra semplificatorio in diverse Regioni alcuni psichiatri dell'adulto propongono la costituzione di strutture dedicate alla fascia di età 12-25 anni, facendo finta di dimenticare i diversi bisogni, le differenti modalità assistenziali necessarie (basti considerare il diverso ruolo della famiglia nelle diverse fasce di età, e i diversi obiettivi evolutivi), la diversa efficacia e tollerabilità (sia clinica che etica) di specifici interventi terapeutici e, non ultime, le diversità di specifica codifica età-dipendente di criteri diagnostici in apparenza simili. Per semplificare al massimo: quale lettore di Medico e Bambino sopporterebbe a cuor leggero di vedere la propria figlia (o anche una propria paziente) tredicenne con ideazione suicidaria nella stessa struttura di un ventitreenne con psicopatologia grave, ricoverato in regime di trattamento sanitario obbligatorio?

Sono scomparsi i telefoni a gettoni, sostituiti dai cellulari, anche se alcuni decisori non se ne sono accorti

Com'è stato da molti ricordato, la prevalenza dei disturbi neuropsichiatrici è raddoppiata nell'ultimo decennio con un rapido incremento, negli ultimi 2 anni di pandemia, soprattutto dei casi ricoverati per psicopatologia grave (nello stesso biennio, in molte realtà regionali è invece significativamente diminuito il numero ricoveri nei reparti di Pediatria generale). A ciò non stanno corrispondendo, nella gran parte delle Regioni, adeguati aggiustamenti organizzativi e programmatori.

A tali differenze nella tipologia e nella numerosità dei pazienti assistiti si è aggiunto un significativo ricambio generazionale tra i NPIA, con maggiori possibilità di formazione continua effettivamente accessibile per chi già lavora nei Servizi. In molte Scuole di Specializzazione, nell'ambito della rivoluzione copernicana di cui abbiamo parlato sopra, si è formata una nuova generazione di giovani colleghi in grado di valutare come gli adulti siano il risultato dell'interazione tra geni e ambiente nelle diverse fasi del neurosviluppo (che dal punto di vista strutturale si completa dopo i 18 anni di età) e come opportune strategie di prevenzione in età evolutiva possano modulare la psicopatologia dell'età adulta (basti pensare alla gestione anche farmacologica dell'ADHD nella prevenzione del disturbo da uso di sostanze; *Figura 2*). Inoltre, il percorso formativo sta sempre più includendo la frequenza degli specializzandi nei Servizi territoriali.

In meno di un anno, SINPIA ha ulteriormente accelerato il processo di potenziamento dei colleghi più giovani e la formazione continua di quelli più anziani, avviato da Antonella Costantino, past-president di SINPIA, stimolando il confronto tra le diverse generazioni e tra le differenti tradizioni cliniche.

Un'alleanza tra pediatri e neuropsichiatri dell'infanzia e dell'adolescenza

Rinnovando la stima e il riconoscimento degli intenti comuni, vorremmo ancora ringraziare *Medico e Bambino* per aver riacceso il dibattito sulle diverse criticità ancora irrisolte. Sulla base di queste poche note ci permettiamo di suggerire brevemente alcune strategie finalizzate a garantire una più accurata ed efficiente assistenza a bambini e adolescenti con disturbi del neurosviluppo, per la definizione, e soprattutto l'implementazione delle quali, sia i pediatri che i NPI, dovrebbero concordare e collaborare:

1. Garantire che in tutti i Servizi sanitari territoriali e ospedalieri venga effettivamente applicata la competenza pediatrica fino al diciottesimo anno di età (quando, sebbene il neurosviluppo non sia ancora concluso, si modificano fortemente se non altro i parametri legali), come già previsto dal Piano di azione italiano sul Sistema europeo di garanzia per i bambini vulnerabili *(Child Guarantee https:// www.minori.gov.it/ it/node/8044)*, dello scorso aprile.
2. Garantire in tutte le Regioni la presenza di Servizi territoriali e ospedalieri di Neuropsichiatria dell'Infanzia e dell'Adolescenza sulla base di chiari standard organizzativi, adeguati a garantire l'effettiva esigibilità dei livelli essenziali di assistenza (LEA) e definiti a livello nazionale.
3. Garantire in ogni Regione la presenza di posti letto di NPIA, sufficienti ad accogliere in modo appropriato sia le patologie neurologiche che quelle psichiatriche, con articolazione organizzativa e logistica specifica e adeguata agli effettivi bisogni, monitorandone efficacia ed efficienza.
4. Provare a parlare la stessa lingua: seguendo l'esempio di Confronti in Pediatria favorendo le occasioni di scambio tra gli specializzandi delle due discipline. Parlare la stessa lingua può aiutare a superare alcune incomprensioni e a rispondere meglio ai bisogni dei bambini, degli adolescenti e delle loro famiglie.

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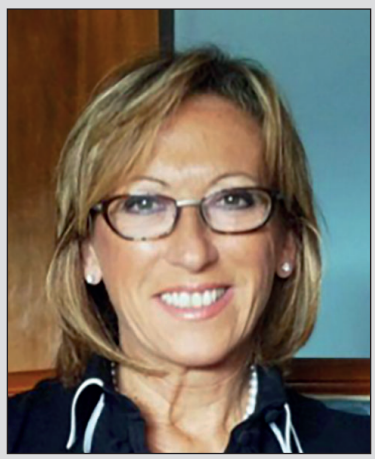
CARLA BERARDI: IL SORRISO DI UNA COMBATTENTE



Carla è stata con noi di *Medico e Bambino* da subito: da quel primo incontro alle Giornate Perugine di Pediatria nell'aprile del 1984. E da subito ci ha generosamente (è questo il moto d'animo che più l'ha sempre caratterizzata) donato tutta la sua passione e tutto il suo impegno per far andare al meglio le cose della Pediatria: soprattutto nell'aiutarci a riconoscere e perseguire le più vere e inderogabili priorità dei bisogni di salute e di sviluppo del bambino. Carla, che ha dovuto dedicare vent'anni della sua vita anche a combattere il suo tumore, è stata fino all'ultimo giorno (sì, letteralmente così) esempio concreto ed entusiastico di quanto valga sempre la pena impegnarsi pienamente per un buon fine, di quanto un buon agire finisca inevitabilmente per essere contagioso per il contesto. Nella sua vita professionale, Carla ha tra l'altro svolto un ruolo rilevante nella promozione delle conoscenze nel campo della violenza e dell'abuso sul bambino, svolgendo personalmente una grande opera di formazione e contribuendo a tracciare, anche con testi di riferimento, le linee guida per gli interventi preventivi e per quelli in urgenza che ogni pediatra dovrebbe saper mettere in atto. Carla si è anche dedicata con abnegazione assoluta alla realizzazione sul campo del progetto "Nati per Leggere" di cui non ha mai smesso di essere convinta e attiva divulgatrice, e dei suoi sviluppi più recenti, come l'esperienza dei "Villaggi per crescere", che ha trovato in Umbria uno dei territori più recettivi. Ha colto subito l'importanza di una formazione dei pediatri anche nel campo dello sviluppo, della sua promozione e dell'identificazione precoce nell'ambito del lavoro del pediatra di famiglia. Carla è stata vicina fino all'ultimo, con i suoi consigli e la sua opera, a chi ha ora meritoriamente realizzato a Perugia uno sportello per bambini e adolescenti con disturbi del funzionamento. In sostanza, Carla ha sempre visto "tutto" il bambino, e il lavoro del pediatra di famiglia come un lavoro veramente comprensivo. Come tanti di noi si sono detti al telefono condividendo il dolore per la sua perdita, Carla è stata più di ogni altra cosa una vera, infaticabile, entusiasta combattente del bene e del giusto. Sempre con il suo luminoso sorriso. Ed è così che la ricorderemo sempre.

Medico e Bambino

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(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, n. 3885 del 30/03/2020)
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