NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD GIUGNO 2020

Addiction. 2020 Jul;115:1368-77.

GENETIC LIABILITY TO ADHD AND SUBSTANCE USE DISORDERS IN INDIVIDUALS WITH ADHD.

Wimberley T, Agerbo E, Horsdal HT, et al.

Aims: 1) To investigate whether genetic liability to attention-deficit/hyperactivity disorder (ADHD), indexed by polygenic risk scores for ADHD (PRS-ADHD), is associated with substance use disorders (SUD) in individuals with ADHD. 2) To investigate whether other individual- or family-related risk factors for SUD could mediate or confound this association.

Design: Population-based cohort study SETTING AND PARTICIPANTS: ADHD cases in the iPSYCH sample (a Danish case-cohort sample of genotyped cases with specific mental disorders), born in Denmark between 1981 and 2003 (N = 13 116). Register-based information on hospital diagnoses of SUD was available until December 31, 2016.

Measurements: We estimated odds ratios (ORs) with 95% confidence intervals (CIs) for any SUD as well as for different SUD types (alcohol, cannabis, and other illicit drugs) and severities (use, abuse, and addiction), with effect sizes corresponding to a comparison of the highest PRS-ADHD decile to the lowest.

Findings: PRS-ADHD were associated with any SUD (OR = 1.30, 95% CI: 1.11-1.51). Estimates were similar across different types and severity levels of SUD. Other risk factors for SUD (male sex, age at ADHD diagnosis, comorbid conduct problems, and parental factors including SUD, mental disorders, and socio-economic status) were independently associated with increased risk of SUD. PRS-ADHD explained a minor proportion of the variance in SUD (0.2% on the liability scale) compared to the other risk factors. The association between PRS-ADHD and any SUD was slightly attenuated (OR = 1.21, 95% CI: 1.03-1.41) after adjusting for the other risk factors for SUD. Furthermore, associations were nominally higher in females than in males (ORfemales = 1.59, 95% CI: 1.19-2.12, ORmales = 1.18, 95% CI: 0.98-1.42).

Conclusions: A higher genetic liability to attention-deficit/hyperactivity disorder appears to be associated with higher risks of substance use disorders in individuals with attention-deficit/hyperactivity disorder.

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

Am J Med Genet B Neuropsychiatr Genet. 2019 Oct;180:483-87.

EXPANDING THE PHENOTYPIC SPECTRUM OF MBOAT7-RELATED INTELLECTUAL DISABILITY.

Jacher JE, Roy N, Ghaziuddin M, et al.

MBOAT7 gene pathogenic variants are a newly discovered and rare cause for intellectual disability, autism spectrum disorder (ASD), seizures, truncal hypotonia, appendicular hypertonia, and below average head sizes (ranging from -1 to -3 standard deviations). There have been only 16 individuals previously reported who have MBOAT7-related intellectual disability, all of whom were younger than 10 years old and from consanguineous relationships. Thus, there is a lack of phenotypic information for adolescent and adult individuals with this disorder. Medical genetics and psychiatric evaluations in a 14-year-old female patient with a history of global developmental delay, intellectual disability, overgrowth with macrocephaly, metrorrhagia, seizures, basal ganglia hyperintensities, nystagmus, strabismus with amblyopia, ASD, anxiety, attention deficit hyperactivity disorder (ADHD), aggressive outbursts, and hyperphagia included a karyotype, methylation polymerase chain reaction for Prader-Willi/Angelman syndrome, chromosome microarray, and whole exome sequencing (WES), ADOS2, and ADI-R. WES identified a homozygous, likely pathogenic variant in the MBOAT7 gene (c.855-2A>G). This is the oldest known patient with MBOAT7-related intellectual disability, whose unique features compared with previously described individuals include overgrowth with macrocephaly, metrorrhagia, ophthalmological abnormalities, basal ganglia hyperintensities, unspecified anxiety disorder, and ADHD; combined type; and hyperphagia with the absence of appendicular hypertonia and cortical atrophy. More individuals need to be identified in order to delineate the full clinical spectrum of this disorder

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Am J Occup Ther. 2020 Mar;74:7402180070p1-7402180070p19.

EFFECTIVENESS OF SOCIAL SKILLS INTERVENTIONS INCORPORATING PEER INTERACTIONS FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Fox A, Dishman S, Valicek M, et al.

IMPORTANCE: Few studies examining the use of peers during interventions have been published, and no systematic review has been conducted to evaluate the available literature.

OBJECTIVE: To examine the effectiveness of social skills interventions incorporating peers for children with attention deficit hyperactivity disorder (ADHD) to improve social interactions.

DATA SOURCES: A search of five databases (CINAHL, PubMed, Web of Science, Google Scholar, and PsycINFO) produced 697 articles. Sixty-one were retrieved for full-text review, and 15 articles met inclusion criteria.

STUDY SELECTION AND DATA COLLECTION: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to abstract data. Inclusion criteria: Participants younger than age 18 yr with any ADHD pattern, social skills interventions with peer involvement, outcome measures within the domain of occupational therapy, written in English, and involved a peer as the sole or primary component at some point in the social skills intervention. Exclusion criteria: Studies older than 20 yr or that used participants with comorbidities or multiple conditions.

FINDINGS: Interventions incorporating both peer categories were effective for increasing play skills, reducing undesirable social behaviors (e.g., inappropriate verbalizations, dominant behaviors, aggression), and improving communication (e.g., pragmatic language, collaboration, joint participation) and social participation. Improvements were maintained over time, as evidenced by follow-up studies.

CONCLUSIONS AND RELEVANCE: Outcomes of these studies demonstrate moderate evidence that supports the use of social skills interventions incorporating peers for children with ADHD to improve social interactions, supporting their use by occupational therapists and the need for more studies.

WHAT THIS ARTICLE ADDS: This article provides guidance to occupational therapy practitioners on social skills intervention options for children with ADHD

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Am J Occup Ther. 2020 Mar;74:7402205070p1-p7.

BRAIN MAPPING PERFORMANCE AS AN OCCUPATIONAL THERAPY ASSESSMENT AID IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chatthong W, Khemthong S, Wongsawat Y.

IMPORTANCE: Brain mapping performance (BMP) may provide strong predictors to analyze primary functional outcomes and support occupational therapy with clients with attention deficit hyperactivity disorder (ADHD).

OBJECTIVE: To clarify the value of quantitative electroencephalography to indicate BMP in children with ADHD. DESIGN: One-year cross-sectional study.

SETTING: Brain Computer Interface Laboratory, Mahidol University, Salaya, Nakhon Pathom, Thailand.

PARTICIPANTS: Thai school-age children with and without ADHD (N = 305).

OUTCOMES AND MEASURES: We used theta relative power in concordance with stepwise multiple regression analysis. Outcomes included measures of 12 brain locations that were compared between children with and without ADHD. RESULTS: Significant differences were found between the groups, especially for Cz, T3, Fp1, Fz, F4, and F7. According to BMP, the group with ADHD had higher emotional awareness and language comprehension than the group without ADHD.

CONCLUSIONS AND RELEVANCE: Occupational therapy practitioners can use BMP as a valuable tool for setting occupational goals to help children with ADHD improve their social-emotional learning performance in school and in the community. BMP may provide an evaluation to support occupational therapy services for clients with ADHD. The result can be applied in clinical settings by quantitative electroencephalography training.

WHAT THIS ARTICLE ADDS: BMP can be used as a neuropsychological and behavioral assessment tool for setting SMART (specific, measurable, attainable, relevant, and time-oriented) goals for occupational therapy services for clients with ADHD

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Am J Perinatol. 2019 Jul;36:949-54.

INFERTILITY TREATMENTS AND LONG-TERM NEUROLOGIC MORBIDITY OF THE OFFSPRING.

Levin S, Sheiner E, Wainstock T, et al.

OBJECTIVE: To determine the risk of long-term neurologic morbidity among children (up to 18 years) born following in vitro fertilization (IVF) or ovulation induction (OI) treatments as compared with spontaneously conceived.

STUDY DESIGN: A population-based cohort analysis was performed, including data from the perinatal computerized database on all singleton infants born at the Soroka University Medical Center (SUMC) between the years 1991 and 2014. This perinatal database was linked and cross-matched with the SUMC computerized dataset of all pediatric hospitalizations.

RESULTS: Neurologic morbidity was significantly more common in IVF (3.7%) and OI (4.1%) offspring as compared with those following spontaneous pregnancies (3.1%; p = 0.017). In particular, attention deficit/hyperactivity disorders and headaches were more common in the OI group and sleep disorders in the IVF group, whereas autism and cerebral palsy were comparable between the groups. In the Weibull multivariable analysis, while controlling for maternal age, preterm delivery, birthweight centile, maternal diabetes, and hypertensive disorders, IVF (adjusted hazard ratio [HR]: 1.40; 95% confidence interval [CI]: 1.14-1.71; p = 0.001), but not OI (adjusted HR: 1.17' 95% CI: 0.92-1.48; p = 0.196), was noted as an independent risk factor for long-term pediatric neurologic morbidity.

CONCLUSION: IVF offspring appear to be at an increased risk of long-term neurologic morbidity up to 18 years of age

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Am J Hum Genet. 2020;106:830-45.

DE NOVO SOX6 VARIANTS CAUSE A NEURODEVELOPMENTAL SYNDROME ASSOCIATED WITH ADHD, CRANIOSYNOSTOSIS, AND OSTEOCHONDROMAS.

Tolchin D, Yeager JP, Prasad P, et al.

SOX6 belongs to a family of 20 SRY-related HMG-box-containing (SOX) genes that encode transcription factors controlling cell fate and differentiation in many developmental and adult processes. For SOX6, these processes include, but are not limited to, neurogenesis and skeletogenesis. Variants in half of the SOX genes have been shown to cause severe developmental and adult syndromes, referred to as SOXopathies. We here provide evidence that SOX6 variants also cause a SOXopathy. Using clinical and genetic data, we identify 19 individuals harboring various types of SOX6 alterations and exhibiting developmental delay and/or intellectual disability; the individuals are from 17 unrelated families. Additional, inconstant features include attention-deficit/hyperactivity disorder (ADHD), autism, mild facial dysmorphism, craniosynostosis, and multiple osteochondromas. All variants are heterozygous. Fourteen are de novo, one is inherited from a mosaic father, and four offspring from two families have a paternally inherited variant. Intragenic microdeletions, balanced structural rearrangements, frameshifts, and nonsense variants are predicted to inactivate the SOX6 variant allele. Four missense variants occur in residues and protein regions highly conserved evolutionarily. These variants are not detected in the gnomAD control cohort, and the amino acid substitutions are predicted to be damaging. Two of these variants are located in the HMG domain and abolish SOX6 transcriptional activity in vitro. No clear genotype-phenotype correlations are found. Taken together, these findings concur that SOX6 haploinsufficiency leads to a neurodevelopmental SOXopathy that often includes ADHD and abnormal skeletal and other features

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Appetite. 2019 May;136:25-32.

ADULTHOOD AND CHILDHOOD ADHD IN PATIENTS CONSULTING FOR OBESITY IS ASSOCIATED WITH FOOD ADDICTION AND BINGE EATING, BUT NOT SLEEP APNEA SYNDROME.

Brunault P, Frammery J, Montaudon P, et al.

INTRODUCTION: The exact mechanisms underlying the established association between ADHD and obesity remain unclear. Food addiction and binge eating may contribute to this link. We examined for the first time the association between childhood/adult ADHD and food addiction/binge eating in patients with obesity, as well as the association between ADHD and sleep apnea syndrome.

METHODS: We included 105 obese patients from the Nutrition Department of the University Hospital of Tours (France) between January and December 2014. We assessed categorical diagnoses of childhood/adulthood ADHD (semi-structured interview DIVA 2.0), food addiction (Yale Food Addiction Scale 2.0), binge eating (Binge Eating Scale), obstructive sleep apnea (clinical assessment), and BMI (clinical assessment).

RESULTS: Patients with adult ADHD were at significantly higher risk of food addiction than patients without adult ADHD (28.6% vs. 9.1%; p=.016). Adult and childhood ADHD were significantly associated with self-reported food addiction, food addiction scores and binge eating scores, with a larger effect size for adult (ORs: 4.00 [1.29-12.40], 1.37 [1.14-1.65] and 1.08 [1.03-1.14], respectively) than childhood (ORs: 3.32 [1.08-10.23], 1.29 [1.08-1.55] and 1.06 [1.01-1.11], respectively) ADHD. ADHD diagnosis was not significantly correlated to obstructive sleep apnea. Mean age of onset of ADHD preceded mean age of onset of obesity.

CONCLUSION: ADHD diagnosis is associated with food addiction and binge eating, with a larger effect size for adult than childhood ADHD. Our results provide a strong rationale for further longitudinal research on the link between ADHD, food addiction, binge eating and obesity, paving the way for evidence-based therapeutic interventions for these patients

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Appetite. 2020 Jul;150:8.

THE RELATIONSHIP BETWEEN SENSORY SENSITIVITY, FOOD FUSSINESS AND FOOD PREFERENCES IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Smith B, Rogers SL, Blissett J, et al.

Heightened sensitivity to sensory information has been associated with food fussiness in both atypical and typical development. Despite food fussiness and sensory dysfunction being reported as common concerns for children with neurodevelopmental disorders, the relationship that exists between them, and whether they differ between disorders, has yet to be established. The current study aimed to examine sensory sensitivity as a predictor of food fussiness in three different neurodevelopmental disorders, whilst controlling for comorbidity amongst these disorders. Ninety-eight caregivers of children with Attention Deficit Hyperactivity Disorder (ADHD; n = 17), Tourette Syndrome (TS; n = 27), Autism Spectrum Disorder (ASD; n = 27), and typical development (TD; n = 27) were compared using parental reports of child food fussiness, food preferences and sensory sensitivity. Children with neurodevelopmental disorders were reported to have significantly higher levels of both food fussiness and sensory sensitivity, with children with ASD and TS also showing significantly less preference for fruit than children with TD. Importantly, higher levels of taste/smell sensitivity predicted food fussiness for all four groups of children. In addition, taste/smell sensitivity fully mediated the differences in food fussiness between each group of neurodevelopmental disorders compared to the TD group. The findings highlight that food fussiness is similar across these neurodevelopmental disorders despite accounting for comorbidity, and that greater sensitivity to taste/smell may explain why children with neurodevelopmental disorders are more likely to be fussy eaters

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Appl Psychophysiol Biofeedback. 2019 Dec;44:291-308.

Z-SCORE NEUROFEEDBACK AND HEART RATE VARIABILITY TRAINING FOR ADULTS AND CHILDREN WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RETROSPECTIVE STUDY.

Groeneveld KM, Mennenga AM, Heidelberg RC, et al.

ADHD is a common condition that causes suffering for those affected and economic loss for society at large. The current standard treatment for ADHD includes stimulant medications, which are not effective for all patients, may include side effects, and can be non-medically misused. Z-score neurofeedback (NFB) and heart rate variability (HRV) biofeedback are alternative treatment strategies that have been associated with Attention-Deficit/Hyperactivity Disorder (ADHD) symptom improvement. We utilized a retrospective pre-post study design to quantify the change in clients' ADHD symptoms after combined NFB + HRV treatment (which included simultaneous z-score training at four sites). We also assessed whether relevant physiological measures changed in accordance with the protocol, which would be consistent with effective NFB + HRV training. Adults (n = 39) and children (n = 100) with Borderline or Clinical ADHD classifications by the Achenbach System of Empirically Based Assessment (ASEBA) received 30 sessions of NFB + HRV training. Measures were compared before and after treatment for the ASEBA, the Integrated Visual and Auditory Continuous Performance Test (IVA), ADHD medication use, HRV and breathing parameters, and quantitative electroencephalogram (QEEG) parameters. Average ASEBA Attention-Deficit/Hyperactive Problems score improved after treatment for adults and children ($p < 0.0001$), with Cohen effect sizes (dz) of -1.21 and -1.17, respectively. 87.2% of adults and 80.0% of children experienced improvements of a magnitude greater than or equal to the Minimal Clinically Important Difference. After treatment, 70.8% of adults and 52.8% of children who began in the ASEBA Clinical range, and 80.0% of adults and 63.8% of children who began in the ASEBA Borderline range, were classified in the Normal range. IVA scores also improved after treatment. Changes in HRV and breathing pattern after treatment were consistent with the protocol. QEEG parameters after treatment were closer to the age-based normative mean, which is consistent with effective z-score NFB training

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Applied Neuropsychology: Adult. 2020 Jul;27:364-75.

PREMORBID ESTIMATES OF NEUROPSYCHOLOGICAL FUNCTIONING FOR DIVERSE GROUPS.

Meyers JE, Miller RM, Rohling ML, et al .

One of the basic tasks performed by a neuropsychologist is to identify the difference between current performance and the premorbid expected performance. Baseline expected performance for Intellectually Impaired (n = 21), Developmentally Delayed (n = 40), Attention Deficit Disorder (n = 98), Learning Disability (n = 42), and â€œNormalâ€• groups (n = 75) were developed along with a demographically corrected prediction of premorbid functioning and a word reading based prediction of premorbid functioning. We utilized a subset of this data pool for development (n = 107) and validation (n = 108) of premorbid functioning estimates. Findings show that a combination of three methods (baseline, demographic, and reading) were superior to any individual method. The effect size (Cohenâ€™s d) calculations show that differences in the prediction of domain level performances were small and likely not clinically meaningful, indicating that the premorbid estimates would be usable as a prediction of expected performance at the domain level. However, the motor domains were not well predicted

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Autism. 2019 Apr;23:566-73.

CHARACTERISTICS OF PSYCHIATRIC EMERGENCY DEPARTMENT USE AMONG PRIVATELY INSURED ADOLESCENTS WITH AUTISM SPECTRUM DISORDER.

Kalb LG, Stuart EA, Vasa RA.

This study examined differences in the rates of psychiatric-related emergency department visits among adolescents with autism spectrum disorder, adolescents with attention deficit hyperactivity disorder, and adolescents without autism spectrum disorder or attention deficit hyperactivity disorder. Additional outcomes included emergency department recidivism, probability of psychiatric hospitalization after the emergency department visit, and receipt of outpatient mental health services before and after the emergency department visit. Data came from privately insured adolescents, aged 12-17 years, with autism spectrum disorder (N = 46,323), attention deficit hyperactivity disorder (N = 408,066), and neither diagnosis (N = 2,330,332), enrolled in the 2010-2013 MarketScan Commercial Claims Database. Adolescents with autism spectrum disorder had an increased rate of psychiatric emergency department visits compared to adolescents with attention deficit hyperactivity disorder (IRR = 2.0, 95% confidence interval: 1.9, 2.1) and adolescents with neither diagnosis (IRR = 9.9, 95% confidence interval: 9.4, 10.4). Compared to the other groups, adolescents with autism spectrum disorder also had an increased probability of emergency department recidivism, psychiatric hospitalization after the emergency department visit, and receipt of outpatient care before and after the visit (all p < 0.001). Further research is required to understand whether these findings extend to youth with other neurodevelopmental disorders, particularly those who are publicly insured

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Autism Res. 2020.

FROM TODDLERHOOD TO ADOLESCENCE, TRAJECTORIES AND PREDICTORS OF OUTCOME: LONG-TERM FOLLOW-UP STUDY IN AUTISM SPECTRUM DISORDER.

Zachor DA, Ben-Itzchak E.

This study is one of a very few prospective long-term studies in autism spectrum disorder (ASD). The study compared outcome trajectories in three adolescent groups (T2): ΓÇ£best outcomeΓÇØ (BO, n = 11) did not meet cut-off points for ASD and IQ scores ΓëÑ85; high functioning (HF-ASD, n = 14); and lower functioning (LF-ASD, n = 43). Additionally, the study searched for characteristics at toddlerhood (T1) that may predict belonging to the above groups. The study included 68 adolescents (63 males) diagnosed with ASD at toddlerhood (mean age: 13:10 years), mean follow-up time was 11:7 years. Participants underwent comprehensive assessments at T1 and T2. Different trajectories were found for the three defined groups. The BO group improved significantly in cognitive ability, autism severity, and adaptive skills in comparison to no improvement for the LF-ASD group or partial progress for the HF-ASD group. At toddlerhood, better cognition and less severe autism social affect symptoms were generally associated with a better outcome.

Early social behaviors including better pointing, facial expression directed to others, showing, and response to joint attention were associated with membership in the BO group. In addition, the BO group had the lowest prevalence of significant T2 inattention and anxiety symptoms. No significant differences between the three outcome groups were noted in the birth and prevalence of medical problems. Higher cognitive ability and better T1 showing and pointing behaviors predicted better outcome. The study points to the change in autism severity over time and to the prognostic value of early developmental abilities, social engagement behaviors, and the existence of comorbidities. Lay Summary: This long-term study compared characteristics of toddlers diagnosed with autism spectrum disorder (ASD) in three outcome groups in adolescence: best outcome (BO-average IQ/not meeting criteria for ASD), high-functioning ASD, and low-functioning ASD (LF-ASD). At toddlerhood, the BO group displayed less severe autism symptoms, mostly in sharing interests, compared to the LF-ASD group. The BO group had fewer inattention and anxiety symptoms than the two ASD groups. Additionally, early cognitive level and social engagement behaviors predicted outcome in ASD

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Behav Sleep Med. 2020 May;18:321-33.

THE SLEEPINESS CURVE OF YOUNG MEN WITH AND WITHOUT ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Cohen A, Dan O, Asraf K, et al .

Objectives: The present study aimed at comparing the sleepiness curve of young men with attention-deficit hyperactivity disorder (ADHD) to that of young men without ADHD before, during, and after a night of sleep deprivation.

Participants: Thirty young men (age 18-30) of whom 14 were diagnosed with ADHD combined type (ADHD-C) and 16 without ADHD. Methods: The participants' sleep was monitored for 5 days via actigraphy. Subsequently, the participants were kept continuously awake in a controlled environment for 25 hr (8:00 a.m.-9:00 a.m.). The sleepiness of the participants was assessed every hour by the Karolinska Sleepiness Scale (KSS) in order to obtain the sleepiness curve of both study groups.

Results: Actigraphy data demonstrated that the two groups did not differ in their total sleep time, sleep onset latency, or sleep efficiency during the 5 nights preceding the experimental session. However, during the experimental session, the ADHD group demonstrated higher sleepiness scores, particularly following midnight and on the morning following the night of sleep deprivation. Moreover, on the morning following sleep deprivation the proportion of participants reporting extreme levels of sleepiness (KSS > 7) was significantly higher in the ADHD group than in the control group.

Conclusions: Young men with ADHD suffer from sleepiness more than their counterparts from the general population, and are particularly vulnerable to the effects of sleep deprivation on sleepiness. As excessive daytime sleepiness negatively affects cognition and increases the risk for motor vehicle crash and other accidents, these findings may have important clinical implications

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Biocybernetics and Biomedical Engineering. 2020;40:927-37.

DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH COMBINED TIME AND FREQUENCY FEATURES.

Altınkaynak M, Dolu N, et al.

The aim of this study was to build a machine learning model to discriminate Attention Deficit Hyperactivity Disorder (ADHD) patients and healthy controls using information from both time and frequency analysis of Event Related Potentials (ERP) obtained from Electroencephalography (EEG) signals while participants performed an auditory oddball task. The study included 23 unmedicated ADHD patients and 23 healthy controls. The EEG signal was analyzed in time domain by nonlinear brain dynamics and morphological features, and in time-frequency domain with wavelet coefficients. Selected features were applied to various machine learning techniques including; Multilayer Perceptron, Na+»ve Bayes, Support Vector Machines, k-nearest neighbor, Adaptive Boosting, Logistic Regression and Random Forest to classify ADHD patients and healthy controls. Longer P300 latencies and smaller P300 amplitudes were observed in ADHD patients relative to controls. In fractal dimension calculation relative to the control group, the ADHD group

demonstrated reduced complexity. In addition, certain wavelet coefficients provided significantly different values in both groups. Combining these extracted features, our results indicated that Multilayer Perceptron method provided the best classification with an accuracy rate of 91.3% and a high level of reliability of concurrence (Kappa = 0.82). The results showed that combining time and frequency domain features can be a useful and discriminative for diagnostic purposes in ADHD. The study presents a supporting diagnostic tool that uses EEG signal processing and machine learning algorithms. The findings would be helpful in the objective diagnosis of ADHD

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Biol Psychiatry. 2019 Jul;86:65-75.

CEREBELLAR GRAY MATTER VOLUME IS ASSOCIATED WITH COGNITIVE FUNCTION AND PSYCHOPATHOLOGY IN ADOLESCENCE.

Moberget T, Alnaes D, Kaufmann T, et al.

BACKGROUND: Accumulating evidence supports cerebellar involvement in mental disorders, such as schizophrenia, bipolar disorder, depression, anxiety disorders, and attention-deficit/hyperactivity disorder. However, little is known about the cerebellum in developmental stages of these disorders. In particular, whether cerebellar morphology is associated with early expression of specific symptom domains remains unclear.

METHODS: We used machine learning to test whether cerebellar morphometric features could robustly predict general cognitive function and psychiatric symptoms in a large and well-characterized developmental community sample centered on adolescence (Philadelphia Neurodevelopmental Cohort, n = 1401, age 8-23 years).

RESULTS: Cerebellar morphology was associated with both general cognitive function and general psychopathology (mean correlations between predicted and observed values: r = .20 and r = .13; p < .001). Analyses of specific symptom domains revealed significant associations with rates of norm-violating behavior (r = .17; p < .001) as well as psychosis (r = .12; p < .001) and anxiety (r = .09; p = .012) symptoms. In contrast, we observed no associations with attention deficits or depressive, manic, or obsessive-compulsive symptoms. Crucially, across 52 brain-wide anatomical features, cerebellar features emerged as the most important for prediction of general psychopathology, psychotic symptoms, and norm-violating behavior. Moreover, the association between cerebellar volume and psychotic symptoms and, to a lesser extent, norm-violating behavior remained significant when adjusting for several potentially confounding factors.

CONCLUSIONS: The robust associations with psychiatric symptoms in the age range when these typically emerge highlight the cerebellum as a key brain structure in the development of severe mental disorders

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BMC Fam Pract. 2019 Nov;20:159.

YOUNG PEOPLE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN TRANSITION FROM CHILD TO ADULT SERVICES: A QUALITATIVE STUDY OF THE EXPERIENCES OF GENERAL PRACTITIONERS IN THE UK.

Newlove-Delgado T, Blake S, Ford T, et al.

BACKGROUND: Many young people with Attention Deficit Hyperactivity Disorder (ADHD) have impairing symptoms that persist into adulthood, yet only a minority experience continuity of care into adult life. Despite growing emphasis on the primary care role in ADHD management in NICE ADHD and transition guidance, little is known about GPs' perspectives, which could hamper efforts to improve outcomes for young people leaving children's services. This study aimed to understand GPs' experiences of involvement with this group and explore their views on the roles and responsibilities of primary and secondary care in transition, to inform recommendations for policy and practice.

METHOD: Qualitative interview study with GPs across the UK. Semi-structured telephone interviews were carried out with 14 GPs recruited through a linked mapping study, social media, and snowballing; data were analysed using thematic analysis.

RESULTS: In the absence of a smooth transition from child to adult services, many GPs became involved 'by default'. GPs reacted by trying to identify suitable specialist services, and were faced with the decision of

whether to continue ADHD prescribing. Such decisions were strongly influenced by perceptions that prescribing carried risks, and concerns over responsibility, particularly where specialist services were lacking. Participants described variation in service availability, and some highlighted tensions around how shared care works in practice.
CONCLUSION: Implementation of NICE guidance is highly variable, with implications for GPs and patients. Risk and responsibility for primary care ADHD prescribing are central concerns that need to be addressed, as is the inclusion of GPs in a planned transition process

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BMC Med. 2020;18.
GUIDANCE FOR IDENTIFICATION AND TREATMENT OF INDIVIDUALS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER BASED UPON EXPERT CONSENSUS.
Young S, Hollingdale J, Absoud M, et al.
Background: Individuals with co-occurring hyperactivity disorder/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) can have complex presentations that may complicate diagnosis and treatment. There are established guidelines with regard to the identification and treatment of ADHD and ASD as independent conditions. However, ADHD and ASD were not formally recognised diagnostically as co-occurring conditions until the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) was published in 2013. Hence, awareness and understanding of both conditions when they co-occur is less established and there is little guidance in the clinical literature. This has led to uncertainty among healthcare practitioners when working with children, young people and adults who present with co-existing ADHD and ASD. The United Kingdom ADHD Partnership (UKAP) therefore convened a meeting of professional experts that aimed to address this gap and reach expert consensus on the topic that will aid healthcare practitioners and allied professionals when working with this complex and vulnerable population.
Method: UK experts from multiple disciplines in the fields of ADHD and ASD convened in London in December 2017. The meeting provided the opportunity to address the complexities of ADHD and ASD as a co-occurring presentation from different perspectives and included presentations, discussion and group work. The authors considered the clinical challenges of working with this complex group of individuals, producing a consensus for a unified approach when working with male and female, children, adolescents and adults with co-occurring ADHD and ASD. This was written up, circulated and endorsed by all authors.
Results: The authors reached a consensus of practical recommendations for working across the lifespan with males and females with ADHD and ASD. Consensus was reached on topics of (1) identification and assessment using rating scales, clinical diagnostic interviews and objective supporting assessments; outcomes of assessment, including standards of clinical reporting; (2) non-pharmacological interventions and care management, including psychoeducation, carer interventions/carer training, behavioural/environmental and Cognitive Behavioural Therapy (CBT) approaches; and multi-agency liaison, including educational interventions, career advice, occupational skills and training, and (3) pharmacological treatments.
Conclusions: The guidance and practice recommendations (Tables 1, 4, 5, 7, 8 and 10) will support healthcare practitioners and allied professionals to meet the needs of this complex group from a multidisciplinary perspective. Further research is needed to enhance our understanding of the diagnosis, treatment and management of individuals presenting with comorbid ADHD and ASD

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BMC Pediatr. 2020;20.
EMERGENCY DEPARTMENT ATTENDANCE FOR INJURY AND BEHAVIOURS SUGGESTIVE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A CROSS-SECTIONAL STUDY.
Conversano E, Tassinari A, Monasta L, et al.
Background: The study aimed to investigate if the behaviours suggestive of ADHD were more frequent in a population of children attending the Emergency Department (ED) for injuries, rather than for other causes.
Methods: A cross-sectional study was carried out. Patients, aged 6 to 17 years, attending the ED for acute injuries and other causes were considered cases and controls, respectively. We used a questionnaire, which

investigates the presence in the child of inattention, hyperactivity, and impulsivity. The primary outcome was the number of children with behaviours suggestive of ADHD in cases and controls.
Results: Five hundred forty-five children were enrolled, 251 with injuries and 294 with other complains. Twenty two out of two hundred fifty one (9%) children visited for injuries, and 30 out of 294 (10%) visited for other causes had behaviours suggestive of ADHD (p = 0.661). Among these cases, children with evocative ADHD scores had a higher probability (OR 4.52; 95% CI 1.45-14.04; p = 0.009) of having had more than five previous ED accesses due to injury, compared to the others.
Conclusions: This study did non shown a difference in behaviours suggestive of ADHD between cases and controls, but identified a population of children with behaviours suggestive of ADHD who more frequently access the ED for injuries

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BMC Psychiatry. 2019 Nov;19:363.

ANXIETY AT AGE 15 PREDICTS PSYCHIATRIC DIAGNOSES AND SUICIDAL IDEATION IN LATE ADOLESCENCE AND YOUNG ADULTHOOD: RESULTS FROM TWO LONGITUDINAL STUDIES.

Doering S, Lichtenstein P, Gillberg C, et al.

BACKGROUND: Anxiety disorders in adolescence have been associated with several psychiatric outcomes. We sought to describe the prospective relationship between various levels of adolescent anxiety and psychiatric diagnoses (anxiety-, bipolar/psychotic-, depressive-, and alcohol and drug misuse disorders) and suicidal ideation in early adulthood while adjusting for childhood attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and developmental coordination disorder (DCD). Furthermore, we aimed to estimate the proportion attributable to the various anxiety levels for the outcomes.
METHODS: We used a nation-wide population-based Swedish twin study comprising 14,106 fifteen-year-old twins born in Sweden between 1994 and 2002 and a replication sample consisting of 9211 Dutch twins, born between 1985 and 1999. Adolescent anxiety was measured with parental and self-report. Psychiatric diagnoses and suicidal ideation were retrieved from the Swedish National Patient Register and via self-report.
RESULTS: Adolescent anxiety, of various levels, predicted, in the Swedish National Patient Register, anxiety disorders: hazard ratio (HR) = 4.92 (CI 3.33-7.28); depressive disorders: HR = 4.79 (3.23-7.08), and any psychiatric outcome: HR = 3.40 (2.58-4.48), when adjusting for ADHD, ASD, and DCD. The results were replicated in the Dutch data. The proportion of psychiatric outcome attributable to adolescent anxiety over time (age 15-21) was 29% for any psychiatric outcome, 43-40% for anxiety disorders, and 39-38% for depressive disorders.
CONCLUSION: Anxiety in adolescence constitutes an important risk factor in the development of psychiatric outcomes, revealing unique predictions for the different levels of anxiety, and beyond the risk conferred by childhood ADHD, ASD, and DCD. Developmental trajectories leading into psychiatric outcomes should further empirically investigated

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BMC Psychiatry. 2019 Nov;19:348.

PROBLEMATIC USE OF THE INTERNET IS A UNIDIMENSIONAL QUASI-TRAIT WITH IMPULSIVE AND COMPULSIVE SUBTYPES.

Tiego J, Lochner C, Ioannidis K, et al.

BACKGROUND: Problematic use of the Internet has been highlighted as needing further study by international bodies, including the European Union and American Psychiatric Association. Knowledge regarding the optimal classification of problematic use of the Internet, subtypes, and associations with clinical disorders has been hindered by reliance on measurement instruments characterized by limited psychometric properties and external validation.
METHODS: Non-treatment seeking individuals were recruited from the community of Stellenbosch, South Africa (N = 1661), and Chicago, United States of America (N = 827). Participants completed an online version of the Internet Addiction Test, a widely used measure of problematic use of the Internet consisting of 20-items, measured on a 5-point Likert-scale. The online questions also included demographic measures, time

spent engaging in different online activities, and clinical scales. The psychometric properties of the Internet Addiction Test, and potential problematic use of the Internet subtypes, were characterized using factor analysis and latent class analysis.
RESULTS: Internet Addiction Test data were optimally conceptualized as unidimensional. Latent class analysis identified two groups: those essentially free from Internet use problems, and those with problematic use of the Internet situated along a unidimensional spectrum. Internet Addiction Test scores clearly differentiated these groups, but with different optimal cut-offs at each site. In the larger Stellenbosch dataset, there was evidence for two subtypes of problematic use of the Internet that differed in severity: a lower severity "impulsive" subtype (linked with attention-deficit hyperactivity disorder), and a higher severity "compulsive" subtype (linked with obsessive-compulsive personality traits).
CONCLUSIONS: Problematic use of the Internet as measured by the Internet Addiction Test reflects a quasi-trait - a unipolar dimension in which most variance is restricted to a subset of people with problems regulating Internet use. There was no evidence for subtypes based on the type of online activities engaged in, which increased similarly with overall severity of Internet use problems. Measures of comorbid psychiatric symptoms, along with impulsivity, and compulsivity, appear valuable for differentiating clinical subtypes and could be included in the development of new instruments for assessing the presence and severity of Internet use problems

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BMC Psychiatry. 2020 Jun;20:13.
Working memory and decision making in children with ADHD: An analysis of delay discounting with the use of the dual-task paradigm.
Fabio RA, Bianco M, CaprÃ¬ T, et al.
Background: Deficits in working memory tasks have been widely documented in Attention Deficit Hyperactivity Disorder (ADHD) studies. The aim of this study is to evaluate the effects of working memory load in impulsivity during decision-making processes. A delayed discounting (DD) paradigm was used, comparing children with ADHD and age-matched controls.
Method: Thirty-two children equally divided between typically developing and ADHD, from 8 to 10 years of age were assigned to sessions of a dual-task paradigm. In the primary task the child has to choose between two different amounts of money at different time delays, while in the secondary task the child has to repeat a random series of digits with different lengths. The experiment was conducted in a school setting.
Results: Compared to peers with typical development, delayed discounting was significantly stronger in children with ADHD and discounting rates increased in both groups for heavier memory loads. Furthermore, the memory load impact on frequency of immediate rewards was stronger in children with ADHD compared to typically developing children.
Discussion: Results are discussed in terms of the relation between working memory load and decision-making processes, their impact on impulsive behaviour in ADHD and the need for future research to understand possible neurocognitive correlates and use that information to develop better inclusive policies

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BMC Psychiatry. 2020 May;20:16.
A TWO ARM RANDOMIZED CONTROLLED TRIAL COMPARING THE SHORT AND LONG TERM EFFECTS OF AN ELIMINATION DIET AND A HEALTHY DIET IN CHILDREN WITH ADHD (TRACE STUDY). RATIONALE, STUDY DESIGN AND METHODS.
Bosch A, Bierens M, de Wit AG, et al.
Background: Food may trigger Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms. Therefore, an elimination diet (ED) might be an effective treatment for children with ADHD. However, earlier studies were criticized for the nature of the control group, potential confounders explaining the observed effects, unsatisfactory blinding, potential risks of nutritional deficiencies and unknown long term and cost-effectiveness. To address these issues, this paper describes the rationale, study design and methods of an ongoing two arm randomized controlled trial (RCT) comparing the short (5 week) and long term (1 year) effects of an elimination diet and a healthy diet compared with care as usual (CAU) in children with ADHD.

Methods: A total of N = 162 children (5-12 years) with ADHD will be randomized to either an ED or a healthy diet. A comparator arm including N = 60 children being solely treated with CAU (e.g. medication) is used to compare the effects found in both dietary groups. The two armed RCT is performed in two youth psychiatry centers in the Netherlands, with randomization within each participating center. The primary outcome measure is response to treatment defined as a 30% reduction on an ADHD DSM-5 rating scale (SWAN) and/or on an emotion dysregulation rating scale (SDQ: dysregulation profile). This is assessed after 5 weeks of dietary treatment, after which participants continue the diet or not. Secondary outcome measures include the Disruptive Behavior Diagnostic Observational Schedule (DB-DOS), parent and teacher ratings of comorbid symptoms, cognitive assessment (e.g. executive functions), school functioning, physical measurements (e.g. weight), motor activity, sleep pattern, food consumption, nutritional quality of the diet, adherence, parental wellbeing, use of health care resources and cost-effectiveness. Assessments take place at the start of the study (T0), after five weeks (T1), four months (T2), eight months (T3) and 12 months of treatment (T4). T0, T1 and T4 assessments take place at one of the psychiatric centers. T2 and T3 assessments consist of filling out online questionnaires by the parents only.
Discussion: This RCT will likely contribute significantly to clinical practice for ADHD by offering insight into the feasibility, nutritional quality, (cost-)effectiveness and long term effects of dietary treatments for ADHD.
Trial registration: www.trialregister.nl, NTR5434. Registered at October 11th, 2015

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BMC Psychiatry. 2020 May;20:11.

PROBLEMATIC INTERNET USE IN CHILDREN AND ADOLESCENTS: ASSOCIATIONS WITH PSYCHIATRIC DISORDERS AND IMPAIRMENT.

Restrepo A, Scheininger T, Clucas J, et al.

Background: Problematic internet use (PIU) is an increasingly worrisome issue, as youth population studies are establishing links with internalizing and externalizing problems. There is a need for a better understanding of psychiatric diagnostic profiles associated with this issue, as well as its unique contributions to impairment. Here, we leveraged the ongoing, large-scale Child Mind Institute Healthy Brain Network, a transdiagnostic self-referred, community sample of children and adolescents (ages 5-21), to examine the associations between PIU and psychopathology, general impairment, physical health and sleep disturbances.
Methods: A total sample of 564 (190 female) participants between the ages of 7-15 (mean = 10.80, SD = 2.16), along with their parents/guardians, completed diagnostic interviews with clinicians, answered a wide range of self-report (SR) and parent-report (PR) questionnaires, including the Internet Addiction Test (IAT) and underwent physical testing as part of the Healthy Brain Network protocol.
Results: PIU was positively associated with depressive disorders (SR: aOR = 2.43, CI: 1.22-4.74, p = .01; PR: aOR = 2.56, CI: 1.31-5.05, p = .01), the combined presentation of ADHD (SR: aOR = 1.91, CI: 1.14-3.22, p = .01; PR: n.s.), Autism Spectrum Disorder (SR: n.s.; PR: aOR = 2.24, CI: 1.34-3.73, p < .001), greater levels of impairment (SR: Standardized Beta = 4.63, CI: 3.06-6.20, p < .001; PR: Standardized Beta = 5.05, CI: 3.67-6.42, p < .001) and increased sleep disturbances (SR: Standardized Beta = 3.15, CI: 0.71-5.59, p = .01; PR: Standardized Beta = 3.55, CI: 1.34-5.75, p < .001), even when accounting for demographic covariates and psychiatric comorbidity.
Conclusions: The association between PIU and psychopathology, as well as its impact on impairment and sleep disturbances, highlight the urgent need to gain an understanding of mechanisms in order to inform public health recommendations on internet use in U.S. youth

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BMC Psychol. 2020 Jan;8:7.

IS THERE AN ASSOCIATION BETWEEN FULL IQ SCORE AND MENTAL HEALTH PROBLEMS IN YOUNG ADULTS? A STUDY WITH A CONVENIENCE SAMPLE.

Melby L, Indredavik MS, Lohaugen G, et al.

BACKGROUND: Intelligence is the aggregate or global capacity of the individual to act purposefully, to think rationally and to deal effectively with the environment. Previous studies have shown that individuals with

intellectual disability, IQ < 70, have increased risk of being diagnosed with one or more mental disorders. We wanted to investigate if this also applies to individuals with IQ between 70 and 85.
METHODS: In this study, data was abstracted from a longitudinal follow-up study of individuals with low birth weight and a control group. In the present study, mental health of participants with borderline IQ, defined as a full IQ score 70-84, were compared with mental health of a reference group with full IQ scores >/=85. Mental health at age 19 was assessed using the Schedule for Affective Disorder and Schizophrenia for School-age Children Present and Lifetime (K-SADS P/L) whereby scores meeting the diagnostic criteria for a mental disorder were defined as having mental health problems. In addition the participants completed the ADHD-rating scale and the Autism Spectrum Quotient form (AQ). Logistic regression analyses were used to calculate odds ratio (OR) with 95% confidence intervals (CI) for high scores on the K-SADS.
RESULTS: Thirty participants with borderline IQ and 146 controls were included. Sixteen (53%) of the participants with borderline IQ met the diagnostic criteria on the K-SADS for any diagnosis compared with 18 (12%) in the reference group (OR: 6.2; CI: 2.6-14.9). In particular the participants with borderline IQ had excess risk of ADHD and anxiety. These associations were slightly attenuated when adjusted for birth weight and parents' socioeconomic status.
CONCLUSIONS: 53% of the participants with borderline IQ had increased risk for a research assessed psychiatric diagnosis compared to about one in ten in the reference group. The group with borderline IQ also had higher total scores and higher scores on some sub-scores included in the Autism Spectrum Quotient form. Our results points towards an increased vulnerability for mental illness in individuals with borderline low IQ.
TRIAL REGISTRATION: The main study is recorded by the Regional Committee for Health Research Ethics in Mid-Norway (as project number 4.2005.2605)

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Brain Dev. 2020.

EXECUTIVE DYSFUNCTION IN MEDICATION-NA+»VE CHILDREN WITH ADHD: A MULTI-MODAL FNIRS AND EEG STUDY.

Kaga Y, Ueda R, Tanaka M, et al.

Objective: Children with attention deficit hyperactivity disorder (ADHD) exhibit deficits in executive function. Since there are no clear biomarkers for the disorder, this study aimed to investigate the neurophysiological biomarkers for deficits in executive function in children with ADHD using functional near-infrared spectroscopy (fNIRS) and electroencephalography.
Methods: Twenty patients diagnosed with ADHD and 19 typically developing children (TDC; 8-11 years old) were included. Event related potentials (ERPs) were recorded using an electroencephalogram (EEG) and oxygenated hemoglobin concentrations (Oxy-Hb) were recorded using fNIRS during a colored Go/NoGo task, simultaneously. Latencies and amplitudes of NoGo-N2 and NoGo/Go-P3 tasks were measured using EEG.
Results: Children with ADHD showed significantly decreased Oxy-Hb in the right frontal cortex as well as longer NoGo-P3 latencies and a decreased NoGo/Go-P3 amplitude. There was a significant positive correlation between the Oxy-Hb and NoGo/Go-P3 amplitude.
Conclusions: These results suggest that children with ADHD experience executive dysfunction. Hemodynamic and electrophysiological findings during the Go/NoGo task might be useful as a biomarker of executive function. Significance: These findings have key implications for understanding the pathophysiology of deficits in executive function in ADHD

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Brain Sciences. 2020;10.

AUDITORY AND VISUAL RESPONSE INHIBITION IN CHILDREN WITH BILATERAL HEARING AIDS AND CHILDREN WITH ADHD.

Bell L, Scharke W, Reindl V, et al.

Children fitted with hearing aids (HAs) and children with attention deficit/hyperactivity disorder (ADHD) often have marked difficulties concentrating in noisy environments. However, little is known about the underlying neural mechanism of auditory and visual attention deficits in a direct comparison of both groups. The current functional near-infrared spectroscopy (fNIRS) study was the first to investigate the behavioral performance and neural activation during an auditory and a visual go/nogo paradigm in children fitted with bilateral HAs, children with ADHD and typically developing children (TDC). All children reacted faster, but less accurately, to visual than auditory stimuli, indicating a sensory-specific response inhibition efficiency. Independent of modality, children with ADHD and children with HAs reacted faster and tended to show more false alarms than TDC. On a neural level, however, children with ADHD showed supra-modal neural alterations, particularly in frontal regions. On the contrary, children with HAs exhibited modality-dependent alterations in the right temporopolar cortex. Higher activation was observed in the auditory than in the visual condition. Thus, while children with ADHD and children with HAs showed similar behavioral alterations, different neural mechanisms might underlie these behavioral changes. Future studies are warranted to confirm the current findings with larger samples. To this end, fNIRS provided a promising tool to differentiate the neural mechanisms underlying response inhibition deficits between groups and modalities

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Braz J Psychiatry. 2020;42:309-13.

ASSESSMENT OF INTRAOCULAR PRESSURE, MACULAR THICKNESS, RETINAL NERVE FIBER LAYER, AND GANGLION CELL LAYER THICKNESSES: OCULAR PARAMETERS AND OPTICAL COHERENCE TOMOGRAPHY FINDINGS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Isik U, Kaygisiz M.

OBJECTIVE: To compare intraocular pressure (IOP) and macular, retinal nerve fiber layer (RNFL), and ganglion cell layer (GCL) thicknesses in treatment-naive children with attention-deficit/hyperactivity disorder (ADHD), children with ADHD on regular methylphenidate (MPH) treatment for at least 3 months, and healthy controls.

METHODS: A total of 58 treatment-naive children with ADHD, 45 children with ADHD on regular MPH treatment, and 44 healthy controls were enrolled in this study. All participants underwent a comprehensive eye examination. Optical coherence tomography (OCT) was used to assess global RNFL thickness, central macular thickness, and GCL thickness in both eyes.

RESULTS: Separate univariate analysis of covariance (ANCOVA) on the outcome variables revealed a significant difference among the research groups with respect to IOP in the left eye. Post-hoc univariate analyses indicated that left IOP was significantly higher in children with ADHD under MPH treatment than among healthy controls. However, global RNFL thickness, central macular thickness, and GCL thickness of both eyes, as well as IOP in the right eye, were not significantly different across groups.

CONCLUSION: Further longitudinal follow-up studies are needed to determine whether MPH treatment has any effect on IOP or OCT findings

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British Journal of Clinical Psychology. 2020 Jun;59:208-23.

MIND-WANDERING IN CHILDREN WITH AND WITHOUT ADHD.

Frick MA, Asherson P, Brocki KC.

Objectives: Mind-wandering (MW) is a commonly experienced phenomenon, characterized by focus of attention drifting away from the present situation to intrinsically originated thoughts. Studies in adults show that MW is related to ADHD symptoms, but this association is understudied in children. We set out to investigate the associations of MW in children with and without ADHD and to simultaneously validate the self-report Mind Excessively Wandering Scale (MEWS) in children.

Design: We used a cross-sectional, correlational, design to examine the research questions.
Methods: The sample consisted of 82 children (61 boys) aged 8-13 years (m = 10.46), of which 35 had a diagnosis of ADHD. Children rated MW; parents and teachers rated ADHD symptoms, emotion regulation and academic achievement. Working memory was assessed with Digit Span.
Results: MW was positively related to ADHD symptoms, and the MEWS could differentiate between cases and controls with a sensitivity of 0.71 and specificity of 0.81. Psychometric properties of the MEWS were satisfactory. In addition, MW contributed independently to working memory (RÂ²Î” = .05, p = .01) and emotion regulation (RÂ²Î” = .04, p = .04) beyond ADHD symptoms.
Conclusions: MW is elevated in children with ADHD and contributes to functional domains. The MEWS is a valid tool for assessing MW in children, and the results are mostly comparable to that of adults (Mowlem et al., 2016, Journal of Attention Disorders, 23, 624), suggesting a similar relationship of MW to ADHD across the lifespan. Practitioner points: 1. Spontaneous mind-wandering is elevated in children with ADHD compared to children without a diagnosis. 2. Elevated spontaneous mind-wandering predicts lower working memory, emotion regulation and academic achievement beyond ADHD symptoms, IQ and socio-economic status. 3. Clinicians should consider evaluating excessive spontaneous mind-wandering and targeting it as an important outcome when treating children with ADHD. 4. The MEWS is a valid tool for assessing excessive mind-wandering in children

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Child Adolesc Psychiatry Ment Health. 2020;14.
COMORBIDITY OF DISRUPTIVE BEHAVIOR DISORDERS AND INTERMITTENT EXPLOSIVE DISORDER.
Radwan K, Coccaro EF.
Background: Aggressive behavior in children and adolescents may be accounted for by several disruptive behavioral disorders (DBD) including attention-deficit/hyperactive (ADHD), conduct (CD), and oppositional defiant (ODD), disorders and intermittent explosive disorder (IED). The comorbidity among the DBDs is well known, but not its comorbidity with IED.
Method: We reanalyzed data from the National Comorbidity Studies (adolescents and adults), and from a large clinical research adult sample, to estimate the comorbidity of IED with each of the DBDs and to explore correlates of these comorbidities.
Results: The rate of current comorbidity between IED and the DBDs ranged from 10 to 19%, in adolescents (5-14% in adults) with odds ratios of about five. The onset of ADHD typically appeared before onset of IED while onset ODD and CD more typically appeared before that of IED in adolescents and about equally before or after IED in adults but IED persisted outside the duration window in many (ADHD) or most (ODD, CD) cases. Measures of impulsive aggression severity were highest in those with IED+DBD but relatively low in those with DBD alone while measures of DBD severity were highest in those with DBD alone and in those with IED+DBD.
Conclusion: Despite the comorbidity of IED with the DBDs, IED can be separated from the DBDs over time and in terms of severity measures of IED and of DBD. Overall, impulsive aggression varies with IED while DBD behaviors vary with DBD. Based on this, clinicians should consider IED in their differential in the workup of impulsively aggressive children and adolescents

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Clin Child Fam Psychol Rev. 2019 Sep;22:348-66.
STAND-ALONE SOCIAL SKILLS TRAINING FOR YOUTH WITH ADHD: A SYSTEMATIC REVIEW.
Willis D, Siceloff ER, Morse M, et al.
Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders, and its symptoms and impairment in multiple domains begin in childhood and can extend into adulthood as well. Many youth with ADHD experience impairment in the social domain, including social skills deficits and difficulties in peer relationships. Social skills interventions, or social skills training (SST), have been developed to target social impairment and improve the social skills and functioning of youth with ADHD. Previous reviews of SST for youth with ADHD have provided mixed conclusions, with many including

comprehensive, multilevel interventions for ADHD and none examining stand-alone SST for ADHD in a systematic way. The present review addresses this gap in the literature by providing the first known comprehensive, systematic review of SST alone, along with ratings of methodological rigor for each evaluation of stand-alone SST. The present review provides insight into the strengths and weaknesses in the existing SST literature, and provides suggestions for improvement and future directions for SST. An outline of "specific ingredients" and characteristics of effective SST are also presented, with the goal of providing both researchers and clinicians guidance for creating and implementing effective SST for youth with ADHD

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Clin Child Fam Psychol Rev. 2019 Sep;22:316-47.

THE TRANSITION OF YOUTH WITH ADHD INTO THE WORKFORCE: REVIEW AND FUTURE DIRECTIONS.

Gordon CT, Fabiano GA.

Previous research suggests that a majority of children with attention-deficit/hyperactivity disorder (ADHD) continue to experience increased impairment across multiple life domains into adulthood. A systematic review of the occupational impairments, and associated educational and financial difficulties, faced by individuals with childhood ADHD was conducted. Systematic searches from PsycINFO and PubMed databases and other sources (i.e., books and consultants with experts) yielded 35 relevant articles that described 19 longitudinal studies on adults with a history of ADHD or related symptoms. Multiple studies indicated that those with a history of ADHD had more educational impairment and were less likely to graduate from high school and college than their peers without a history of ADHD. Subsequently, they faced lower occupational attainment, had more job instability, and demonstrated more impaired job performance, and these outcomes were largely consistent regardless of sex, medication history, or symptom persistence. Similar results were found in clinical and representative national studies in both U.S. and abroad, although older studies tended to indicate less occupational impairment. In addition, ADHD was associated with a number of financial challenges, including lower annual income, more reliance on public aid, and increased risk for homelessness. Future research should use more varied informant sources and utilize innovative measures of occupational impairment at both a macro- and micro-level of analyses. In addition, studies of effective supports and interventions in occupational settings for individuals with ADHD are needed

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Clinical and Experimental Dermatology. 2020.

QUALITY OF LIFE, EMOTION DYSREGULATION, ATTENTION DEFICIT AND PSYCHIATRIC COMORBIDITY IN CHILDREN AND ADOLESCENTS WITH VITILIGO.

Ucuz I, Altunisik N, Sener S, et al.

Background: Vitiligo is an acquired pigmentation disorder, which can have a negative effect on patient quality of life (QoL).

Aim: To evaluate QoL and psychiatric comorbidity in paediatric patients with vitiligo.

Methods: In total, 30 patients aged 8-18 years who were diagnosed with vitiligo and 30 age- and sex-matched healthy controls (HCs) were included in the study. The Children's Depression Inventory, Screen for Child Anxiety Related Disorders, State-Trait Anxiety Inventory for Children and Child Somatization Inventory were completed for both patients and controls. The Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL) was administered to all patients by a child psychiatrist. Families were also asked to complete the Pediatric Quality of Life Inventory and Emotion Regulation Checklist for children.

Results: The K-SADS-PL evaluation showed that 90% of the patients in the vitiligo group had at least one psychiatric diagnosis, whereas this rate was 20% in the HCs (P-á<-á0.001). There were statistically significant differences between vitiligo and HCs in terms of anxiety, state and trait anxiety scores (P-á<-á0.05). Attention deficit and hyperactivity disorder (ADHD) was detected in 36.6% of the patients.

Conclusion: The most important finding of this study is that anxiety disorders are more prominent than depression in childhood vitiligo. Another important finding of this study is that the prevalence of ADHD is significantly higher than the normal population

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Clin Pediatr. 2020.

SYMPTOM LEVEL ASSOCIATIONS BETWEEN ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND SCHOOL PERFORMANCE.

Rigoni M, Blevins LZ, Rettew DC, et al.

Attention-deficit hyperactivity disorder (ADHD) is associated with reduced school performance. To determine which ADHD symptoms and subtypes have the strongest association, we used type and frequency of symptoms on the 2014 National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome (NS-DATA) to create symptom scores for inattention and hyperactivity-impulsivity and define subtypes (ADHD-Inattentive [ADHD-I], ADHD-Hyperactive-Impulsive, ADHD-Combined [ADHD-C]). Regression methods were used to examine associations between symptoms and subtype and a composite measure of school performance. Children with ADHD-C and ADHD-I had higher adjusted odds of having reduced overall school performance (ADHD-C = 5.8, 95% confidence interval [CI] = 3.1-10.9; ADHD-I = 5.5, 95% CI = 3.1-10.1) compared with children without ADHD. All inattentive symptoms were significantly related to reduced school performance in reading, writing, and handwriting, while 6 of 9 symptoms were significantly associated in mathematics. Children with ADHD-I were significantly more likely than children with other ADHD subtypes to receive a school-based Individualized Education Program or 504 Plan. ADHD-I symptoms may be broadly linked to reduced school performance

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Clin Pract Pediatr Psychol. 2020 Jun;8:189-94.

EXPANDING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SERVICE PROVISION IN URBAN SOCIOECONOMICALLY DISADVANTAGED COMMUNITIES: A PILOT STUDY.

Chacko A, Hopkins K, Acri M, et al.

Objective: Access to evidence-based psychosocial interventions for the treatment of attention-deficit/hyperactivity disorder (ADHD) is a challenge in urban, socioeconomically disadvantaged communities. Approaches that leverage existing but underdeveloped workforces and connects these with well-established settings that treat ADHD offers an opportunity to address this barrier. This pilot study focused on a preliminary test of the potential utility of paraprofessional-delivered behavioral parent training (BPT) to parents of children with ADHD being treated in a developmental behavioral pediatric practice.

Method: In an open clinical trial of 7 families, Family Peer Advocate paraprofessionals delivered BPT to parents of children with ADHD. Parent reports of their child's ADHD symptoms/oppositional defiant behaviors and functional impairment were assessed before, weekly during BPT, and immediately after BPT. Parents report of their positive and negative parenting behaviors were assessed before and immediately after BPT.

Results: Findings demonstrated that participation in BPT was associated with improvements in child- and parent-level outcomes, with moderate to large effects across outcomes.

Conclusions: Integrating existing service systems with oversight through pediatric psychologists offers opportunities to efficiently utilize resources, thereby increasing access to evidence-based interventions for ADHD in urban, socioeconomically disadvantaged communities. (PsycInfo Database Record (c) 2020 APA, all rights reserved) (Source: journal abstract) Impact statement Implications for Impact Statement This study advances the scope of paraprofessional involvement in formal pediatric settings. In addition, it highlights the potential effectiveness of peer-to-peer delivered services

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Clin Psychopharmacol Neurosci. 2020;18:75-80.

Effect of omega-3 and Korean red ginseng on children with attention deficit hyperactivity disorder: An open-label pilot study.

Lee J, Lee A, Kim J-H, et al.

Objective: The purpose of the present study was to evaluate the efficacy of omega-3 and Korean red ginseng on improving attention deficit hyperactivity disorder (ADHD) symptoms and cognitive function in children with ADHD.

Methods: A total of 40 children aged 6 to 12 years diagnosed with ADHD participated in this open-label trial. Participants received daily supplements containing 500 mg of omega-3 (eicosapentaenoic acid, 294 mg; docosahexaenoic acid, 206 mg) and 3 mg of Korean red ginseng extract (combination of ginsenoside Rg1, Rb1, and Rg3) for 12 weeks. No psychotropic drug was allowed during the study period. ADHD symptoms were assessed using the ADHD Rating Scale (ADHD-RS) and Clinical Global Impression-Severity (CGI-S) scale. Neuropsychological tests on sustained attention, short-term memory, and executive function were also assessed.

Results: After 12 weeks, participants showed significant improvements on ADHD-RS (31.12 -¦ 8.82 at baseline, 24.15 -¦ 11.45 at endpoint; p 0.001) and CGI-S (3.38 -¦ 1.18 at baseline, 2.94 -¦ 1.00 at endpoint; p 0.001). On the Continuous Performance Test, commission errors significantly decreased, while reaction time significantly increased. Immediate recall and delayed recall on both Auditory Verbal Learning Test and Complex Figure Test showed significant improvements. Scores of Color Word Task from Stroop Color Word Test also showed significant improvements after the treatment. The supplement was well tolerated.

Conclusion: The results of this pilot study suggest that the combination of omega-3 and Korean red ginseng may improve ADHD symptoms and cognitive function including attention, memory, and executive function in children with ADHD. Future randomized placebo-controlled trials with a larger sample is warranted

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Dev Med Child Neurol. 2020 May;62:587-92.

PSYCHOSOCIAL AND FUNCTIONAL OUTCOMES IN YOUNG ADULTS WITH CHILDHOOD-ONSET EPILEPSY: A 10-YEAR FOLLOW-UP.

Friefeld KR, McMillan T, Lee B, et al.

AIM: To compare long-term psychosocial and functional outcomes of young adults with uncomplicated childhood-onset epilepsy (COE) to population norm controls utilizing a controlled prospective cohort study.

METHOD: Psychosocial and functional outcomes were assessed at 10-year follow-up. Fifty-three young adults (27 males, 26 females) with COE (n=21 remission; 18y 1mo-30y 9mo; mean age 23y 4mo [SD 3y 4mo]; mean age of epilepsy onset 12y [SD 3y 2mo]) were compared to 55 (23 males, 32 females) first-degree cousin controls (18y 5mo-29y 8mo; mean age 23y 6mo [SD 3y]). Seizure remission status and baseline comorbidities (attention-deficit/hyperactivity disorder [ADHD], depressive disorders, anxiety disorders, and academic problems) were examined as possible risk factors for significant differences in functional outcomes.

RESULTS: Poorer functional outcomes, indicated by patient rated cognition and overall disability, were evident among young adults with epilepsy compared to controls (all $p<0.05$). These difficulties were due to baseline comorbid ADHD and academic problems. Remission status was not related to measured cognition and overall disability.

INTERPRETATION: Psychosocial outcomes of young adults with COE were similar to controls. In contrast, functional outcomes were worse in epilepsy across cognition and overall disability. Baseline comorbid ADHD and academic problems were identified as risk factors at 10-year follow-up suggesting that these early recognized comorbidities at or near diagnosis have long-term impacts.

WHAT THIS PAPER ADDS: Young adults with childhood-onset epilepsy (COE) and controls have similar psychosocial outcomes 10 years after diagnosis. Young adults with COE report greater limitations in cognition and overall disability than controls. Baseline presence of attention-deficit/hyperactivity disorder and academic problems significantly affect cognitive and overall disability scores

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Dev Neuropsychol. 2020 May;45:246-61.

HOW IS TEMPORAL PROCESSING AFFECTED IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Suarez I, De Los Reyes AragÃ³n C, Diaz E, et al.

We compared the performance of children with ADHD and typically developing children on two temporal tasks, a bisection task and a reproduction task, in auditory and visual modalities. Children with ADHD presented a larger variability when performing auditory and visual temporal tasks. Moreover, they overestimated the durations in bisection tasks and underproduced duration intervals in the visual reproduction task. In the context of the pacemaker-accumulator model, these results suggest that temporal deficits might result from a dysfunction in the switch and/or memory impairment

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Drug Alcohol Depend. 2019 Dec;205:107683.

MOMENTARY FLUCTUATIONS IN IMPULSIVITY DOMAINS: ASSOCIATIONS WITH A HISTORY OF CHILDHOOD ADHD, HEAVY ALCOHOL USE, AND ALCOHOL PROBLEMS.

Pedersen SL, King KM, Louie KA, et al.

BACKGROUND: The current study examined if fluctuation in in-the-moment impulsivity was more pronounced for adults with, versus without, a childhood history of ADHD and if ADHD group moderated the association between fluctuation in impulsivity and alcohol use behaviors.

METHODS: Two hundred and eleven adult drinkers (52% ADHD) completed a 10-day, 6 times/day, momentary assessment of state impulsivity. Self-reported trait impulsivity, alcohol problems, and frequency of 5+ drinks in the past 12 months were also assessed.

RESULTS: The ADHD group had more variability in three domains of state impulsivity (negative urgency, positive urgency, sensation seeking) compared to the nonADHD group. After including global trait impulsivity, the ADHD and nonADHD groups only differed on state sensation seeking. Fluctuation in two domains of state impulsivity were related to frequency of 5+ drinks (lack of planning: ADHD RR=3.60, p<0.001, nonADHD RR=0.90, p=0.81; negative urgency: ADHD RR=4.32, p=0.01, nonADHD RR=0.49, p=0.24) and number of different alcohol problems (lack of planning: ADHD RR=4.87, p<0.001, nonADHD RR=0.58, p=0.29; negative urgency: ADHD RR=4.96, p=0.01, nonADHD RR=0.24, p=0.04) for participants with a history of ADHD but were not related (or related to fewer problems) for those without childhood ADHD. Higher variability in positive urgency was related to more alcohol problems for the participants with childhood ADHD but not the nonADHD participants (ADHD RR=3.00, p=0.03, nonADHD RR=0.50, p=0.25).

CONCLUSIONS: Findings highlight the importance of assessing fluctuation in several domains of impulsivity and may elucidate important treatment targets for alcohol problems for adults with ADHD histories

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Encephale. 2020.

HOW DO CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) EXPERIENCE LOCKDOWN DURING THE COVID-19 OUTBREAK?

Bobo E, Lin L, Acquaviva E, et al.

Objectives: During the COVID-19 pandemic, the French government has decided a general lockdown. This unprecedented situation has raised concerns about children's and adolescent's mental health. Children and adolescents diagnosed with attention deficit hyperactivity disorder (ADHD) may find this context of restrained activity particularly tricky. The objectives of our study are to gather information about the well-being and global life conditions of children and adolescents with ADHD during the COVID-19 outbreak in France.

Methods: We designed a survey including both open-ended questions and questionnaire items for parents of children and adolescents with ADHD. Parents responded to the following open-ended questions: 1) How is your child doing since the lockdown? 2) How is life at home since the lockdown? 3) If you had a remote service provision with a mental health professional (e.g. by telephone or video technology), please share your thoughts and any suggestions with us 4) Please share any other items that you think are important about ADHD symptoms of your child and the lockdown situation. This survey was posted on social media on

the 6th of April and disseminated by French ADHD-parent and patient organizations. The present article reports the descriptive, qualitative and textometrical analyses of the survey.
Results: Between day 20 and 30 of lockdown, 538 parents responded to the survey, and we included 533 responses in the final analysis. The vast majority of responders were women 95 % (95 % CI 93,50; 97,18) with children whose mean age was 10,5 (95 % CI 7.58; 13.44). Since the lockdown, 34.71 % (95 % CI 30.70; 38.94) of children experienced a worsening in well-being, 34.33 % (95 % CI 30.34; 38.56) showed no significant changes and 30.96 % (95 % CI 27.09; 35.10) were doing better according to their parents. The thematic analysis showed that an improvement of their children's anxiety was one of the main topics addressed by parents. This improvement related to less school-related strain and flexible schedules that respected their children's rhythm. Improved self-esteem was another topic that parents linked with a lesser exposure of their children to negative feed-back. Parents repeatedly reported both inattention and hyperactivity/impulsivity. However, optimal lockdown life conditions seemed to compensate for the impact of ADHD symptoms (e.g. sufficient space at home, presence of a garden). Some parents reported worsening of general well-being in their children, and this manifested as oppositional/defiant attitudes and emotional outbursts. Parents also cited sleep problems and anxiety in this context. As regards everyday life during lock-down, at-home schooling was another major topic-parents described that their children struggled to complete school-related tasks and that teachers seemed to have forgotten about academic accommodations. The lockdown situation seems to have raised parents awareness of the role of inattention and ADHD symptoms in their children's learning difficulties. Due to potential selection biases, the results of our survey may not be generalizable to all children and adolescents with ADHD. The main strengths of this rapid survey-based study lies in the reactivity of the participants and the quality and diversity of their responses to the open-ended questions.
Conclusions: According to their parents, most children and adolescents with ADHD experience stability or improvement of their well-being. An improvement in school-related anxiety and the flexible adjustment to the children's rhythms as well as parents increased awareness of the difficulties their children experience are among the key topics in parents' descriptions

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eNeuro. 2020;7.

TOPOLOGICAL DATA ANALYSIS REVEALS ROBUST ALTERATIONS IN THE WHOLE-BRAIN AND FRONTAL LOBE FUNCTIONAL CONNECTOMES IN ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Gracia-Tabuenca Z, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by difficulty to control the own behavior. Neuroimaging studies have related ADHD with the interplay of fronto-parietal attention sys-tems with the default mode network (DMN; Castellanos and Aoki, 2016). However, some results have been in-consistent, potentially due to methodological differences in the analytical strategies when defining the brain functional network, i.e., the functional connectivity threshold and/or the brain parcellation scheme. Here, we make use of topological data analysis (TDA) to explore the brain connectome as a function of the filtration value (i.e., the connectivity threshold), instead of using a static connectivity threshold. Specifically, we characterized the transition from all nodes being isolated to being connected into a single component as a function of the filtration value. We explored the utility of such a method to identify differences between 81 children with ADHD (45 male, age: 7.26-17.61 years old) and 96 typically developing children (TDC; 59 male, age: 7.17 17.96 years old), using a public dataset of resting state (rs)fMRI in human subjects. Results were highly con-gruent when using four different brain segmentations (atlases), and exhibited significant differences for the brain topology of children with ADHD, both at the whole-brain network and the functional subnetwork levels, particularly involving the frontal lobe and the DMN. Therefore, this is a solid approach that complements con-nectomics-related methods and may contribute to identify the neurophysio-pathology of ADHD

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Epilepsy Behav. 2019 May;94:144-50.

GENDER AND PSYCHIATRIC DISORDERS IN CHILDREN WITH EPILEPSY. A META-ANALYSIS.

Lax-Pericall MT, Bird V, Taylor E.

OBJECTIVE: The objective of the study was to assess the influence of gender on psychiatric disorders in children with epilepsy (CWE).

METHOD: A systematic review of the literature on risk factors for psychiatric disorder in CWE published between 2004 and June 2018 was undertaken. Studies including data on gender that permitted the calculation of a risk ratio (RR) were included in the meta-analysis. A meta-regression was conducted to examine the contribution of setting of the survey and the inclusion of learning disabilities.

RESULTS: Thirty-nine papers were included in the review. The male/female RR in CWE for Attention Deficit Hyperactivity Disorder (ADHD) was 1.49 (Confidence Interval (CI): 1.24-1.79), autistic spectrum disorder (ASD) 1.67 (CI: 1.47 to 1.90), anxiety 1.00 (CI: 0.90-1.12), and depression 0.93 (CI 0.41-2.09). More boys than girls had ADHD and ASD, but in relative terms, the RR male/female was lower in CWE than the RR in the general population reported in other studies. Meta-regression indicated that the inclusion of children with intellectual disability (mental retardation) or the setting (community vs hospital) did not have a significant impact.

CONCLUSION: Compared with girls in the general population, girls with epilepsy seem to be at a higher risk of being diagnosed with ADHD/ASD as the gender ratio is more equal. This could be related to differences in the assessment of CWE and/or a shared pathogenesis between psychiatric conditions and epilepsy

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Eur Child Adolesc Psychiatry. 2020 Mar;29:287-97.

GUT MICROBIOTA AND DIETARY PATTERNS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang LJ, Yang CY, Chou WJ, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, but the underlying pathophysiological mechanisms of ADHD remain unclear. Gut microbiota has been recognized to influence brain function and behaviors. Therefore, this study aimed to determine whether imbalanced gut microbiomes identified by a 16S rRNA sequencing approach are involved in the pathophysiology of ADHD. We recruited a total of 30 children with ADHD (mean age: 8.4 years) and a total of 30 healthy controls (mean age: 9.3 years) for this study. The dietary patterns of all participants were assessed with the food frequency questionnaire. The microbiota of fecal samples were investigated using 16S rRNA V3V4 amplicon sequencing, followed by bioinformatics and statistical analyses. We found that the gut microbiota communities in ADHD patients showed a significantly higher Shannon index and Chao index than the control subjects. Furthermore, the linear discriminant analysis effect size (LEfSe) analysis was used to identify differentially enriched bacteria between ADHD patients and healthy controls. The relative abundance of Bacteroides coprocola (B. coprocola) was decreased, while the relative abundance of Bacteroides uniformis (B. uniformis), Bacteroides ovatus (B. ovatus), and Sutterella stercoricanis (S. stercoricanis) were increased in the ADHD group. Of all participants, S. stercoricanis demonstrated a significant association with the intake of dairy, nuts/seeds/legumes, ferritin and magnesium. B. ovatus and S. stercoricanis were positively correlated to ADHD symptoms. In conclusion, we suggest that the gut microbiome community is associated with dietary patterns, and linked to the susceptibility to ADHD

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Eur Child Adolesc Psychiatry. 2020.

GUIDELINE ADHERENCE IN GERMAN ROUTINE CARE OF CHILDREN AND ADOLESCENTS WITH ADHD: AN OBSERVATIONAL STUDY.

Mücke K, Plück J, Steinhauser S, et al.

Although guidelines for the assessment and treatment of mental disorders in childhood and adolescence have been available in Germany for several years, there are barely any data on adherence to guidelines in national routine care. Therefore, the study aimed at a nationwide evaluation of guideline adherence (GA) for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder

(ADHD) in German routine care in various groups of health care providers (HCPs). Besides a detailed description of GA, the study focused on examining possible differences between professional groups. Furthermore, data based on global self-reports of clinicians were compared with ratings of documented care in individual patients. Protocols of 73 clinicians regarding their handling of ADHD in routine care for 167 patients were rated according to German guideline recommendations for ADHD care. GA was measured as the proportion of components fulfilled in each individual patient as documented by the HCP. The results were compared to a preceding interview with clinicians regarding their GA. Multilevel models were constructed to detect differences in GA between professional groups. Based on mandatory guideline components, adherence rates of 38.9-72.7% were found and classified as moderate 33.3% < GA ≤ 66.6%) to high (GA > 66.6%). The comparison of the GA between the professional groups generally yielded only small differences. Correlations between GA reported globally by the HCPs and GA documented and rated for individual cases were low. Overall, most rates of GA for ADHD in German routine care lay within a moderate range. Targets for enhancement of GA may be the involvement of teachers and schools in the treatment process, the implementation of psychoeducational methods in general, as well as a careful examination of patients, including monitoring of treatment effects during titration trials. The development of further strategies to monitor the quality of ADHD routine care is needed

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Eur Child Adolesc Psychiatry. 2020.

PREDICTING ADHD SYMPTOMS AND DIAGNOSIS AT AGE 14 FROM OBJECTIVE ACTIVITY LEVELS AT AGE 7 IN A LARGE UK COHORT.

Brandt V, Patalay P, Kerner auch KJ.

Hyperactivity is one of the three core symptoms in children with attention deficit hyperactivity disorder (ADHD). Diagnosing ADHD typically involves self-report, third party report and observations. Objective activity data can make a valuable contribution to the diagnostic process. Small actigraphy studies in clinical samples have shown that children with ADHD move more than children without ADHD. However, differences in physical activity between children with and without ADHD have not been assessed in large community samples or longitudinally. This study used data from the Millennium Cohort Study to test whether symptoms of ADHD (parent-rating Strengths and Difficulties Questionnaire) and ADHD diagnosis at age 14 (reported by parents) could be predicted from objective activity data (measured with actigraphs) at age 7 in N = 6675 children (final N = 5251). Regressions showed that less sedentary behavior at age 7 predicted more ADHD symptoms at age 14 (β = − 0.002, CI − 0.004 to − 0.001). The result remained significant when controlled for ADHD symptoms at age 7, sex, BMI, month of birth, SES and ethnicity (β = − 0.001, CI − 0.003 to − 0.0003). ADHD diagnosis at age 14 was also significantly predicted by less sedentary behavior at age 7 (β = − 0.008). Our findings show that symptoms of ADHD can be predicted by objective activity data 5 years in advance and suggest that actigraphy could be a useful instrument aiding an ADHD diagnosis. Interestingly, the results indicate that the key difference between children with and without ADHD lies in reduced sedentary activity, i.e., times of rest.

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Eur Child Adolesc Psychiatry. 2020.

NEGATIVE PARENTING BEHAVIOUR AS A MEDIATOR OF THE EFFECTS OF TELEPHONE-ASSISTED SELF-HELP FOR PARENTS OF PHARMACOLOGICALLY TREATED CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Dose C, Hautmann C, B++rger M, et al.

A previous randomised-ácontrolled trial demonstrated the effects of a telephone-assisted self-help (TASH) intervention for parents of pharmacologically treated children with attention-deficit/hyperactivity disorder (ADHD) on ADHD symptoms, oppositional symptoms, functional impairment, and negative parenting behaviour (per-protocol analyses). In the current study, we examined whether changes in positive and negative parenting behaviour mediated the effects on symptoms and impairment. Parents in an enhancement group (n = 51) participated in a 12-month TASH intervention (eight booklets plus up to 14 telephone consultations) as an adjunct to routine clinical care, whereas parents in a waitlist control group (n = 52)

received routine clinical care only. Parents completed measures of child symptoms, child functional impairment, and parenting behaviour at baseline, at 6-ámonths, and at 12-ámonths. The mediating effects of parenting behaviour were examined using regression analyses. Per-protocol analyses (n = 74) revealed a significant indirect intervention effect on functional impairment through negative parenting behaviour at 6-ámonths as well as indirect intervention effects on oppositional symptoms and functional impairment through negative parenting behaviour at 12-ámonths. The indirect effect on ADHD symptoms through negative parenting behaviour at 12-ámonths just failed to reach significance. The analyses yielded no indirect intervention effects through positive parenting behaviour. The study provides some, albeit limited, support for the importance of changes in negative parenting behaviour to achieve changes in symptoms and functional impairment during parent training. In consideration of the inconsistent results of previous studies concerning the mediating role of positive and negative parenting behaviour, further research is required to better understand the mechanisms of change during parent training, also including other possible mediators like parenting stress and parental self-efficacy

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Evidence-Based Practice in Child and Adolescent Mental Health. 2020.

BEHAVIORAL TREATMENT FOR THE SOCIAL-EMOTIONAL DIFFICULTIES OF PREADOLESCENT AND ADOLESCENT GIRLS WITH ADHD.

Babinski DE, Mills HS, Bansal PS, et al.

Girls with attention-deficit/hyperactivity disorder (ADHD) are at high risk for peer difficulties that often persist into adolescence and adulthood and portend risk for additional difficulties, such as depression, anxiety, and borderline personality disorder. However, very little research has examined interventions that address the widespread peer difficulties of girls with ADHD. This paper describes two open trials of behavior therapy aimed at addressing their social-emotional difficulties. The first trial includes 33 preadolescent girls (ages 7ΓÇô11) with ADHD enrolled in an eight-week treatment and the second trial includes 22 adolescent girls (ages 12ΓÇô16) with ADHD enrolled in a 12-week treatment. Measures of treatment feasibility and acceptability and measures of social functioning and psychopathology were collected in both trials. High levels of treatment feasibility and acceptability were reported in both the preadolescent and adolescent trial. In addition, improvements were reported in areas of social functioning and reductions in psychopathology, although the magnitude and specific areas of improvement differed somewhat in the preadolescent versus adolescent group. These preliminary findings provide a first step toward addressing the widespread social-emotional difficulties of girls with ADHD and offer insight into continuing efforts to address their treatment needs

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Front Psychol. 2020 May;11:8.

CHARACTERIZATION OF CLINICAL MANIFESTATIONS IN THE CO-OCCURRING PHENOTYPE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Carta A, Fucà E, Guerrera S, et al.

Comorbidity between attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) is a frequently reported condition. However, the clinical overlaps between the two disorders are not well characterized. The Child Behavior Checklist (CBCL) is a well-documented measure of emotional and behavioral problems in children and adolescents. The aim of the present study was to evaluate whether CBCL scales were able to detect psychopathological comorbidities as well as emotional and behavioral profiles across three groups of children with ASD, ADHD, and with the co-occurrence of both disorders. The results show that around 30% of participants with ASD exhibited internalizing problems, which was in line with previous findings. Co-occurrence condition showed a clinical intermediate phenotype: relative to ADHD and ASD, youths with co-occurrence of ADHD and ASD phenotype showed respectively lower ($p < 0.000$) and higher externalizing problems ($p < 0.000$). No differences emerged in internalizing problems ($p > 0.05$) across groups. CBCL is a useful measure to study the psychopathological conditions as well as emotional and behavioral profiles associated with ASD, ADHD, and the co-occurrence of ADHD and ASD. The

identification of psychopathological and behavioral profiles associated with ASD and ADHD is crucial to perform specific and individualized treatments. Our preliminary findings suggested the existence of an intermediate and independent phenotype between ADHD and ASD that seems to be defined by the externalizing problems. Internalizing problems do not significantly differ between the combined phenotype and the two groups

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Health Place. 2019 Jan;55:71-79.

EXPOSURE TO NATURE FOR CHILDREN WITH AUTISM SPECTRUM DISORDER: BENEFITS, CAVEATS, AND BARRIERS.

Li D, Larsen L, Yang Y, et al.

Autism spectrum disorder (ASD) is the fastest growing developmental disorder in countries across the world. Although recent studies have demonstrated the health benefits of nature for typically developing children and children with attention deficit hyperactivity disorder, it is unclear whether these benefits extend to children with ASD. In this study, we investigated whether benefits associated with exposure to nature could be observed by parents of children diagnosed with ASD. We conducted semi-structured interviews with 22 parents and caregivers of children on the spectrum from two cities in China. Results showed that exposure to nature provided motor-sensory, emotional and social benefits to children with ASD, although some of the identified benefits also come with concerns. Participants identified a wide range of barriers that make exposing their children to nature difficult. Among them, inappropriate behaviors, safety concerns, phobias and issues with the public realm emerged as critical hurdles. These findings suggest that practitioners should consider nature exposure as an intervention strategy, and planners and designers should create places that better accommodate the needs of children with ASD

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Holist Nurs Pract. 2020 Jan;34:65-67.

SAFFRON (CROCUS SATIVUS L.): A PHYTOMEDICINE AS EFFECTIVE AS METHYLPHENIDATE IN TREATING ADHD IN CHILDREN.

Ross SM.

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Indian Journal of Public Health Research and Development. 2020;11:1658-62.

CORRECTION OF THE MANIFESTATIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PRIMARY SCHOOL CHILDREN.

Ivanovichalifirov A.

Context: Currently, attention deficit hyperactivity disorder remains very common among children. The ongoing attempts to correct this condition, including using an integrated approach through the use of several individually selected method at once, have not yet yielded satisfactory results. In the course of the study, the correctional possibilities of the author's methodology of teaching chess for children aged 7-9 years with attention deficit hyperactivity disorder were evaluated. The technique turned out to be effective due to the integrated use of multimedia accompaniment and special techniques for switching the attention of children during classes. It is established that the author's technique helps to reduce the severity of symptoms in children with attention deficit hyperactivity disorder. Semi-annual classes provided in all cases the elimination of existing violations and the achievement in children of a balance of excitation and inhibition in the cerebral cortex during the development of a game of chess according to the author's method

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Int J Environ Res Public Health. 2020;17.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ITS PHARMACOTHERAPY, AND ADRENAL GLAND DYSFUNCTION: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN.

Peng P-H, Tsai M-Y, Lee S-Y, et al.

This study aims to examine the co-occurrence rate of attention deficit hyperactivity disorder (ADHD) and adrenal gland disorders, as well as whether pharmacotherapy may affect ADHD patientsΓÇÖ risk of developing adrenal gland disorder. One group of patients newly diagnosed with ADHD (n = 75,247) and one group of age-and gender-matching controls (n = 75,247) were chosen from TaiwanΓÇ¦s National Health Insurance database during the period of January 1999 to December 2011. Both patients and controls were monitored through December 31, 2011, in order to identify the occurrence of adrenal gland disorders (ICD-9-CM code 255.X). We also explored the potential effect of methylphenidate (MPH) and atomoxetine (ATX) treatments on the risk of developing adrenal gland disorders. We found that ADHD patients showed a significantly increased probability of developing an adrenal gland disorder compared to the control group (0.2% of ADHD vs. 0.1% of controls). However, neither MPH nor ATX treatment significantly influenced the patients' risk of developing adrenal gland dysfunction. We propose that patients with ADHD had greater comorbid rates with adrenal gland dysfunction than the control subjects. Nevertheless, undergoing treatment with MPH or ATX did not significantly influence the risk of developing adrenal gland dysfunction among ADHD patients

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Int J Psychiatry Clin Pract. 2020.

CHILDHOOD AND ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN FIBROMYALGIA: ASSOCIATIONS WITH DEPRESSION, ANXIETY AND DISEASE IMPACT.

Karaş H, et al.

Objective: The first aim of this study was to determine the prevalence of childhood and current attention deficit hyperactivity disorder (ADHD) symptoms in patients with fibromyalgia. The second aim is to assess the role of depression and anxiety on the relationship between childhood and adult ADHD symptoms with disease impact in this population.

Methods: Sixty-four patients with fibromyalgia were compared to matched 58 healthy controls. All participants completed the Wender Utah Rating Scale (WURS), Adult ADHD Self-Report Scale (ASRS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Fibromyalgia Impact Questionnaire (FIQ).

Results: Patients with fibromyalgia had significantly higher mean scores of depression (BDI), anxiety (BAI), childhood ADHD symptoms (WURS) and adult ADHD symptoms (ASRS total, ASRS hyperactivity/impulsivity subscale and ASRS attention deficit subscale) than the control group. Fibromyalgia impact (FIQ) was significantly correlated with depression (BDI; r = 0.57, p <.001), anxiety (BAI; r = 0.56, p <.001) and childhood ADHD symptoms (WURS; r = 0.41, p <.001) in fibromyalgia group. There was no significant correlation between fibromyalgia impact (FIQ) and adult ADHD symptoms (ASRS total or sub-scale scores). Hierarchical multiple regression indicated that childhood ADHD symptoms (WURS), anxiety (BAI) and depression (BDI) predicted fibromyalgia impact. Both anxiety (BAI) and depression (BDI) mediated the relationship between childhood ADHD symptoms (WURS) and fibromyalgia impact (FIQ).

Conclusion: Childhood ADHD symptoms may be a contributory factor to poorer functioning in the patients with fibromyalgia. The relationship was more pronounced in the presence of depression and anxiety symptoms. Evaluation of childhood and adult ADHD symptoms in patients with fibromyalgia is important for recognition and treatment of ADHD comorbidity and also for attenuating the severity of the disease

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Ir J Med Sci. 2020 Feb;189:261-65.

ADCOM STUDY-ADOLESCENT COMMUNICATION GROUP THERAPY FOR EXTERNALISING DISORDERS.

Sadiq F, Mulligan A.

BACKGROUND: Communication difficulties are associated with oppositional symptoms in young people. We hypothesise that a communication group intervention will reduce oppositional symptoms in young people.

Previous research on communication and social skills training in young people with externalising disorders is limited. AIMS: We aimed to (1) develop and describe a group communication intervention to promote social competence in adolescents with behaviour difficulties, for use in CAMHS with those with attention-deficit/hyperactivity disorder (ADHD)/externalising disorders, and (2) collect pilot data on the effectiveness of this intervention.
METHODS: We developed and delivered a programme of eight sessions to eight adolescents aged 12 to 13 years. We describe the intervention and challenges running the programme. We present pilot study data on pre- and post-oppositional symptoms.
RESULTS: Our programme was relatively well attended; pilot data indicated a small reduction in oppositional symptoms in all participants. Challenges in running the group were noted.
CONCLUSIONS: Our pilot study data suggest that further research is needed to study the effects of a communication group intervention on oppositional symptoms in a larger number of adolescents

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Ir J Psychol Med. 2020.
ADHD AND COVID-19: CURRENT ROADBLOCKS AND FUTURE OPPORTUNITIES.
McGrath J.
Attention Deficit Hyperactivity Disorder is the commonest disorder presenting to Child and Adolescent Mental Health Services in Ireland. ADMiRE is a specialist ADHD service in South Dublin that provides assessment and intervention for >200 children and adolescents with ADHD.The first section of this article considers the impact of the Covid-19 pandemic on the provision of mental health services for young people with ADHD with specific reference to the difficulties that have been experienced in ADMiRE since the outbreak of Covid-19 in Ireland. In ADMiRE, there has been a significant reduction of face to face consultations, postponement of new assessments, difficulties with physical monitoring, delays in medication initiation, suspension of medication titration, lack of group interventions and problems with access to controlled drug prescriptions. Current guidelines and alternative ways of ensuring adequate service provision are discussed.Restrictions to mitigate the spread of Covid-19 are likely to continue for many months, and child and adolescent mental health services need to find new ways to provide a sustainable service to young people in Ireland. There is a growing evidence base for telepsychiatry, the use of technology such as video conferencing to deliver mental health care remotely, and this approach may be particularly useful in assessment and management of ADHD. The second section of this article discusses the evidence base for telepsychiatry in ADHD, and outlines factors that should be considered when developing a telepsychiatry service for children and adolescents with ADHD

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J Abnorm Child Psychol. 2019 Feb;47:333-44.
BROODING, INATTENTION, AND IMPULSIVITY AS PREDICTORS OF ADOLESCENT SUICIDAL IDEATION.
Sarkisian KL, van Hulle CA, Hill GH.
Although suicide remains a leading cause of death for adolescents, risk factors beyond diagnoses and suicide attempt history remain unclear. We examined whether cognitive style and temperament impact risk for an early, yet still clinically relevant and distressing, form of suicidality: active suicidal ideation. We used binary logistic regression to test whether brooding, inattention, and impulsivity predicted significantly increased risk for suicidal ideation in a sample of 134 twins, 46 of whom endorsed active suicidal ideation (i.e., probands), as well as probands' cotwins and matched controls. When comparing probands with controls and controlling for depression diagnoses, brooding (B = 0.73, Odds Ratio [OR] = 2.07, p = 0.021), inattention (B = 1.09, OR = 2.98, p < 0.001), and impulsivity (B = 0.91, OR = 2.47, p = 0.001) differentiated probands from controls, individually. We compared probands with their cotwins using the same approach, which allowed us to account for variance in suicidal ideation risk related to twins' shared, familial characteristics (e.g., prenatal environment, neighborhood); inattention was the only significant predictor of suicidal ideation risk (B = 0.66, OR = 1.93, p = 0.020). We then fit a logistic regression model that included all three predictors. Only inattention predicted significantly increased likelihood of suicidal ideation in proband versus controls and

proband versus cotwin comparisons (B = 0.88, OR = 2.40, p = 0.024 and B = 0.67, OR = 1.96, p = 0.045, respectively). These results highlight the potential utility of examining novel, more proximal risk factors for suicidal ideation in addition to more established distal factors, like suicide attempt history and psychiatric diagnoses

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J Am Acad Child Adolesc Psychiatry. 2019 Feb;58:167-79.

META-REVIEW: NETWORK META-ANALYSES IN CHILD AND ADOLESCENT PSYCHIATRY.

Cortese S, Tomlinson A, Cipriani A.

OBJECTIVE: Network meta-analyses (NMAs) are gaining traction as the preferred method for evidence synthesis of intervention studies. This review aimed to summarize the basics of NMAs and conduct a meta-review of available NMAs on the treatment of child and adolescent psychiatric disorders by appraising their quality.

METHOD: PubMed (Medline), PsycInfo, Embase, Ovid Medline, and Web of Knowledge were systematically searched (last update January 9, 2018). The quality of each included NMA was appraised using the AMSTAR-2 tool and the PRISMA-NMA checklist, which includes specific items for NMAs.

RESULTS: Eighteen NMAs (6 on attention-deficit/hyperactivity disorder; 4 on psychotic disorders; 2 on depression; 2 on anxiety disorders; 1 on obsessive-compulsive disorder; 1 on disruptive behavior disorder, 1 on bipolar disorder, and 1 on antipsychotics across disorders) were retrieved. Results from the AMSTAR-2 assessment showed that only 27% of appraised NMAs were rated as moderate quality; most were rated as low (33%) or critically low (40%) quality. Only 3 of the appraised NMAs reported on all PRISMA-NMA items specific for NMAs; the network structure was graphically presented in most NMAs (80%), and inconsistency was described in only 47%.

CONCLUSION: Given the paucity of head-to-head trials in child and adolescent psychiatry, NMAs have the potential to contribute to the field, because they provide evidence-based hierarchies for treatment decision making, even in the absence of trials directly comparing at least 2 treatments. However, because of important limitations in the included NMAs, additional methodologically sound NMAs are needed to inform future guidelines and clinical practice in child and adolescent psychiatry

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J Am Coll Health. 2019 May;67:320-27.

ASSOCIATIONS AMONG SLEEP PROBLEMS, EXECUTIVE DYSFUNCTIONS, AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOM DOMAINS IN COLLEGE STUDENTS.

Bolden J, Gilmore-Kern JE, Fillauer JP.

Objective: The present study examined whether executive functions (EFs) and sleep problems operate together to predict four attention-deficit/hyperactivity disorder (ADHD) symptom domains.

Methods: A sample of 306 college students completed ratings of sleep quality, EFs, and ADHD symptoms from January to December 2014. Simultaneous multiple regressions were used to examine (a) the unique contribution of EFs and sleep problems to ADHD symptoms, (b) the relations among EFs, sleep problems, and GPA, and (c) the relations between specific EF facets (i.e., time management, emotion regulation, problem solving, self-restraint, and self-motivation) and ADHD symptoms.

Results: While approximately 52.8% of participants were categorized as poor-quality sleepers, 10.6% of the sample reported an ADHD diagnosis. EF ratings were associated uniquely with ADHD symptoms after controlling for sleep quality. All EF facets were related to ADHD symptoms.

Conclusion: ADHD symptoms are associated with all EF facets even after controlling for sleep quality

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J Appl Anim Welf Sci. 2020 Jan;23:10-28.

INVESTIGATION OF PHYSIOLOGICAL AND BEHAVIORAL RESPONSES IN DOGS PARTICIPATING IN ANIMAL-ASSISTED THERAPY WITH CHILDREN DIAGNOSED WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Melco AL, Goldman L, Fine AH, et al.

This study evaluated the impact that participation in sessions with children with Attention-Deficit Hyperactivity Disorder (ADHD) has on therapy dogs. Nine certified therapy dogs were paired for 6 sessions with groups of 3-4 children. Sessions consisted of 5 different activities. Activities 1 and 5 involved interactions solely with each dog and their owner, as a control. Activities 2-4 consisted of interactions with the dogs and the children which included social skills training, dog training, and reading in the company of dogs. One-zero interval sampling of stress-associated behaviors was conducted at 20-second intervals for a 10-minute duration during each of the 5 activities. At the end of each activity, heart rate was monitored, and a saliva sample was obtained for cortisol analysis. Dogs demonstrated only occasional behavioral responses and no significant findings related to cortisol or heart rate when the different activities were compared. The results indicate that with proper supervision and well-trained therapy staff, including suitable therapy dogs and their handlers, canine stress can be minimal in a therapy setting

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J Atten Disord. 2019 Mar;23:435-50.

DOES PARENT STRESS PREDICT THE QUALITY OF LIFE OF CHILDREN WITH A DIAGNOSIS OF ADHD? A COMPARISON OF PARENT AND CHILD PERSPECTIVES.

Galloway H, Newman E, Miller N, et al.

OBJECTIVE: There are indicators that parental psychological factors may affect how parents evaluate their child's quality of life (QoL) when the child has a health condition. This study examined the impact of parents' perceived stress on parent and child ratings of the QoL of children with ADHD.

METHOD: A cross-sectional sample of 45 matched parent-child dyads completed parallel versions of the KIDSCREEN-27. Children were 8 to 14 years with clinician diagnosed ADHD.

RESULTS: Parents who rated their child's QoL lower than their child had higher perceived stress scores. Parent stress was a unique predictor of child QoL from parent proxy-rated but not child-rated QoL scores.

CONCLUSION: Parents' perceived stress may play an important role in their assessments of their child's QoL, suggesting both parent and child perspectives of QoL should be utilized wherever possible. Interventions that target parent stress may contribute to improvements in the child's QoL

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J Atten Disord. 2019 Dec;23:1691-702.

ADDRESSING DISCREPANCIES BETWEEN ADHD PREVALENCE AND CASE IDENTIFICATION ESTIMATES AMONG U.S. CHILDREN UTILIZING NSCH 2007-2012.

Song M, Dieckmann NF, Nigg JT.

Objective: Among U.S. children, ADHD epidemiological estimates (3%-5%) vary significantly from case identification rates (over 11%), leading to confusion about true incidence and prevalence. We investigated the extent to which this discrepancy could be resolved by definitional issues through reexamining the most cited U.S. survey of case identification, the National Survey of Children's Health (NSCH).

Method: Using NSCH 2007/2008 and 2011/2012, we stratified identification of ADHD by current status, severity, psychiatric comorbidity, and ADHD medication usage. Using those criteria, definitional strength was coded into "Definite," "Probable," "Doubtful," and "No."

Results: "Definite" ADHD in caseness in 2007/2008 was 4.04%, increasing to 5.49% in 2011/2012, roughly corresponding to epidemiological estimates. "Definite" ADHD was the primary contributor to an overall increase in caseness over that period.

Conclusion: This analysis strengthens understanding of discrepancies in estimated ADHD rates. When low confidence identification is considered false positives, ADHD case identification rates match epidemiological estimates more closely

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J Atten Disord. 2019 Feb;23:293-304.

A Randomized Effectiveness Trial of a Behavioral Teacher Program Targeting ADHD Symptoms.

Veenman B, Luman M, Hoeksma J, et al.

OBJECTIVE: This study investigated the effectiveness of the Positivity & Rules Program (PR program), a behavioral teacher program targeting ADHD symptoms in the classroom involving both student-focused and classroom-focused programs.

METHOD: Primary school children with ADHD symptoms (N = 114) were randomly assigned to the PR program (n = 58) or control group (n = 56). Teacher and parent ratings were used to assess behavioral, social, and emotional functioning at baseline, during and after the intervention. Intervention effects were assessed using intention-to-treat multilevel analyses.

RESULTS: Teachers reported positive effects on ADHD symptoms and social skills (.01 < f(2) > .36). Effects did not generalize to the home setting.

CONCLUSION: The PR program holds promise for improving classroom behavior in children with ADHD symptoms and might prevent escalation of problem behavior

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J Atten Disord. 2019 Dec;23:1703-10.

Sluggish Cognitive Tempo Predicts Academic Fluency, Beyond Contributions of Core Academic Skills, Attention, and Motor Speed.

Jacobson LA, Mahone EM.

OBJECTIVE: Sluggish Cognitive Tempo (SCT) is a distinct behavioral phenotype characterized by such symptoms as being slow to complete tasks, appearing drowsy or sleepy, and lacking initiative. Subcomponents of SCT appear differentially associated with inattention symptoms and child outcomes. Much of the work in this area has examined associations between SCT symptoms and ratings of behavior; few studies have examined associations with child performance.

METHOD: We examined associations between SCT and timed reading and math skills in 247 referred youth (M age = 11.55, range = 6-20; 67.6% male), controlling for the untimed academic skills, inattention, and graphomotor speed.

RESULTS: SCT consistently predicted timed academic fluency, after controlling for other component skills, for both reading (SCT DeltaR(2) = .039, p = .001) and math (DeltaR(2) = .049, p = .001).

CONCLUSION: Results provide initial evidence for the unique association of SCT with timed academic performance. Understanding associations of SCT with actual child performance may allow for greater specificity in targeting interventions to address speed of performance

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J Atten Disord. 2019 Feb;23:282-92.

A Cooperative Learning Classroom Intervention for Increasing Peer's Acceptance of Children With ADHD.

Capodieci A, Rivetti T, Cornoldi C.

OBJECTIVE: The hypothesis behind this study was that trained teachers using cooperative learning procedures with children in their classroom (aged from 6 to 10 years) can influence the social skills of children with ADHD symptoms and their acceptance by their peers.

METHOD: The study involved 30 children with ADHD symptoms attending 12 different classes, where cooperative learning was adopted in some, and standard practices in others. ADHD children's symptoms,

social skills, and cooperative behavior were assessed by means of a teacher's questionnaire, and the social preferences of the children in their class were collected.
RESULTS: Changes emerged in teachers' assessments of the children's cooperative behavior in the experimental classes. Improvements in the sociometric status of children with ADHD symptoms were only seen in the cooperative learning classes.
CONCLUSION: These results show the importance of well-structured intervention in classes that include children with ADHD symptoms. Implications of these findings for future intervention are discussed

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J Atten Disord. 2019 Mar;23:493-505.
MATERNAL ADHD SYMPTOMS AND PARENTING STRESS: THE ROLES OF PARENTING SELF-EFFICACY BELIEFS AND NEUROTICISM.
Williamson D, Johnston C.
OBJECTIVE: ADHD symptoms in adults are consistently related to stress in a variety of domains, although whether the link between ADHD symptoms and stress is direct, or accounted for or moderated by other variables, is little studied. We used a cross-sectional design to examine whether parenting self-efficacy accounts for the relation between maternal ADHD symptoms and parenting stress, and whether levels of maternal neuroticism moderate this relation.
METHOD: A nonclinical sample of mothers of 120, six- to 12-year-old children completed surveys online.
RESULTS: Maternal ADHD symptoms were associated with parenting stress, but this relation was accounted for by parenting self-efficacy beliefs. Neuroticism did not moderate the relations among these variables. Covariate analyses indicated that although parenting self-efficacy beliefs remain a robust predictor of parenting stress, the relation between maternal ADHD symptoms and parenting stress can be better accounted for by other variables.
CONCLUSION: The results highlight the importance of self-efficacy beliefs and demonstrate that ADHD symptoms are not sufficient to understand the experience of parenting

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J Atten Disord. 2019 Mar;23:487-92.
THE EFFECT OF CHILDHOOD ADD/ADHD ON PARENTAL WORKFORCE PARTICIPATION.
Callander EJ, Allele F, Roberts H, et al.
OBJECTIVE: This research aimed to examine the impact of attention deficit disorder (ADD)/ADHD in children on parental labor force participation across different child age groups.
METHOD: This study utilized a longitudinal, quantitative analyses approach. All data were collected from Wave 6 of the Growing Up in Australia: The Longitudinal Study of Australian Children (LSAC) survey.
RESULTS: After adjusting for various confounders, mothers whose children were 10/11 years old and had been diagnosed with ADD/ADHD were significantly more likely to be out of the labor force compared with those mothers whose child had not been diagnosed with ADD/ADHD. The impact was more pronounced for single mothers. No significant influence on paternal labor force participation was found.
CONCLUSION: In assessing the cost-effectiveness of interventions for ADD/ADHD, policy makers and researchers must consider the long-term social and economic effects of ADD/ADHD on maternal workforce participation when considering costs and outcomes

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J Atten Disord. 2019 Feb;23:246-56.
CHILDREN'S DEVIANT BEHAVIOR IN PRIMARY EDUCATION: COMPARING PHYSICAL EDUCATOR'S IMPLICIT THEORY WITH DIAGNOSTIC CRITERIA.
Efstratopoulou MA, Janssen R, Simons J.
OBJECTIVE: Physical educators' implicit theory of children's deviant behavior in primary education was investigated and compared with diagnostic criteria.

METHOD: A total of 60 physical education (PE) teachers reported deviant behaviors during lessons. Experts sorted these behaviors together with the official diagnostic criteria into categories based on perceived similarity in content.
RESULTS: Hierarchical cluster analysis on the derived similarity matrix among the behaviors suggested that PE teachers focus more on attention problems, disobedience, and aggressiveness when internalizing behaviors, such as anxiety and low energy, were less reported.
CONCLUSION: PE teachers may be important and useful informants on children's behavior in school settings

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J Atten Disord. 2019 Dec;23:1759-65.
EXECUTIVE FUNCTIONING AND IMPAIRMENT IN EMERGING ADULT COLLEGE STUDENTS WITH ADHD SYMPTOMS.
Dorr MM, Armstrong KJ.
Objective: To better understand current issues with adult ADHD assessment contributing to adult ADHD being under recognized and undertreated.
Method: This study examined the relationship between symptoms, impairment, and executive functioning (EF) in a college sample.
Results: Among individuals screening negative for ADHD, those higher in EF experienced significantly less impairment than those lower in EF. Executive functioning was shown to have a negative relationship with impairment while ADHD symptomology was shown to have a positive relationship with impairment. In addition, impairment was significantly predicted by ADHD symptom level and EF, and there was a significant interaction between EF and ADHD symptom level in predicting impairment. However, high EF did not significantly protect against impairment in individuals reporting a significant level of ADHD symptoms.
Conclusion: Further research is needed to clarify the relationships between these variables in emerging adult college students

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J Atten Disord. 2019 Mar;23:423-34.
SHORT- AND LONG-TERM EFFECTS OF PARENT TRAINING FOR PRESCHOOL CHILDREN WITH OR AT RISK OF ADHD: A SYSTEMATIC REVIEW AND META-ANALYSIS.
Rimestad ML, Lambek R, Zacher CH, et al.
OBJECTIVE: The aim of the study was to synthesize the evidence of parent training (PT) as an early intervention for preschool children aged 2.5 to 6 years with ADHD or ADHD symptoms.
METHOD: A systematic review and meta-analysis was conducted.
RESULTS: Sixteen studies including 1,003 children were analyzed. Parent-rated outcomes revealed moderate effect sizes (ESs; Hedges' g) of 0.51 for ADHD symptoms, 0.4 for conduct problems, and 0.63 for negative parenting. Based on independent assessment, results were only significant for negative parenting. Parent-rated outcomes were sustained at follow-ups of 3 to 12 months. Program type, intervention modality, and child diagnostic status did not moderate the effect.
CONCLUSION: PT was partially supported as an efficacious intervention for preschool children with ADHD or ADHD symptoms with moderate ESs on parent-rated outcomes, but no significant results on independently assessed ADHD symptoms

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J Atten Disord. 2019 Mar;23:451-62.
EXAMINING THE RELATIONSHIP BETWEEN CHILDREN'S ADHD SYMPTOMATOLOGY AND INADEQUATE PARENTING: THE ROLE OF HOUSEHOLD CHAOS.
Wirth A, Reinelt T, Gawrilow C, et al.
OBJECTIVE: This study examines the interrelations of parenting practices, emotional climate, and household chaos in families with children with and without ADHD. In particular, indirect pathways from children's ADHD

symptomatology to inadequate parenting and negative emotional climate via household chaos were investigated.
METHOD: Parenting, emotional climate, and household chaos were assessed using questionnaires and a speech sample of parents of 31 children with and 53 without ADHD, aged 7 to 13 years.
RESULTS: Group differences were found for certain parenting dimensions, the parent-child relationship, critical comments, and household chaos. While we found significant indirect effects between children's ADHD and certain parenting dimensions through household chaos, no effects were found for any aspect of emotional climate.
CONCLUSION: Children's ADHD symptoms translate into inadequate parenting through household chaos, which underlines the need for interventions to improve household organization skills in parents of children with ADHD

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J Atten Disord. 2019 Mar;23:475-86.
MOTHERS' ATTRIBUTIONS FOR POSITIVE AND NEGATIVE CHILD BEHAVIOR: ASSOCIATIONS WITH MOTHERS' ADHD SYMPTOMS.
Park JL, Johnston C.
OBJECTIVE: Previous research has shown that parent attributions for child behavior have important implications on the parent-child relationship. The current study investigates whether mothers' level of ADHD symptoms is associated with their child-responsibility attributions for positive and negative child behavior.
METHOD: Seventy-nine mothers of 6- to 11-year-old boys participated in this online study. Mothers completed questionnaires assessing their attributions, their ADHD symptoms, and their child's behavior.
RESULTS: All mothers offered more child-responsibility attributions for positive behaviors than for negative behaviors. However, mothers with greater levels of ADHD symptoms did this to a lesser extent, blaming their child relatively more for negative behavior and giving their child relatively less credit for positive behavior.
CONCLUSION: This is the first study demonstrating the association between mothers' ADHD symptoms and child-responsibility attributions. It is possible that these relatively more negative attributions could be underlying some of the parenting difficulties reported by parents with ADHD

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J Atten Disord. 2019 Feb;23:257-69.
Web-Based Intervention for Teachers of Elementary Students With ADHD: Randomized Controlled Trial.
Corkum P, Elik N, Blotnicky-Gallant PAC, et al.
OBJECTIVE: To test the acceptability, satisfaction, and effectiveness of a web-based intervention for teachers of elementary school-aged children with ADHD.
METHOD: Elementary classroom teachers (N = 58), along with their students with ADHD, participated in a randomized controlled trial. The program consisted of six sessions that included evidence-based intervention strategies for reducing ADHD symptoms and impairment in the classroom setting. Teachers also had access to a moderated Discussion Board and an online ADHD coach. Questionnaire data were electronically collected from teachers and parents pre-intervention, post-intervention (6 weeks), and after an additional 6-week follow-up.
RESULTS: Intent-to-treat analyses found significant improvements based on teacher (but not parent) reports of core ADHD symptoms and impairment for the Teacher Help for ADHD treatment group. Teachers reported a high level of acceptability and satisfaction.
CONCLUSION: Web-based ADHD interventions have the potential to reduce the barriers to treatment utilization and implementation that are common problems for school-based ADHD interventions

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J Atten Disord. 2019 Mar;23:517-26.

PREDICTORS OF BURDEN OF CARE AMONG CAREGIVERS OF DRUG-NAIVE CHILDREN AND ADOLESCENTS WITH ADHD: A CROSS-SECTIONAL CORRELATIVE STUDY FROM MUSCAT, OMAN.

Al-Balushi N, Al-Alawi M, Al SM, et al.

OBJECTIVE: the study assessed the prevalence of burden of care among caregivers of children with ADHD in Oman. A related aim is to explore the predictors of the burden of care, subtypes of ADHD, and socio-demographic factors.

METHOD: Arabic version of the Zarit Burden Interview (ZBI) was administered to 117 caregivers of drug-naive children with ADHD. Sociodemographic background and clinical data were gathered from medical records and from the attending caregivers themselves. The ADHD symptoms were grouped under three categories : hyperactive, inattentive, or mixed.

RESULTS: the prevalence of the burden of care was estimated to be 34%. Income levels and the child's ADHD diagnosis being of "mixed" type have significant impact on the burden of care.

CONCLUSION: the results of this study indicate that the prevalence of the burden of care among the caregivers of ADHD children in Oman is comparable with that in the other regions of the world

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J Atten Disord. 2019 Feb;23:206-19.

WHAT DO PRIMARY AND SECONDARY SCHOOL TEACHERS KNOW ABOUT ADHD IN CHILDREN? FINDINGS FROM A SYSTEMATIC REVIEW AND A REPRESENTATIVE, NATIONWIDE SAMPLE OF DANISH TEACHERS.

Mohr-Jensen C, Steen-Jensen T, Bang-Schnack M, et al.

OBJECTIVE: To identify what primary and secondary school teachers know about ADHD in children and, furthermore, to identify which factors predict their knowledge.

METHOD: A 29-item questionnaire about ADHD was distributed to a random, nationwide, and representative sample of Danish primary and secondary school teachers. Data were analyzed descriptively and by hierarchical regression analysis.

RESULTS: A total of 528 teachers were included. Most teachers identified the symptoms of ADHD (79%-96%) and effective classroom intervention strategies (75%-98%). However, knowledge about other characteristics, etiology, prognosis, and treatment was inconsistent, for example, only 56% and 17% correctly rejected diet as a cause and effective treatment for ADHD. Among the strongest predictors for correct knowledge was having been provided postgraduate education about ADHD.

CONCLUSION: Teachers require knowledge about ADHD to successfully include and manage children with ADHD and, additionally, to ensure positive working environments for teachers and support constructive school-home working collaborations

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J Atten Disord. 2019 Mar;23:506-16.

PARENTAL STRESS AND PARENTAL SELF-EFFICACY AS MEDIATORS OF THE ASSOCIATION BETWEEN CHILDREN'S ADHD AND MARITAL SATISFACTION.

Ben-Naim S, Gill N, Laslo-Roth R, et al.

Parents of children with ADHD often experience low marital satisfaction, since the child's increased susceptibility to maladjustment can affect family dynamics as a whole.

OBJECTIVES: To explore this association by examining parental stress and parental self-efficacy as two possible mediators.

METHOD: Totally, 182 Israeli parents of children in the first to ninth grades (63 parents of children with ADHD and 119 without) completed parental self-efficacy, marital satisfaction, and parental stress questionnaires.

RESULTS: As expected, parents of children with ADHD reported higher parental stress, and lower self-efficacy and marital satisfaction than non-ADHD parents. The association between ADHD parents and marital satisfaction was fully explained by parental stress and self-efficacy, suggesting that personal characteristics and situation appraisal are tapped when facing strain and hardship.

CONCLUSION: These findings provide a window of hope for an otherwise deterministic view of the ADHD-marital dissolution relationship and propose individual and familial interventions that may minimize these damaging effects

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J Atten Disord. 2019 Mar;23:463-74.

ASSOCIATION BETWEEN PARENTING STYLE AND SOCIO-EMOTIONAL AND ACADEMIC FUNCTIONING IN CHILDREN WITH AND WITHOUT ADHD: A COMMUNITY-BASED STUDY.

Bhide S, Sciberras E, Anderson V, et al.

OBJECTIVE: In a community-based study, we examined parenting style and its relationship to functioning in 6- to 8-year-old children (n = 391; 66.2% male) with ADHD (n = 179), compared with non-ADHD controls (n = 212).

METHOD: Parenting style was assessed using parent-reported (93.5% female) measures of warmth, consistency, and anger. Child socio-emotional and academic functioning was measured via parent- and teacher-reported scales, and direct academic assessment.

RESULTS: Parents reported less consistency and more anger in the ADHD group compared with non-ADHD controls, with no differences in warmth. Parenting warmth, consistency, and anger were associated with parent-reported aspects of socio-emotional functioning for children with ADHD and non-ADHD controls, after adjusting for socio-demographic variables, externalizing comorbidities, and ADHD symptom severity. Parenting style was no longer related to academic functioning and most teacher-reported outcomes after adjustment.

CONCLUSION: Generic parenting interventions that promote warm, consistent, and calm parenting may help alleviate socio-emotional impairments in children with ADHD

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J Atten Disord. 2019 Feb;23:234-45.

STUDENT-PERCEIVED SCHOOL CLIMATE IS ASSOCIATED WITH ADHD MEDICATION TREATMENT AMONG ADOLESCENTS IN MEDICAID.

Visser SN, Kramer D, Snyder AB, et al.

OBJECTIVE: The objective of this study was to evaluate the relationship between school climate and ADHD medication treatment among adolescents in Medicaid in Georgia.

METHOD: School climate and Medicaid claims data were aggregated for 159 GA counties. County-level school climate percentile and medicated ADHD prevalence were calculated. The t tests and regression models evaluated the relationship between school climate, medicated ADHD, and demographics, weighted by county population. Poorer 2008 school climate (<25th percentile) was regressed on 2011 medicated ADHD prevalence, controlling for potential confounders.

RESULTS: The prevalence of medicated ADHD was 7.8% among Medicaid-enrolled GA adolescents. The average county-level prevalence of medicated ADHD was 10.0% (SD = 2.9%). Poorer school climate was associated with lower rates of medicated ADHD ($p < .0001$); along with demographics, these factors accounted for 50% of the county variation in medicated ADHD.

CONCLUSION: School climate is associated with medicated ADHD among adolescents in Medicaid. Additional research may reveal whether high medicated ADHD may reflect a lack of access to non-pharmacological therapies in some communities

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J Child Adolesc Psychiatr Nurs. 2019 Nov;32:171-76.

INCREASED RISK OF HEAD INJURY IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Grigorian A, Nahmias J, Dolich M, et al.

OBJECTIVE: The prevalence of attention deficit hyperactivity disorder (ADHD) in the general pediatric population is 7%, whereas the prevalence in trauma is unknown. We hypothesized pediatric patients with

ADHD would have a higher risk of involvement in a mechanism of injury (MOI) requiring constant attention to surroundings, such as a bicycle collision.
METHODS: The Pediatric Trauma Quality Improvement Program (2014-2016) was queried for patients with ADHD. Patients, less than 16 years of age, with ADHD were compared to those without ADHD.
RESULTS: The prevalence of ADHD was 2.5% (2,866). ADHD patients had higher risk for bicycle collision (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.59-2.15; p < .001). ADHD bicyclists were less likely to wear a helmet (9.4% vs. 18.2%, p = .003) and had a higher rate of traumatic brain injury (TBI; 55.6% vs. 39.7%, p < .001), compared to non-ADHD bicyclists.
CONCLUSIONS: Pediatric ADHD patients have a 60% higher risk of being involved in a bicycle collision. ADHD patients that are involved in a bicycle collision are less likely to wear a helmet with a higher rate of TBI. Increased public awareness, education, and supervision may help reduce risk of bicycle collisions and TBI in this population

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J Child Adolesc Psychopharmacol. 2018 Dec;28:699-710.
LONG-TERM EFFICACY AND SAFETY OF PEDIATRIC PROLONGED-RELEASE MELATONIN FOR INSOMNIA IN CHILDREN WITH AUTISM SPECTRUM DISORDER.
Maras A, Schroder CM, Malow BA, et al.
Objective: A recent double-blind randomized placebo-controlled study demonstrated 3-month efficacy and safety of a novel pediatric-appropriate prolonged-release melatonin (PedPRM) for insomnia in children and adolescents with autism spectrum disorder (ASD) and neurogenetic disorders (NGD) with/without attention-deficit/hyperactivity disorder comorbidity. Long-term efficacy and safety of PedPRM treatment was studied.
Methods: A prospective, open-label efficacy and safety follow-up of nightly 2, 5, or 10 mg PedPRM in subjects who completed the 13-week double-blind trial (51 PedPRM; 44 placebo). Measures included caregiver-reported Sleep and Nap Diary, Composite Sleep Disturbance Index (CSDI), caregiver's Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, and quality of life (WHO-5 Well-Being Index).
Results: Ninety-five subjects (74.7% males; mean [standard deviation] age, 9 [4.24]; range, 2-17.5 years) received PedPRM (2/5 mg) according to the double-blind phase dose, for 39 weeks with optional dose adjustment (2, 5, or 10 mg/day) after the first 13 weeks. After 52 weeks of continuous treatment (PedPRM-randomized group) subjects slept (mean [SE]) 62.08 (21.5) minutes longer (p = 0.007); fell asleep 48.6 (10.2) minutes faster (p < 0.001); had 89.1 (25.5) minutes longer uninterrupted sleep episodes (p = 0.001); 0.41 (0.12) less nightly awakenings (>50% decrease; p = 0.001); and better sleep quality (p < 0.001) compared with baseline. The placebo-randomized group also improved with PedPRM. Altogether, by the end of 39-week follow-up, regardless of randomization assignment, 55/72 (76%) of completers achieved overall improvement of >/=1 hour in total sleep time (TST), sleep latency or both, over baseline, with no evidence of decreased efficacy. In parallel, CSDI child sleep disturbance and caregivers' satisfaction of their child's sleep patterns (p < 0.001 for both), PSQI global (p < 0.001), and WHO-5 (p = 0.001) improved in statistically significant and clinically relevant manner (n = 72) compared with baseline. PedPRM was generally safe; most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2% of patients).
Conclusion: PedPRM, an easily swallowed formulation shown to be efficacious versus placebo, is an efficacious and safe option for long-term treatment (up to 52 weeks reported here) of children with ASD and NGD who suffer from insomnia and subsequently improves caregivers' quality of life

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J Child Adolesc Psychopharmacol. 2019 May;29:268-75.
IMMUNOGLOBULIN A DYSGAMMAGLOBULINEMIA IS ASSOCIATED WITH PEDIATRIC-ONSET OBSESSIVE-COMPULSIVE DISORDER.
Williams K, Shorser-Gentile L, Sarvode MS, et al.
Background: Inflammation and immune dysregulation have been implicated in the pathogenesis of pediatric-onset obsessive-compulsive disorder (OCD) and tic disorders such as Tourette syndrome (TS). Though few replicated studies have identified markers of immune dysfunction in this population, preliminary studies

suggest that serum immunoglobulin A (IgA) concentrations may be abnormal in these children with these disorders.
Methods: This observational retrospective cohort study, conducted using electronic health records (EHRs), identified 206 children with pediatric-onset OCD and 1024 adults diagnosed with OCD who also had testing for serum levels of IgA. IgA deficiency and serum IgA levels in pediatric OCD were compared with IgA levels from children diagnosed with autism spectrum disorders (ASD; n = 524), tic disorders (n = 157), attention-deficit/hyperactivity disorder (ADHD; n = 534), anxiety disorders (n = 1206), and celiac disease, a condition associated with IgA deficiency (n = 624).
Results: Compared with ASD and anxiety disorder cohorts, the pediatric OCD cohort displayed a significantly higher likelihood of IgA deficiency (OR = 1.93; 95% CI = 1.18-3.16, and OR = 1.98; 95% CI = 1.28-3.06, respectively), though no difference was observed between pediatric OCD and TS cohorts. Furthermore, the pediatric OCD cohort displayed similar rates of IgA deficiency and serum IgA levels when compared with the celiac disease cohort. The pediatric OCD cohort also displayed the highest percentage of IgA deficiency (15%,) when compared with TS (14%), celiac disease (14%), ADHD (13%), ASD (8%), and anxiety disorder (8%) cohorts. When segregated by sex, boys with OCD displayed a significantly higher likelihood of IgA deficiency when compared with all comparison cohorts except for celiac disease and tic disorders; no significant difference in IgA deficiency was observed between female cohorts. Pediatric OCD subjects also displayed significantly lower adjusted serum IgA levels than the ASD and anxiety disorder cohorts. Adults with OCD were also significantly less likely than children with OCD to display IgA deficiency (OR = 2.71; 95% CI = 1.71-4.28). When compared with children with celiac disease, no significant difference in IgA levels or rates of IgA deficiency were observed in the pediatric OCD cohort.
Conclusions: We provide further evidence of IgA abnormalities in pediatric-onset OCD. These results require further investigation to determine if these abnormalities impact the clinical course of OCD in children

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J Child Adolesc Psychopharmacol. 2019 May;29:285-304.

WEIGHT AND HEIGHT IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A LONGITUDINAL DATABASE STUDY ASSESSING THE IMPACT OF GUANFACINE, STIMULANTS, AND NO PHARMACOTHERAPY.

Schneider G, Banaschewski T, Feldman BL, et al.

Objectives: To assess the impact of long-term pharmacotherapy with guanfacine immediate- or extended-release (GXR), administered alone or as an adjunctive to a stimulant, on weight and height in children and adolescents with attention-deficit/hyperactivity disorder (ADHD).
Methods: Data were extracted from U.S. Department of Defense medical records for patients 4-17 years of age at index date (initiation of any study medication following a year without ADHD medications, or diagnosis if unmedicated) with weight/height measurements for the analysis period (January 2009-June 2013) and the previous year (baseline). Longitudinal weight and height z-scores were analyzed using multivariable regression in three cohorts: guanfacine (initial period of guanfacine exposure), first-line stimulant monotherapy (initial period of exposure), and unmedicated. Guanfacine cohort subgroups were based on previous/concurrent stimulant exposure.
Results: The weight analyses included 47,910 patients (66.8% male) and the height analyses 41,248 (67.2% male). Mean initial exposure in the weight analyses was 237 days (standard deviation [SD] = 258, median = 142) for guanfacine and 257 days (SD = 284, median = 151) for first-line stimulant monotherapy, and was similar in the height analyses. Modeling indicated that guanfacine monotherapy was not associated with clinically meaningful deviations from normal z-score trajectories for weight (first-line, n = 943; nonfirst-line, n = 796) or height (first-line, n = 741; nonfirst-line, n = 644). In patients receiving guanfacine adjunctive to a stimulant, modeled weight (n = 1657) and height (n = 1343) z-scores followed declining trajectories. In this subgroup, mean standardized weight/height had decreased during previous stimulant monotherapy. For first-line stimulant monotherapy, modeled weight (n = 32,999) and height (n = 28,470) z-scores followed declining trajectories during year 1. In the unmedicated cohort, modeled weight (n = 11,515) and height (n = 10,050) z-scores were stable.
Conclusions: Guanfacine monotherapy (first-line or nonfirst-line) was not associated with marked deviations from normal growth in this modeling study of children and adolescents with ADHD. In contrast, growth

trajectories followed an initially declining course with stimulants, whether given alone or with adjunctive guanfacine

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J Child Adolesc Psychopharmacol. 2019 May;29:318-20.
STIMULANT-INDUCED PUNDING AND STIMULANT DISCONTINUATION-INDUCED MANIC-LIKE SYMPTOMS IN A PREADOLESCENT MALE.
Friedland S, Kahlon S, Carlson GA, et al.

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J Child Adolesc Psychopharmacol. 2019 Apr;29:220-34.
A QUANTITATIVE COMPARISON APPROACH FOR METHYLPHENIDATE DRUG REGIMENS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATMENT.
Soufsaf S, Robaey P, Bonnefois G, et al.
OBJECTIVE: Different methylphenidate (MPH) formulations, immediate release (IR) or extended release (ER), have been developed to treat Attention-Deficit/Hyperactivity Disorder (ADHD). A better use of these formulations, with a proper choice of their timing, dosage, and combination, can help to attain optimal therapeutic effect while maintaining a good quality of life. In this study, we aim at presenting a quantitative comparison approach to help identify drug regimens that provide best therapeutic performances and respect patients' specific needs.
METHODS: Using pharmacokinetic (PK) models of various MPH formulations constructed with data in hand and a formerly developed performance metric for MPH regimens, we proposed a statistical integral strategy for regimen comparison, which comprises a sequential, a relative, and a probability-over-threshold method. The first is hierarchical in nature and sequentially compares the regimen performance, the total daily dose, and the administration frequency. The second compares two regimens by quantifying their similarity. The third computes the probability of an incremental regimen performance over a specified threshold. The first two comparison approaches are used for naive patients, whereas the third one is for patients under treatment.
RESULTS: PK models of one compartment effectively describe both the IR and ER data. Applied to three frequent MPH clinical situations, the three-methods strategy is able to distinguish the regimens proposed for each. A combined regimen of IR and ER taken at the same time performs better than a single ER dose.
CONCLUSION: The proposed statistical strategy is able to differentiate ADHD regimens in various clinically relevant situations, and adapt the use of MPH drugs to a patient's daily routine. Since it does not compare fixed doses and formulations but rather any MPH regimen, our approach generalizes the current context of bioequivalence study and provides an accessible computational tool for objectively selecting MPH regimens

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J Child Neurol. 2019 Apr;34:237-47.
PHARMACOLOGIC TREATMENTS FOR SLEEP DISORDERS IN CHILDREN: A SYSTEMATIC REVIEW.
McDonagh MS, Holmes R, Hsu F.
Sleep problems are common in children, especially those with neurodevelopmental disorders, and can lead to consequences in behavior, functioning, and quality of life. We systematically reviewed the efficacy and harms of pharmacologic treatments for sleep disorders in children and adolescents. We searched MEDLINE, Cochrane library databases, and PsycINFO through June 2018. We included 22 placebo-controlled randomized controlled trials (1-13 weeks' duration), involving 1758 children (mean age 8.2 years). Single randomized controlled trials of zolpidem and eszopiclone in children with attention-deficit/hyperactivity disorder (ADHD) showed no improvement in sleep or ADHD ratings. Clinical Global Impression Improvement/Severity scores significantly improved with zolpidem (P = .03 and P = .006, respectively). A single, small randomized controlled trial of diphenhydramine reported small improvements in sleep outcomes (8-10 minutes' better sleep latency and duration) after 1 week. In 19 randomized controlled trials, melatonin

significantly improved sleep latency (median 28 minutes; range 11-51 minutes), sleep duration (median 33 minutes; range 14-68 minutes), and wake time after sleep onset (range 12-43 minutes), but not number of awakenings per night (range 0-2.7). Function and behavior improvement varied. Improvement in sleep was greatest in children with autism or other neurodevelopmental disorders, and smaller in adolescents and children with chronic delayed sleep onset. Adverse events were infrequent with melatonin, but more frequent than placebo in children taking eszopiclone or zolpidem. These findings show that melatonin was useful in improving some sleep outcomes in the short term, particularly those with comorbid ASD and neurodevelopmental disorders. Other drugs and outcomes are inadequately studied

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J Child Neurol. 2019 Jun;34:382-86.

WHEN AN EARLY DIAGNOSIS OF AUTISM SPECTRUM DISORDER RESOLVES, WHAT REMAINS?

Shulman L, D'Agostino E, Lee S, et al.

A chart review was performed of 38 children diagnosed with autism spectrum disorder (ASD) by 3 years of age at an inner-city developmental program who subsequently experienced resolution of ASD symptomatology and no longer met diagnostic criteria for ASD at follow-up an average of 4 years later. Demographic, developmental/cognitive data, Childhood Autism Rating Scale, and Autism Diagnostic Observation Schedule data as available were reviewed from the initial diagnostic evaluation and at the time of follow-up. Services received by the children between the time of diagnosis and follow-up, educational setting at the time of follow-up, and emotional/behavioral and learning diagnoses made by the multidisciplinary team at follow-up were reviewed. The findings indicate that residual emotional/behavioral and learning problems were present at follow-up in the vast majority of children in this group and that the majority continued to require educational support

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J Child Psychol Psychiatry. 2019 Feb;60:160-68.

MATERNAL INFECTION REQUIRING HOSPITALIZATION DURING PREGNANCY AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN OFFSPRING: A QUASI-EXPERIMENTAL FAMILY-BASED STUDY.

Ginsberg Y, et al.

BACKGROUND: Maternal infection during pregnancy (IDP) has been associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring. However, infection is associated with social adversity, poor living conditions and other background familial factors. As such, there is a need to rule out whether the observed association between maternal IDP and ADHD might be attributed to such confounding.
METHODS: This nationwide population-based cohort study using a family-based, quasi-experimental design included 1,066,956 individuals born in Sweden between 1992 and 2002. Data on maternal IDP (bacterial or viral) requiring hospitalization and ADHD diagnosis in offspring were gathered from Swedish National Registers, with individuals followed up through the end of 2009. Ordinary and stratified Cox regression models were used for estimation of hazard ratios (HRs) and several measured covariates were considered. Cousin- and sibling-comparisons accounted for unmeasured genetic and environmental factors shared by cousins and siblings.
RESULTS: In the entire population, maternal IDP was associated with ADHD in offspring (HR = 2.31, 95% CI = 2.04-2.61). This association was attenuated when accounting for measured covariates (HR = 1.86, 95% CI = 1.65-2.10). The association was further attenuated when adjusting for unmeasured factors shared between cousins (HR = 1.52, 95% CI = 1.12-2.07). Finally, the association was fully attenuated in sibling comparisons (HR = 1.03, 95% CI = 0.76-1.41).
CONCLUSIONS: This study suggests that the association between maternal IDP and offspring ADHD is largely due to unmeasured familial confounding. Our results underscore the importance of adjusting for unobserved familial risk factors when exploring risk factors for ADHD

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J Child Psychol Psychiatry. 2019 Feb;60:133-50.

PRACTITIONER REVIEW: EMOTIONAL DYSREGULATION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER - IMPLICATIONS FOR CLINICAL RECOGNITION AND INTERVENTION.

Faraone SV, Rostain AL, Blader J, et al.

BACKGROUND: Because emotional symptoms are common in attention-deficit/hyperactivity disorder (ADHD) patients and associate with much morbidity, some consider it to be a core feature rather than an associated trait. Others argue that emotional symptoms are too nonspecific for use as diagnostic criteria. This debate has been difficult to resolve due, in part, to the many terms used to describe emotional symptoms in ADHD and to concerns about overlap with mood disorders.

METHODS: We sought to clarify the nature of emotional symptoms in ADHD by reviewing conceptual and measurement issues and by examining the evidence base regarding specificity of such symptoms for ADHD. We reviewed the various terms used to define emotional symptoms in ADHD, clarify how these symptoms are demarcated from mood disorders, and assess the possibility that symptoms of emotional impulsivity and deficient emotional self-regulation should be considered as core symptoms. We addressed psychiatric comorbidities, the effects of ADHD treatments on associated emotional dysregulation, and the utility of current rating scales to assess emotional symptoms associated with ADHD.

RESULTS: Emotional symptoms are common and persistent in youth and adults with ADHD. Although emotional symptoms are common in other psychiatric disorders, emotional impulsivity (EI), and deficient emotional self-regulation (DESR) may be sufficiently specific for ADHD to function as diagnostic criteria.

CONCLUSIONS: Emotional symptoms in ADHD cause clinically significant impairments. Although there is a solid theoretical rationale for considering EI and DESR to be core symptoms of ADHD, there is no consensus about how to define these constructs sin a manner that would be specific to the disorder. An instrument to measure EI and DESR which demarcates them from irritability and other emotional symptoms could improve the accuracy of diagnostic criteria for ADHD

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J Med Internet Res. 2019 Nov;21:e13478.

THE EFFECTIVENESS OF WEB-BASED INTERVENTIONS DELIVERED TO CHILDREN AND YOUNG PEOPLE WITH *Neurodevelopmental Disorders: Systematic Review and Meta-Analysis*.

BACKGROUND: The prevalence of certain neurodevelopmental disorders, specifically autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), has been increasing over the last four decades. Nonpharmacological interventions are available that can improve outcomes and reduce associated symptoms such as anxiety, but these are often difficult to access. Children and young people are using the internet and digital technology at higher rates than any other demographic, but although Web-based interventions have the potential to improve health outcomes in those with long-term conditions, no previous reviews have investigated the effectiveness of Web-based interventions delivered to children and young people with neurodevelopmental disorders.

OBJECTIVE: This study aimed to review the effectiveness of randomized controlled trials (RCTs) of Web-based interventions delivered to children and young people with neurodevelopmental disorders.

METHODS: Six databases and one trial register were searched in August and September 2018. RCTs were included if they were published in a peer-reviewed journal. Interventions were included if they (1) aimed to improve the diagnostic symptomology of the targeted neurodevelopmental disorder or associated psychological symptoms as measured by a valid and reliable outcome measure; (2) were delivered on the Web; (3) targeted a youth population (aged </=18 years or reported a mean age of </=18 years) with a diagnosis or suspected diagnosis of a neurodevelopmental disorder. Methodological quality was rated using the Joanna Briggs Institute Critical Appraisal Checklist for RCTs.

RESULTS: Of 5140 studies retrieved, 10 fulfilled the inclusion criteria. Half of the interventions were delivered to children and young people with ASDs with the other five targeting ADHD, tic disorder, dyscalculia, and specific learning disorder. In total, 6 of the 10 trials found that a Web-based intervention was effective in improving condition-specific outcomes or reducing comorbid psychological symptoms in children and young people. The 4 trials that failed to find an effect were all delivered by apps. The meta-analysis was conducted on five of the trials and did not show a significant effect, with a high level of heterogeneity detected (n=182

[33.4%, 182/545], 5 RCTs; pooled standardized mean difference=-0.39; 95% CI -0.98 to 0.20; Z=-1.29; P=.19 [I(2)=72%; P=.006]).
CONCLUSIONS: Web-based interventions can be effective in reducing symptoms in children and young people with neurodevelopmental disorders; however, caution should be taken when interpreting these findings owing to methodological limitations, the minimal number of papers retrieved, and small samples of included studies. Overall, the number of studies was small and mainly limited to ASD, thus restricting the generalizability of the findings.
TRIAL REGISTRATION: PROSPERO International Prospective Register of Systematic Reviews: CRD42018108824; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108824

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J Neural Eng. 2019 Jun;16:036016.
EEG REPRESENTATION USING MULTI-INSTANCE FRAMEWORK ON THE MANIFOLD OF SYMMETRIC POSITIVE DEFINITE MATRICES.
Sadatnejad K, Rahmati M, Rostami R, et al.
OBJECTIVE: The generalization and robustness of an electroencephalogram (EEG)-based system are crucial requirements in actual practices.
APPROACH: To reach these goals, we propose a new EEG representation that provides a more realistic view of brain functionality by applying multi-instance (MI) framework to consider the non-stationarity of the EEG signal. In this representation, the non-stationarity of EEG is considered by describing the signal as a bag of relevant and irrelevant concepts. The concepts are provided by a robust representation of homogeneous segments of EEG signal using spatial covariance matrices. Due to the nonlinear geometry of the space of covariance matrices, we determine the boundaries of the homogeneous segments based on adaptive segmentation of the signal in a Riemannian framework. Each subject is described as a bag of covariance matrices of homogeneous segments and the bag-level discriminative information is used for classification.
MAIN RESULTS: To evaluate the performance of the proposed approach, we examine it in a cultural neuroscience application for classification Iranian versus Swiss normal subjects to discover if strongly differing cultures can result in distinguishing patterns in brain electrical activity of the subjects. To confirm the effectiveness of the proposed representation, we also evaluate the proposed representation in EEG-based mental disorder diagnosis application for attention deficit hyperactivity disorder (ADHD)/bipolar mood disorder (BMD), Schizophrenia/ normal, and Major Depression Disorder/normal diagnosis applications.
SIGNIFICANCE: Experimental results confirm the superiority of the proposed approach, which is gained due to the robustness of covariance descriptor, the effectiveness of Riemannian geometry, the benefits of considering the inherent non-stationary nature of the brain by applying bag-level discriminative information, and automatic handling the artifacts

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J Neurosurg Pediatr. 2019 Apr;24:54-61.
CLINICAL PREDICTORS OF SYMPTOM RESOLUTION FOR CHILDREN AND ADOLESCENTS WITH SPORT-RELATED CONCUSSION.
Howell DR, Potter MN, Kirkwood MW, et al.
OBJECTIVE: The goal of this study was to determine which variables assessed during an initial clinical evaluation for concussion are independently associated with time until symptom resolution among pediatric patients.
METHODS: Data collected from a prospective clinical registry of pediatric patients with concussion were analyzed. The primary outcome variable was time from injury until symptom resolution. Predictor variables assessed within 10 days after injury included preinjury factors, Health and Behavior Inventory scores, headache severity, and balance, vestibular, and oculomotor test performances. The researchers used univariate Cox proportional models to identify potential predictors of symptom resolution time and constructed

a multivariate Cox proportional hazards model in which total duration of concussion symptoms remained the outcome variable.
RESULTS: The sample consisted of 351 patients (33% female, mean age 14.6 +/- 2.2 years, evaluated 5.6 +/- 2.6 days after concussion). Univariate Cox proportional hazards models indicated that several variables were associated with a longer duration of symptoms, including headache severity (hazard ratio [HR] 0.90 [95% CI 0.85-0.96]), headache frequency (HR 0.83 [95% CI 0.71-0.96]), confusion (HR 0.79 [95% CI 0.69-0.92]), forgetfulness (HR 0.79 [95% CI 0.68-0.92]), attention difficulties (HR 0.83 [95% CI 0.72-0.96]), trouble remembering (HR 0.84 [95% CI 0.72-0.98]), getting tired often (HR 0.86 [95% CI 0.76-0.97]), getting tired easily (HR 0.86 [95% CI 0.76-0.98]), dizziness (HR 0.86 [95% CI 0.75-0.99]), and abnormal performance on the Romberg test (HR 0.59 [95% CI 0.40-0.85]). A multivariate Cox proportional hazards model indicated that an abnormal performance on the Romberg test was independently associated with a longer duration of symptoms (HR 0.65 [95% CI 0.44-0.98]; p = 0.038).
CONCLUSIONS: For children and adolescents evaluated within 10 days after receiving a concussion, abnormal performance on the Romberg test was independently associated with a longer duration of symptoms during recovery. In line with findings of other recent studies investigating predictors of symptom resolution, postural stability tests may provide useful prognostic information for sports medicine clinicians

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J Pediatr Health Care. 2019 May;33:e1-e8.
SOMNOLENCE-PRODUCING AGENTS: A 5-YEAR STUDY OF PRESCRIBING FOR MEDICAID-INSURED CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Klein T, Woo TM, Panther S, et al.
INTRODUCTION: Researchers evaluated the prescribing of medications that induce somnolence to children with attention deficit hyperactivity disorder (ADHD) insured by Medicaid.
METHOD: An observational study of prescription claims for children ages 3-18 with ADHD-associated ICD 9 diagnoses filled between January 1, 2012 and December 31, 2016 in Oregon.
RESULTS: There were 14,567 prescriptions written for a 30-day supply of sleep medication for 2,518 children. Most were written for males (66.3%) and to those ages 12-18 (63.8%). Trazodone, hydroxyzine, quetiapine, clonazepam, and amitriptyline were frequently prescribed. There were few prescriptions for zaleplon and zolpidem.
DISCUSSION: Trazodone, hydroxyzine, and amitriptyline are commonly prescribed without clinical efficacy or guidance for children with ADHD. Quetiapine is prescribed off label in sub-therapeutic doses for its somnolence effect. Mental health drugs, which have voluntary formulary guidance in Oregon, and antihistamines on formulary, are more frequently prescribed for children with ADHD than drugs with FDA approval for insomnia

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J Pediatr Health Care. 2019 May;33:234-41.
SLEEP EVALUATION IN THE ASSESSMENT OF PEDIATRIC ATTENTION DEFICIT DISORDERS.
Teague MS, Hockenberry M, Kinney JL, et al.
INTRODUCTION: Examining the impact of appropriate sleep evaluation on diagnosis of attention deficit disorders can improve the standard of care in pediatrics. This quality improvement project examined current practice and subsequent implementation of a validated standardized sleep evaluation tool in the assessment of children with symptoms of attention deficit.
METHODS: Retrospective chart review and implementation of the Children's Sleep Habits Questionnaire (CSHQ) for children 6 to 14years old with attention deficit symptoms.
MEASURES: Rates of sleep screening, sleep referrals, diagnosis of sleep and attention deficit disorders, Vanderbilt scores, CSHQ scores.
RESULTS: In the retrospective group (n=41), 76% of patients had attention deficit disorder/attention deficit hyperactivity disorder, 19.5% had sleeping disorders. There were significant provider differences in diagnosing sleep problems (p=.007). In the intervention group (n=5), 60% had abnormal CSHQ scores.

DISCUSSION: There was considerable incidence of sleeping problems in children with symptoms of attention deficit and provider variation in sleep evaluation and diagnosis, with minimal referral to specialist care. Our findings support a more comprehensive and standardized evaluation of sleep when assessing for attention deficit disorders to improve appropriate referrals, diagnosis, and treatment in pediatrics

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J Pediatr Psychol. 2019 Jun;44:517-26.

FEATURED ARTICLE: TECHNOLOGY USE AND SLEEP IN ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bourchtein E, Langberg JM, Cusick CN, et al.

OBJECTIVES: This study used a multi-informant approach to examine differences in types and rates of technology used by adolescents with and without attention-deficit/hyperactivity disorder (ADHD), associations between technology use and sleep/daytime sleepiness, and whether technology use was differentially related to sleep/daytime sleepiness in adolescents with and without ADHD.

METHODS: Eighth graders with (n = 162) and without (n = 140) ADHD were recruited. Adolescents completed questionnaires assessing time spent using technology, sleep-wake problems, school-night time in bed, and daytime sleepiness. Parents and teachers reported on adolescents' technology use and daytime sleepiness, respectively.

RESULTS: Adolescents with ADHD had significantly greater total technology, television/movie viewing, video game, and phone/video chatting use than adolescents without ADHD. Adolescents with ADHD engaged in twice as much daily video game use compared to those without ADHD (61 vs. 31 min). Controlling for medication use, ADHD status, pubertal development, sex, and internalizing symptoms, greater parent- and adolescent-reported technology use was associated with more sleep-wake problems and less time in bed. ADHD status did not moderate the relations between technology use and these sleep parameters. In contrast, ADHD status moderated the association between parent-reported technology use and teacher-reported daytime sleepiness, such that this association was significant only for adolescents with ADHD.

CONCLUSIONS: Technology use, although more prevalent in adolescents with ADHD, is linked with more sleep problems and reduced school-night sleep duration regardless of ADHD status. Technology use is associated with teacher-rated daytime sleepiness only in adolescents with ADHD. Clinicians should consider technology usage when assessing and treating sleep problems

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J Pediatr Psychol. 2019 Oct;44:1097-110.

META-ANALYSIS: ASSOCIATION OF PARENT AND CHILD MENTAL HEALTH WITH PEDIATRIC HEALTH CARE UTILIZATION.

Lavigne JV, Meyers KM.

OBJECTIVE: To examine the association of psychological factors and pediatric health care utilization.

METHOD: Ovid Medline and PsychInfo were searched and archival and forward searchers were conducted of relevant articles. Studies of the association between psychological risk factors and pediatric health care utilization of outpatient services, emergency department, inpatient length of stay, and costs were identified. Effect sizes were expressed in the form of the standardized mean difference. From 4,546 studies identified in the search, 69 studies met inclusion criteria.

RESULTS: There were significant low-moderate associations between higher outpatient visits and general child mental health (MH) problems (mean ES [mES] = 0.35), overall psychopathology (mES = 0.44), and internalizing symptoms (mES = 0.16). Results were significant for any parent MH problem (mES = 0.18). For emergency department (ED) visits, there were significant association between more ED visits and any child MH problems (mES = 0.25), internalizing symptoms (mES = 0.24), externalizing symptoms (mES = 0.16), and Attention Deficit/Hyperactivity Disorder (mES= 0.14), as well as parent MH (mES = 0.24) and maternal depression (mES = 0.21). Increased hospitalizations were associated with any child MH problem (mES = 0.3), overall child psychopathology (mES = 0.49), child depression (ES = 0.41), and any parent MH problem (mES = 0.54). For costs, results were significant for any child MH problem (mES = 0.38).

CONCLUSIONS: Child and parent MH problems are significantly associated with increased HCU

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J Pediatr Psychol. 2019 Jun;44:576-88.
POSITIVE ILLUSORY BIAS STILL ILLUSORY? INVESTIGATING DISCREPANT SELF-PERCEPTIONS IN GIRLS WITH ADHD.
Tu JW, Owens EB, Hinshaw SP .
OBJECTIVE: To examine whether girls with attention deficit/hyperactivity disorder (ADHD) demonstrate positive illusory self-perceptions during adolescence and young adulthood.
METHODS: We tested, across a 5-year longitudinal span, whether self-perceptions versus external-source ratings were more strongly predictive of young adulthood impairment and depressive symptoms. Participants included an ethnically diverse sample of 140 girls with ADHD and 88 comparison girls, aged 11-18 years (M = 14.2) at adolescent and 19-24 years (M = 19.6) at young adult assessment.
RESULTS: Although girls with ADHD rated themselves more positively than indicated by external ratings, their self-reports still did not differ significantly from external ratings in both scholastic competence and social adjustment domains. Comparison girls, on the other hand, rated themselves significantly less positively than indicated by external ratings in social adjustment. Positive discrepancy scores in adolescence did not significantly predict depressive symptoms in young adulthood and vice versa. Crucially, measures of actual competence in adolescence were more strongly associated with young adulthood impairments than were inaccurate self-perceptions for girls with ADHD.
CONCLUSIONS: Our findings continue to challenge the existence of a positive illusory bias among girls with ADHD, including any association of such bias with key indicators of impairment

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J Rural Health. 2019 Jun;35:298-307.
PATTERNS OF TELEHEALTH USE AMONG RURAL MEDICAID BENEFICIARIES.
Talbot JA, Burgess AR, Thayer D, et al.
PURPOSE: Few studies have examined telehealth use among rural Medicaid beneficiaries. This study produced a descriptive overview of telehealth use in 2011, including the prevalence of telehealth use among rural and urban Medicaid beneficiaries, characteristics of telehealth users, types of telehealth services provided, and diagnoses associated with telehealth use.
METHODS: Using data from the 2011 Medicaid Analytic eXtract (MAX), we conducted bivariate analyses to test the associations between rurality and prevalence and patterns of telehealth use among Medicaid beneficiaries.
FINDINGS: Rural Medicaid beneficiaries were more likely to use telehealth services than their urban counterparts, but absolute rates of telehealth use were low-0.26% of rural nondual Medicaid beneficiaries used telehealth in 2011. Psychotropic medication management was the most prevalent use of telehealth for both rural and urban Medicaid beneficiaries, but the proportion of users who accessed nonbehavioral health services through telehealth was significantly greater as rurality increased. Regardless of telehealth users' residence, mood disorders were the most common reason for obtaining telehealth services. As rurality increased, significantly higher proportions of telehealth users received services to address attention-deficit/hyperactivity disorder (ADHD) and other behavioral health problems usually diagnosed in childhood.
CONCLUSIONS: These findings provide a baseline for further policy-relevant investigations including examinations of changes in telehealth use rates in Medicaid since 2011. Reimbursement policies and unique rural service needs may account for the observed differences in rural-urban Medicaid telehealth use rates

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J Sch Psychol. 2019 Dec;77:67-76.

ACADEMIC IMPAIRMENT AMONG HIGH SCHOOL STUDENTS WITH ADHD: THE ROLE OF MOTIVATION AND GOAL-DIRECTED EXECUTIVE FUNCTIONS.

Sibley MH, Graziano PA, Ortiz M, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with academic failure in high school; however the underpinnings of these difficulties are insufficiently understood. This study examined deficits in self-regulated learning in a sample of high school students with ADHD (n=32) compared to demographically similar classmates without ADHD (n=18). A multimethod battery of self and parent rating scales and cognitive tasks measured aspects of intrinsic motivation, extrinsic motivation, and goal-directed executive functions. A multiple regression modeled predictors of current Grade Point Average (GPA). Results indicated that high school students with ADHD placed lower value on academics (d = .99), were less likely to use goal-setting strategies (d = .95), possessed lower levels of metacognition (d = 1.86), and showed significant deficits in task-based cognitive flexibility (d = .80). After controlling for covariates, the set of self-regulated learning variables explained 23% of the variance in GPA, with metacognition (6% of variance explained) and cognitive flexibility (7% of variance explained) serving as significant predictors of outcome. Findings suggest that higher-order executive function deficits play a critical role in the academic functioning of high school students and students with ADHD show large deficits in these areas. Thus, interventions that target metacognition and cognitive flexibility (i.e., the ability to think through decisions before acting, inhibit automatic responses, and make effective decisions for a desired goal) may be particularly promising to remediate ADHD-related academic problems in high school

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JAMA Netw Open. 2019 Aug;2:e1910236.

ASSOCIATION OF CESAREAN DELIVERY WITH RISK OF NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS IN THE OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Zhang T, Sidorchuk A, Sevilla-Cermeno L, et al.

Importance: Birth by cesarean delivery is increasing globally, particularly cesarean deliveries without medical indication. Children born via cesarean delivery may have an increased risk of negative health outcomes, but the evidence for psychiatric disorders is incomplete.

Objective: To evaluate the association between cesarean delivery and risk of neurodevelopmental and psychiatric disorders in the offspring.

Data Sources: Ovid MEDLINE, Embase, Web of Science, and PsycINFO were searched from inception to December 19, 2018. Search terms included all main mental disorders in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

Study Selection: Two researchers independently selected observational studies that examined the association between cesarean delivery and neurodevelopmental and psychiatric disorders in the offspring.

Data Extraction and Synthesis: Two researchers independently extracted data according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines and assessed study quality using the Newcastle-Ottawa Scale. Random-effects meta-analyses were used to pool odds ratios (ORs) with 95% CIs for each outcome. Sensitivity and influence analyses tested the robustness of the results.

Main Outcomes and Measures: The ORs for the offspring with any neurodevelopmental or psychiatric disorder who were born via cesarean delivery compared with those were born via vaginal delivery.

Results: A total of 6953 articles were identified, of which 61 studies comprising 67 independent samples were included, totaling 20607935 deliveries. Compared with offspring born by vaginal delivery, offspring born via cesarean delivery had increased odds of autism spectrum disorders (OR, 1.33; 95% CI, 1.25-1.41; I2 = 69.5%) and attention-deficit/hyperactivity disorder (OR, 1.17; 95% CI, 1.07-1.26; I2 = 79.2%). Estimates were less precise for intellectual disabilities (OR, 1.83; 95% CI, 0.90-3.70; I2 = 88.2%), obsessive-compulsive disorder (OR, 1.49; 95% CI, 0.87-2.56; I2 = 67.3%), tic disorders (OR, 1.31; 95% CI, 0.98-1.76; I2 = 75.6%), and eating disorders (OR, 1.18; 95% CI, 0.96-1.47; I2 = 92.7%). No significant associations were found with depression/affective psychoses or nonaffective psychoses. Estimates were comparable for emergency and elective cesarean delivery. Study quality was high for 82% of the cohort studies and 50% of the case-control studies.

Conclusions and Relevance: The findings suggest that cesarean delivery births are associated with an increased risk of autism spectrum disorder and attention-deficit/hyperactivity disorder, irrespective of cesarean delivery modality, compared with vaginal delivery. Future studies on the mechanisms behind these associations appear to be warranted

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JAMA Netw Open. 2019 Dec;2:e1917880.

EMERGING INSIGHTS INTO THE ASSOCIATION BETWEEN NATURE EXPOSURE AND HEALTHY NEURONAL DEVELOPMENT.

Baroni A, Castellanos FX.

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JAMA Netw Open. 2019 Aug;2:e1910005.

ASSOCIATION OF PARENTAL INCARCERATION WITH PSYCHIATRIC AND FUNCTIONAL OUTCOMES OF YOUNG ADULTS.

Gifford EJ, Eldred KL, Golonka M, et al.

Importance: In 2016, an estimated 8% of US children younger than 18 years had experienced the incarceration of a parent, and rates were substantially higher among children from racial and ethnic minority backgrounds and disadvantaged groups. Little is known about whether parental incarceration during childhood is associated with adult psychiatric problems and functional outcomes.

Objective: To examine whether parental incarceration is associated with increased levels of psychiatric diagnosis and poor outcomes in health, legal, financial, and social domains in adulthood.

Design, Setting, and Participants: This cohort study used data from the community-representative, prospective, longitudinal Great Smoky Mountains Study. Children and their parents were interviewed up to 8 times from January 1993 to December 2000 (ages 9-16 years; 6674 observations of 1420 participants) using the Child and Adolescent Psychiatric Assessment, which assessed parental incarceration, childhood psychiatric diagnoses, and other adversities. Young adults were followed up at ages 19, 21, 25, and 30 years from January 1999 to December 2015 (4556 observations of 1334 participants) to assess psychiatric diagnoses and functional outcomes indicative of a disrupted transition to adulthood. Data analysis was conducted from June 2018 to June 2019.

Results: By age 16 years, 475 participants (weighted percentage, 23.9%) had a parental figure who had been incarcerated, including 259 young men (22.2%) and 216 young women (25.5%). Parental incarceration was associated with higher prevalence of childhood psychiatric diagnoses (eg, any depressive diagnosis: adjusted odds ratio [aOR], 2.5; 95% CI, 1.3-4.6; P = .006; attention-deficit/hyperactivity disorder: aOR, 2.3; 95% CI, 1.0-5.5; P = .06; and conduct disorder: aOR, 2.5; 95% CI, 1.4-4.3; P = .001). After accounting for childhood psychiatric diagnoses and adversity exposure, parental incarceration remained associated with increased odds of having an adult anxiety disorder (aOR, 1.7; 95% CI, 1.0-3.0; P = .04), having an illicit drug use disorder (aOR, 6.6; 95% CI, 2.6-17.0; P < .001), having a felony charge (aOR, 3.4; 95% CI, 1.8-6.5; P < .001), incarceration (aOR, 2.8; 95% CI, 1.4-5.4; P = .003), not completing high school (aOR, 4.4; 95% CI, 2.2-8.8; P < .001), early parenthood (aOR, 1.7; 95% CI, 1.0-3.0; P = .04), and being socially isolated (aOR, 2.2; 95% CI, 1.2-4.0; P = .009).

Conclusions and Relevance: This study suggests that parental incarceration is associated with a broad range of psychiatric, legal, financial, and social outcomes during young adulthood. Parental incarceration is a common experience that may perpetuate disadvantage from generation to generation

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JAMA Psychiatry. 2019 Jul;76:730-38.

MULTI-POLYGENIC SCORE APPROACH TO IDENTIFYING INDIVIDUAL VULNERABILITIES ASSOCIATED WITH THE RISK OF EXPOSURE TO BULLYING.

Schoeler T, Choi SW, Dudbridge F, et al.

Importance: Exposure to bullying is a prevalent experience with adverse consequences throughout the life span. Individual vulnerabilities and traits, such as preexisting mental health problems, may be associated with increased likelihood of experiencing bullying. Identifying such individual vulnerabilities and traits is essential for a better understanding of the etiology of exposure to bullying and for tailoring effective prevention.

Objective: To identify individual vulnerabilities and traits associated with exposure to bullying in childhood and adolescence.

Design, Setting, and Participants: For this study, data were drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based birth cohort study. The initial ALSPAC sample consisted of 14062 children born to women residing in Avon, United Kingdom, with an expected date of delivery between April 1, 1991, and December 31, 1992. Collection of the ALSPAC data began in September 6, 1990, and the last follow-up assessment of exposure to bullying was conducted when participants were 13 years of age. Data analysis was conducted from November 1, 2017, to January 1, 2019.

Exposures: The polygenic score approach was used to derive genetic proxies that indexed vulnerabilities and traits. A total of 35 polygenic scores were computed for a range of mental health vulnerabilities (eg, depression) and traits related to cognition (eg, intelligence), personality (eg, neuroticism), and physical measures (eg, body mass index), as well as negative controls (eg, osteoporosis).

Main Outcomes and Measures: Single and multi-polygenic score regression models were fitted to test the association between indexed traits and exposure to bullying. Children completed the Bullying and Friendship Interview Schedule at the ages of 8, 10, and 13 years. A mean score of exposure to bullying across ages was used as the main outcome.

Results: A total of 5028 genotyped individuals (2481 boys and 2547 girls) with data on exposure to bullying were included. Among the 35 initially included polygenic scores, 11 were independently associated with exposure to bullying; no significant association was detected for the 24 remaining scores. In multivariable analyses, 5 polygenic scores were associated with exposure to bullying; the largest associations were present for genetic risk relating to mental health vulnerabilities, including diagnosis of depression (standardized b = 0.065; 95% CI, 0.035-0.095) and attention-deficit/hyperactivity disorder (standardized b = 0.063; 95% CI, 0.035-0.091), followed by risk taking (standardized b = 0.041; 95% CI, 0.013-0.069), body mass index (standardized b = 0.036; 95% CI, 0.008-0.064), and intelligence (standardized b = -0.031; 95% CI, -0.059 to 0.003).

Conclusion and Relevance: Using the multi-polygenic score approach, the findings implicate preexisting mental health vulnerabilities as risk factors for exposure to bullying. A mechanistic understanding of how these vulnerabilities link to exposure of bullying is important to inform prevention strategies

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JAMA Psychiatry. 2019 May;76:536-43.

ASSOCIATION OF FETAL GROWTH WITH GENERAL AND SPECIFIC MENTAL HEALTH CONDITIONS.

Pettersson E, Larsson H, D'Onofrio B, et al.

Importance: It is unclear if the associations between fetal growth and later mental health conditions remain after controlling for familial factors and psychiatric comorbidity.

Objective: To examine the associations between fetal growth and general and specific mental health conditions, controlling for familial factors.

Design, Setting, and Participants: This register-based study conducted in Sweden analyzed 546 894 pairs of full siblings born between January 1, 1973, and December 31, 1998. Sibling pairs were followed up through December 31, 2013. First, population-based and within-sibling pair associations (which controlled for time-invariant familial confounders) between fetal growth and the outcomes were estimated. Second, exploratory factor analysis was applied to the outcomes to derive 1 general factor and 4 specific and independent factors. Third, the general and specific factors were regressed on fetal growth. Statistical analysis was performed from March 27, 2017, to October 27, 2018.

Main Outcome and Measures: The outcomes were 11 psychiatric diagnoses (depression, anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, alcohol abuse, drug use, attention-deficit/hyperactivity disorder, autism, schizophrenia, and schizoaffective disorder) and court convictions of violent crimes. Birth weight (in kilograms) statistically adjusted for gestational age was the exposure.
Results: The mean (SD) age of the 1093788 participants was 27.2 (6.8) years (range, 15.1-40.9 years) and 51.5% were male. Nine outcomes were significantly associated with birth weight in the population at large: depression (odds ratio [OR], 0.96; 95% CI, 0.95-0.98), anxiety (OR, 0.94; 95% CI, 0.92-0.95), posttraumatic stress disorder (OR, 0.91; 95% CI, 0.89-0.93), bipolar disorder (OR, 0.94; 95% CI, 0.89-1.00), alcohol abuse (OR, 0.89; 95% CI, 0.87-0.91), drug use (OR, 0.83; 95% CI, 0.80-0.85), violent crimes (OR, 0.85; 95% CI, 0.83-0.86), attention-deficit/hyperactivity disorder (OR, 0.88; 95% CI, 0.86-0.90), and autism (OR, 0.95; 95% CI, 0.92-0.97). Only depression (OR, 0.95; 95% CI 0.92-0.98), obsessive-compulsive disorder (OR, 0.93; 95% CI, 0.87-0.99), attention-deficit/hyperactivity disorder (OR, 0.86; 95% CI, 0.82-0.89), and autism (OR, 0.72; 95% CI, 0.69-0.76) remained significantly associated within sibling pairs. An exploratory factor analysis indicated that 1 general and 4 specific factors (capturing anxiety, externalizing, neurodevelopmental, and psychotic conditions) fit the outcomes well. Across almost all sensitivity analyses, an increase in birth weight by 1 kg significantly reduced the general (beta, -0.047; 95% CI, -0.071 to -0.023) and the specific neurodevelopmental factors (beta, -0.159; 95% CI, -0.190 to -0.128) within sibling pairs.
Conclusions and Relevance: Controlling for familial confounders, reduced fetal growth was associated with a small but significant increase in the general factor of psychopathology and a moderate increase in a specific neurodevelopmental factor

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J Affective Disord. 2020;274:494-99.

NARCISSISTIC TRAITS AS PREDICTORS OF EMOTIONAL PROBLEMS IN CHILDREN WITH OPPOSITIONAL DEFIANT DISORDER: A LONGITUDINAL STUDY.

Muratori P, Milone A, Levantini V, et al.

Background: Children's self-views encompass two independent dimensions: self-esteem and narcissism, which recently have received growing attention from researchers and clinicians. The current study sought to test whether these dimensions might predict the developmental course of children with Oppositional Defiant Disorder diagnosis.
Method: The sample (N = 64, M age = 10.1 years, 57 boys) included children with Oppositional Defiant Disorder diagnosis. We examined longitudinal relationships between self-views (both self-esteem and narcissism) and parent-reported internalizing and externalizing behavioral problems.
Results: The study spanned two time-points, spaced 12 months apart. None of the predictors were longitudinally associated with the levels of externalizing behavioral problems in children. However, narcissism predicted the levels of children's internalizing problems at the follow-up, whereas self-esteem did not. Limitations: The relatively small sample and the lack of assessing causality limit the generalizability of the findings. Results need to be replicated in larger samples.
Conclusions: These findings illustrate the value of taking into account children's narcissistic traits in clinical assessment. By broadening knowledge of narcissistic traits in clinical samples of children, we hope to inform assessment procedures in standard clinical practice, as well as the development of tailored interventions to curb the emergence of later negative outcomes related to childhood narcissism, such as internalizing problems

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J Affective Disord. 2020;274:500-07.

VARIABILITY IN POSITIVE AND NEGATIVE AFFECT AMONG ADOLESCENTS WITH AND WITHOUT ADHD: DIFFERENTIAL ASSOCIATIONS WITH FUNCTIONAL OUTCOMES.

Breaux R, Langberg JM, Swanson CS, et al.

Introduction. This study examined whether adolescents with and without attention-deficit/hyperactivity disorder (ADHD) differed in affect variability and whether variability in positive and negative affect was associated with functional outcomes.

Method. Participants were 302 adolescents (12-14 years, Mage=13.17, 55% male; 54% diagnosed with ADHD; 82% white) and their caregivers who each completed the 10-item Positive and Negative Affect Scale via daily diaries for approximately two weeks. Multi-informant ratings of emotional, behavioral, social, and academic outcomes were assessed.

Results. Adolescents with ADHD were found to experience greater variability in self- and parent-reported positive affect, fear, and distress. For adolescents with ADHD, greater variability in self- and parent-reported positive affect, fear, and distress were associated with more internalizing symptoms, greater variability in parent-reported positive affect was associated with worse social functioning, and greater variability in self- and parent-reported fear was associated with more externalizing symptoms. In contrast, greater variability in self- and parent-reported positive affect, fear, and distress were associated with better social functioning in adolescents without ADHD.

Limitations. Future work should examine affect variability in adolescents with ADHD within the same day rather than across days. The limited age range and demographic diversity of our sample may limit generalizability of findings.

Conclusions. Findings suggest the significant affect variability found among children with ADHD is also present in adolescents with ADHD and is associated with social and behavior impairment. Interventions for adolescents with ADHD should target emotion regulation abilities to help reduce the extremes of and shifts in affective experiences in this population

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J Autism Dev Disord. 2020.

EFFECT OF CO-OCCURRING PSYCHIATRIC DISORDERS ON TREATMENT OF CHILDREN WITH AUTISM SPECTRUM DISORDER AND ANXIETY.

Meyer AT, Moody EJ, Keefer A, et al.

Co-occurring psychiatric diagnoses are very common in individuals with ASD. Little is known about the effect that co-occurring psychiatric conditions may have on treatment response to CBT for children with ASD and anxiety. The present study examined the relationship between co-occurring psychiatric diagnoses and response to CBT for anxiety in ninety youth with ASD. Psychiatric complexity did not appear to differentially impact treatment response. A notable portion of youth with anxiety and externalizing disorders such as ADHD, no longer met criteria for those externalizing diagnoses following intervention. Results indicate that youth with ASD and anxiety present with complex psychiatric profiles and CBT for anxiety may positively affect co-occurring diagnoses. In addition, thorough and nuanced assessment of psychiatric symptoms in youth with ASD is needed to ensure the differentiation between diagnoses of anxiety and other co-occurring psychiatric symptoms

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Journal of Gastroenterology and Hepatology. 2019;34:704.

WILSON DISEASE PRESENTED WITH PSYCHIATRIC SYMPTOMS: A CASE REPORT AND DIAGNOSTIC CHALLENGES.

Goyal M, Goyal M.

Introduction: Wilson disease is an inherited disorder of copper metabolism that affects liver and brain. The diagnosis is often missed initially. The presentation is usually neurologic or hepatic, seen in 40% of patients. Psychiatric presentation of WD is reported in only 15% of patients. It is caused by homozygous mutation in ATP7B gene. Our aim is to present the clinical and laboratory characteristics and point out the diagnostic difficulties.

Case Description: Twelve year old boy was referred for incidental finding of hepatomegaly. He had normal motor milestones with delayed social and speech development. He was diagnosed earlier as attention deficit hyperactivity disorder. On examination Liver function tests were normal. USG abdomen revealed liver parenchymal disease. Magnetic resonance (MR) of the brain revealed sym-metric changes in putamen and globi pallidi. Wilson disease was suspected. Serum copper was normal and ceruloplasmin was low. Kayser-Fleisher rings was not present on slit lamp examination. Genetic testing showed a compound heterozygous mutation in ATP7B gene: Exon 2, c.813C>A, and Exon 2, c.442C>T. Parents were found to be carrier of same gene variant confirming the diagnosis of Wilson disease. He was started on pencillamine and Zinc.
Discussion: Our proband was misdiagnosed and treated as psychiatric case. Wilson disease is suspected with varying combinations of hepatic, neurologic, and psychiatric findings and confirmed by a low serum copper and ceruloplasmin, and increased urinary copper or Kayser Fleischer corneal ring or homozygous mutation. Anticopper treatment may improve hepatic and neurological features. Unfortunately guideline to manage psychiatric features in WD is not present. Conclusion: Although such patients are more commonly seen in neurological and hepatological settings, should be consider in differential diagnosis of psychiatric nature. Drugs that may cause extrapyramidal symptoms should be avoided in patients with WD. Molecular confirmation is essential in view of prenatal counseling and testing

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Journal of Mazandaran University of Medical Sciences. 2020;30:142-47.

PREVALENCE OF MOOD DISORDERS IN MOTHERS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hamzehpour R, Hamidia A, Kheirkhah F, et al.

Background and purpose: Parents of children with attention deficit hyperactivity disorder (ADHD) have more problems than parents of normal children due to the prevalence of behavioral abnormalities in children with ADHD. Mood disorders in parents, including mothers can lead to lower tolerance thresholds and the use of punitive methods to control the children, which can cause other complications. Therefore, evaluation of mood disorders and timely treatment could be of great help in treating these children and improving the prognosis of the disease.
Materials and methods: This cross-sectional study was conducted in 125 mothers of children with ADHD attending two psychiatric clinics in Babol, Iran 2014-2016. Data were collected using the Conners' Parent Rating Scales-Revised (CPRS-R) and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Data analysis was done in SPSS V22.
Results: The prevalence of mood disorders in mothers of 6-14 year-old children with ADHD was 44% (n=55). Among the mood disorders, dysthymia (27%) was the most common disorder. Forty-five mothers (36%) had depression and 9 (7.2%) had bipolar disorder.
Conclusion: According to current study, depression was the most common mood disorder in mothers. Maternal depression influences the management of a child with ADHD, so, early diagnosis and treatment of maternal depression play major roles in the prognosis of ADHD in a child with this disorder

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J Neural Transm. 2020 Jun;127:977-85.

SEX AND PSYCHIATRIC COMORBIDITY CORRELATES OF THE PREMONITORY URGE FOR TIC SCALE IN YOUTH WITH PERSISTENT TIC DISORDERS.

Edwards KR, Raines JM, Winnick JB, et al.

The premonitory urge for tics scale (PUTS) is a common self-report measure of premonitory sensations preceding tics. The present study aimed to examine the internal consistency and concurrent validity of the PUTS by sex and psychiatric comorbidity status; and explored interactions between sex and psychiatric comorbidity in predicting premonitory urge and tic symptom severity. Seventy-four youth and young adults with persistent tic disorders completed the PUTS, while their parents completed the parent tic questionnaire (PTQ) and a demographic measure. Independent samples t-tests revealed no significant sex differences in PUTS items or total score. The PUTS total score also did not significantly differ between participants with and without attention-deficit hyperactivity disorder (ADHD) and/or obsessive-compulsive disorder (OCD)

comorbidity. Internal consistency did not significantly differ between females (Î± = 0.85) and males (Î± = 0.75), and those with comorbid ADHD and/or OCD (Î± = 0.83) relative to those without (Î± = 0.69). With respect to concurrent validity, the PUTS total was significantly correlated with PTQ tic frequency, intensity, number, and severity for males but not for females. Among those with ADHD and/or OCD, the PUTS total score was correlated significantly and strongly with tic number and moderately with tic intensity. Interactions between sex and psychiatric comorbidity performed using 2 Ã— 2 analysis of variance did not significantly predict the PUTS total or PTQ subscale scores. Findings suggest sex and comorbidity status may influence premonitory urge expression. Results have implications for understanding and measurement of the premonitory urge

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J Popul ther Clin Pharmacol. 2020;27:e56-e61.

THE EFFECTS OF MEDICATION ON INTRAOCULAR PRESSURE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PROSPECTIVE STUDY.

Guvenmez O, Cubuk M, Gunes S.

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions in childhood. Psychopharmacological therapy is an effective treatment for ADHD. In this study, we primarily aim to investigate the effects of psychopharmacological agents on intraocular pressure (IOP) in children with ADHD. The sample included 82 children with ADHD and 36 healthy children aged between 8 and 12 years who were referred to the Department of Child and Adolescent Psychiatry in Hatay State Hospital, Hatay, Turkey. Children with ADHD were divided into two groups according to the medication used: methylphenidate (MPH) group and atomoxetine (ATX) group. Before treatment and after 1-and 6-month treatment period, IOP was measured by Goldmann applanation tonometry. There were no statistical differences in terms of age, gender, and IOP between the three groups (P > 0.05). After 1-and 6-month treatment, the IOP did not change significantly between baseline and 1 month or 6 months (P > 0.05). Children with ADHD may have an IOP similar to healthy children. Six-month treatment with MPH or ATX may not cause significant changes in IOP

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J Am Acad Child Adolesc Psychiatry. 2020 Jun;59:705-14.

SYSTEMATIC REVIEW AND META-ANALYSIS: THE PREVALENCE OF MENTAL ILLNESS IN CHILD AND ADOLESCENT REFUGEES AND ASYLUM SEEKERS.

Blackmore R, Gray KM, Boyle JA, et al.

Objective: Over half of the worldâ€™s refugee population are under the age of 18 years. This systematic review aims to summarize the current body of evidence for the prevalence of mental illness in child and adolescent refugee populations.

Method: Eight electronic databases, gray literature, and Google Scholar were searched for articles from 1 January 2003 to 5 February 2018. Strict inclusion criteria regarding the diagnosis of mental illness were imposed. Study quality was assessed using a template according to study design, and study heterogeneity using the I2 statistic. Random effects meta-analyses results were presented given heterogeneity among studies. The protocol for this systematic review was registered with PROSPERO (CRD42016046349).

Results: Eight studies were eligible, involving 779 child and adolescent refugees and asylum seekers, with studies conducted in 5 countries. The overall prevalence of posttraumatic stress disorder (PTSD) was 22.71% (95% CI 12.79â˜32.64), depression 13.81% (95% CI 5.96â˜21.67), and anxiety disorders 15.77% (95% CI 8.04â˜23.50). Attention-deficit/hyperactivity disorder (ADHD) was 8.6% (1.08â˜16.12) and oppositional defiant disorder (ODD) was 1.69% (95% CI â˜0.78 to 4.16). Because of the high heterogeneity, further subgroup analyses were conducted.

Conclusion: Refugee and asylum seeker children have high rates of PTSD, depression, and anxiety. Without the serious commitment by health and resettlement services to provide early support to promote mental health, these findings suggest that a high proportion of refugee children are at risk for educational disadvantage and poor social integration in host communities, potentially affecting their life course

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J Can Acad Child Adolesc Psychiatry. 2020;29:44-52.

THERAPEUTIC RESPONSE TO METHYLPHENIDATE IN ADHD: ROLE OF CHILD AND OBSERVER GENDER.

Bhat V, Sengupta SM, Grizenko N, et al.

Objective: This study aims to examine the interaction between the gender of the child and the gender of the observers (teachers, parents) on the therapeutic response (TR) noted with methylphenidate (MPH) in children with ADHD.

Method: Children with ADHD participated in a two week double-blind, randomized, cross-over clinical trial with MPH and placebo, and the difference between the week of treatment with MPH and placebo was calculated for each measure to obtain the treatment response (TR) with MPH. The TR for differences based on the gender of child and the observer was examined by using a univariate analysis of covariance (ANCOVA).

Results: 299 children (269-male, 30-female; average age 8.9-¦1.8 years) were evaluated by 52 male teachers, 212 female teachers; 269 female parents and 30 male parents. For the baseline week, the ANCOVA analysis for teachers yielded a significant teacher's gender x child's gender interaction. For the evaluation of TR, the ANCOVA analysis revealed a significant teacher's gender x child's gender interaction whereas no parent's gender x child's gender interactions were noted, all noted interactions were of a small effect size (eta squared <0.02).

Conclusions: These results suggest that there are differences in symptom assessment between parents and teachers at baseline and with TR based on the gender of the observer and the child. While clinicians need to be aware of these interactions, it remains unclear if these interactions will be clinically useful due to the small effect sizes

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Lancet Child Adolesc Health. 2020 Jun;4:412-14.

ADHD MANAGEMENT DURING THE COVID-19 PANDEMIC: GUIDANCE FROM THE EUROPEAN ADHD GUIDELINES GROUP.

Cortese S, Asherson P, Sonuga-Barke E, et al.

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Lancet Planet Health. 2019 May;3:e200-e201.

EXPOSURE TO GREEN SPACES AS A MODIFIABLE RISK FACTOR IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Rucklidge JJ.

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Med J Malaysia. 2019 Oct;74:372-76.

CLINICAL CHARACTERISTICS AND DEMOGRAPHIC PROFILE OF CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD) AT CHILD DEVELOPMENT CLINIC (CDC), PENANG HOSPITAL, MALAYSIA.

Sathyabama R.

OBJECTIVE: To explore socio-demographics and clinical characteristics of children with Autism Spectrum Disorder (ASD) at Child Development Clinic (CDC), Penang Hospital.

STUDY DESIGN: A record review study of 331 children with ASD attending CDC, Penang Hospital from September 2013 to April 2017.

RESULTS: Out of 331 children with ASD, 82.5% were males, 17.5% females, with male to female ratio of 4.7:1. Mean age at consultation was 5 years and 6 months (SD 31.68 months) with age range from 19 months to 18 years and 4 months. 85.8% were term infants with normal birth weight. History of speech regression was noted in 14.8%, epilepsy and genetic disorders in 9.4% and 5.7% respectively. Sleep problems was reported in 29.3%, dietary issues 22.1%, challenging behaviour 24.2% and ADHD 14.2%. Mean age of the father and mother at birth was 33.6 and 31.6 years respectively.
CONCLUSION: In this study, we report a higher male to female ratio and mean age at referral with some similar rates of neurodevelopmental and medical comorbidities and relatively younger parental age with higher parental education levels

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Neurology India. 2020;68:352-57.
THE DEVELOPMENT AND VALIDATION OF DSM 5-BASED AIIMS-MODIFIED INDT ADHD TOOL FOR DIAGNOSIS OF ADHD: A DIAGNOSTIC TEST EVALUATION STUDY.
Gulati S, Saini L, Kaushik J, et al.
Background: The current study was planned at a tertiary centre in northern India to develop and validate a Diagnostic and Statistical Manual-5 (DSM-5)-based diagnostic tool and design a severity score for attention deficit hyperactivity disorder (ADHD) in children aged 6-18 years. An existing DSM-IV-based tool, INDT (International Clinical Epidemiology Network [INCLEN] diagnostic tool) for ADHD has been modified and named All India Institute of Medical Sciences (AIIMS)-modified INDT ADHD tool.
Method: The first phase was development of the tool and the second phase was validation of the same against the gold standard of diagnosis by the DSM-5. A severity score was developed for ADHD in concordance with the Conners rating scale.
Results: The tool was validated in 66 children with a sensitivity and specificity of 100 per cent and 90 per cent, respectively. A cut-off score of 12 was decided for labelling severity of ADHD, which corresponded to 63 in the Conners rating scale.
Conclusion: This diagnostic tool for ADHD based on DSM-5 has acceptable psychometric properties. The severity score will be useful for prognostication, monitoring treatment response, and designing intervention trials

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Neuropsychiatr Dis Treat. 2020;16:1331-37.
A PREDICTIVE MODEL OFFOR ATTENTION DEFICIT HYPERACTIVITY DISORDER BASED ON CLINICAL ASSESSMENT TOOLS.
Han D, Fang Y, Luo H.
Background: At present, clinicians diagnose that the clinical diagnosis of attention deficit hyperactivity disorder (ADHD) in children is mainly on the basis of the information provided by their parents, the behaviour of children in clinical clinics and the assessments of clinical rating scales and neuropsychological tests. Notably, no unified standard exists currently for analysing the results of various measurement tools for diagnosing ADHD. Therefore, clinicians interpret the results of clinical rating scales and neuropsychological tests entirely based on their clinical experience.
Methods and subjects: To provide guidance for clinicians on how to analyse the results of various clinical assessment tools when diagnosing ADHD, this study assessed children with ADHD and children in the control group using two clinical assessment scales-parent rating scale (PSQ) and Child Behavior Checklist (CBCL) and one neuropsychological test (Integrated Visual and Auditory Continuous Performance Testing). The two-sample t-test (FDR correction) screened the parameters of the three assessment tools with significant inter-group differences. LibSVM was used to establish a classification prediction model for analysing the accuracy of ADHD prediction using parameters of the three assessment tools and weight values of each parameter for classification prediction.
Results: A total of 19 parameters (16 from clinical rating scales, 3 from neuropsychological tests) with significant inter-group differences were screened. The accuracy of classification modelling was higher for the

clinical rating scales (61.635%) than for the neuropsychological test (59.784%), whereas the accuracy of classification modelling was higher for the clinical rating scales combined with the neuropsychological test (70.440%) than for the former two parameters alone. The three parameters with the highest weight values were learning problem (0.731), hyperactivity/impulsiv-ity (0.676) and activity capacity (0.569). The three parameters with the lowest weight values are integrated control force (0.028), visual attention (0.028) and integrated attention (0.034).
Conclusion: Our study findings indicate that the diagnosis of ADHD should be based on multidimensional assessment. For a more accurate diagnosis of ADHD, assessments and that more assessment parameters should be developed on the basis of different dimensions of physiology or psychology in the future to obtain a more accurate diagnosis of ADHD. Furthermore, the predictive model for ADHD may improve our understanding and help in optimisation of the treatment of such a condition

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Neuropsychiatr Dis Treat. 2020;16:1309-19.
DECREASED RISK OF INFLUENZA IN CHILD AND ADOLESCENT PATIENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER FOLLOWING METHYLPHENIDATE TREATMENT: A NATIONWIDE COHORT STUDY IN TAIWAN.
Lee H, Chen VCH, Yang Y-H, et al.
Background: Young individuals with attention-deficit hyperactivity disorder (ADHD) may have an elevated risk of influenza because of the difficulty in complying with the behavioral procedures that help protect against influenza. Moreover, the effects of sufficient methyl-phenidate treatment on influenza have received little attention.
Objective: This study evaluated the association between ADHD medication usage and influenza and assessed the effect of duration of ADHD treatment on the risk of influenza using a nationwide population-based database.
Methods: This study investigated methylphenidate usage and the risk of influenza among children and adolescents with ADHD. We identified 5259 young individuals aged less than 18 years who were diagnosed as having ADHD between 1996 and 2013 from the National Health Insurance Research Database of Taiwan, and we tested whether methylphenidate use affects influenza risk using Cox proportional hazard models.
Results: After controlling for confounding factors, the results indicated that influenza risk significantly reduced in the group of ADHD patients who were prescribed methylphenidate for 90 days and more (hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.52ΓÇô0.75, p<0.001), demonstrating a 38% reduction in the risk of influenza in this group. However, this was not observed in the group of ADHD patients who used methylphenidate for 1-90 days (HR: 0.69, 95% CI: 0.89 –1.05, p=0.12).
Conclusion: The lower incidence of influenza observed in the group prescribed with methylphenidate for a longer period highlights the importance of compliance to medication and psychoeducation with regard to ADHD management

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Neuropsychiatr Dis Treat. 2020;16:1349-57.
PEANUT SENSITIVITY AND ALLERGIC RHINITIS IN YOUNG CHILDREN ARE ASSOCIATED WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN ADOLESCENCE.
Guo MMH, Wang L-J, Hsu T-Y, et al.
Objective: Although childhood allergic diseases have been found to be associated with symptoms of attention-deficit hyperactivity disorder, the temporal relationship between these diseases remains unclear. In this study of 97 children, clinical examination and blood samples for total and specific IgE were collected at 6 and 12 years old.
Patients and Methods: We followed a total of 97 children from 6 to 12 years old. Clinical examination and blood samples for total and specific IgE were collected at 6 and 12 years old. Attention-deficit hyperactivity disorder and oppositional defiant disorder symptoms at 12 years old were evaluated using the Swanson, Nolan, and Pelham, Version IV Scale Parent Form.

Results: After accounting for the affect of confounding variables, we found that allergic rhinitis at 6 years old was associated with higher inattention score at 12 years old (+¦-coefficient 0.356, 95% CI 0.104ΓÇô0.609, p = 0.006). In addition, higher specific IgE levels for peanuts at 6 years of age were correlated with higher hyperactivity/impulsivity scores (+¦-coefficient 0.088, 95% CI 0.049-0.126, p < 0.001), and higher specific IgE for peanuts at 12 years of age were correlated with higher opposition/defiance scores (+¦-coefficient 0.054, 95% CI 0.012-0.096, p = 0.012) at 12 years old in our final linear regression models.
Conclusion: Allergic rhinitis and peanut sensitization in childhood may be associated with more symptoms of attention-deficit hyperactivity and oppositional defiant disorder in adolescence

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Neurosci Lett. 2020;734.

SPATIOTEMPORAL CONSISTENCY ANALYSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CHILDREN.

Wang D, Hu R, Wang Q, et al.

Purpose: To identify the local spatiotemporal consistency of spontaneous brain activity of attention-deficit/hyperactivity disorder (ADHD) adolescents and its relation with clinical performance.
Materials and methods: A cohort of 50 adolescents with ADHD-I or ADHD-C and a cohort of age- and gender- matched 46 typical development controls (TDC) were recruited from ADHD-200 dataset. FOur-dimensional (spatiotemporal) Consistency of local neural Activities (FOCA) metric was used to analyze the local spatiotemporal consistency, which integrating local temporal homogeneity and regional stability of brain activity states. The difference of normalized FOCA (nFOCA) values among ADHD-Inattentive (ADHD-I), ADHD-Combined (ADHD-C) and TDC were detected using ANOVA and post-hoc analysis. Furthermore, partial correlations were analyzed to investigate the relationship between nFOCA values and clinical manifestations.
Results: Compared with TDC, ADHD-C and ADHD-I adolescents demonstrated alterations of FOCA in bilateral middle temporal gyrus, superior occipital gyrus, postcentral gyrus, precuneus, and right inferior temporal gyrus, lingual gyrus, superior frontal gyrus, left middle cingulum gyrus, middle occipital gyrus and cerebellum area.
Conclusions: Our study suggests that the FOCA method perhaps has potential to provide important insights into understanding the pathophysiological mechanism of ADHD and its subtypes

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Neurotherapeutics. 2019;16:915.

PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES EVALUATING EFFICACY AND SAFETY OF EXTENDED-RELEASE VILOXAZINE (SPN-812) FOR PEDIATRIC ADHD: UPDATE ON THE SECOND ADOLESCENT STUDY (P304).

Nasser A, Hull JT, Chowdhry FA, et al.

SPN-812, a structurally distinct, bicyclic norepinephrine reuptake inhibitor with selective serotonergic activity, is currently in development for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. Here we provide an update on the second ongoing Phase 3 study of SPN-812 use in adolescents. P304 is a randomized, double-blind, placebo-controlled, multicenter study investigating the efficacy and safety of SPN-812 dosed at 400 mg or 600 mg once daily as an extended-release monotherapy in adolescents ages 12-17 with ADHD. Key inclusion criteria are Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnosis of ADHD confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), baseline ADHD Rating Scale-5 (ADHD-RS-5) score 28 and Clinical Global Impression-Severity (CGI-S) score 4, and subjects free fromADHDmedication ΓëÑ1 week prior to randomization and throughout the study.Atotal of 300 subjects will be randomized 1:1:1 to placebo:400 mg SPN-812:600 mg SPN-812. The treatment period includes up to 2 weeks of dose titration and 5 weeks of maintenance dosing. The primary efficacy endpoint is the change from baseline to end of study in the ADHD-RS-5 total score. Secondary endpoints include the Clinical Global Impression-Improvement scale (CGI-I), Conners 3-Parent and -Self composite T-scores, Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) average score, 50% responder rate based on ADHD-RS-5 total

score, the hyperactivity/impulsivity and inattention subscales of the ADHD-RS-5, and the Stress Index for Parents of Adolescents (SIPA) total score. SPN-812 safety and tolerability are assessed using adverse events, clinical laboratory tests, vital signs, physical examinations, electrocardiograms, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Completers can enroll in an openlabel extension. As of December 20, 2018, topline results are expected by the end of the first quarter of 2019. Based on efficacy and safety in the Phase 2 program and supported by three recently completed Phase 3 studies, two in children and one in adolescents, SPN-812 is being investigated in this fourth randomized, placebo-controlled, Phase 3 study for the treatment of adolescent ADHD

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Neurotherapeutics. 2019;16:914-15.

EXTENDED-RELEASE VILOXAZINE (SPN-812) FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN ADOLESCENTS: TOPLINE RESULTS OF A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (P302).

Nasser A, Hull JT, Chowdhry FA, et al.

SPN-812, a structurally distinct, bicyclic norepinephrine reuptake inhibitor with selective serotonergic activity, is in development for ADHD treatment in children/adolescents. Here we present results of the first Phase 3 study evaluating the efficacy and safety of 2 SPN-812 doses for ADHD treatment in adolescents. P302 was a randomized, double-blind, placebocontrolled, study of once-daily SPN-812 monotherapy dosed at 200mg or 400mg in adolescents ages 12-17with ADHD. Key inclusion criteria were DSM-5 diagnosis of ADHD confirmed with theMINI-KID, ADHD-RS-5 score ΓëÑ28, CGI-S score ΓëÑ4, and free from ADHD medication ΓëÑ1 week before randomization. Subjects were randomized 1:1:1 to placebo:200mg SPN-812:400mg SPN-812. The treatment period included up to 1 week of titration and 5 weeks of maintenance. The primary efficacy endpoint was change from baseline (CFB) to end of study (EOS) in ADHD-RS-5 total score. Selected secondary endpoints included ADHD-RS-5 hyperactivity/ impulsivity and inattention subscales and theCGI-I. Safety and tolerability were assessed using AEs, laboratory tests, vital signs, physical examinations, electrocardiograms, and the C-SSRS. The ITT population included 301 subjects (N=104, placebo; N=94, 200mg; N=103, 400mg). CFB to EOS in ADHD-RS-5 scores were -11.4 (placebo), -16.0 (200mg, p=0.0232), and -16.5 (400mg, p=0.0091). SPN-812 400mg reached statistical significance vs. placebo as early as week 1 (p=0.0085), which was maintained throughout the trial. CFB to EOS on the ADHD-RS-5 hyperactivity/impulsivity and inattention subscales were statistically significant vs. placebo in both SPN-812 groups, with p-values of 0.0069 (200mg) and 0.0005 (400mg), and 0.0424 (200mg) and 0.0390 (400mg), respectively. CGI-I scores at EOS were 3.0 (placebo), 2.5 (200mg, p=0.0042), and 2.4 (400mg, p=0.0003). Treatment-related AEs reported in ΓëÑ5% of SPN-812 subjects were somnolence, decreased appetite, fatigue, headache, and nausea. This Phase 3 study of 200mg and 400mg SPN-812 met the primary endpoint with robust statistical significance. SPN-812 exhibited a broad spectrum of efficacy across both the hyperactivity/impulsivity and inattention subscales of the ADHD-RS-5. The primary efficacy endpoint, CFB to EOS in ADHD-RS-5 total score, was met following 1 week of SPN-812 treatment; significance was maintained throughout the 6-week trial. In this study, SPN-812 was efficacious, well tolerated, and associated with low discontinuation rates

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Neurotherapeutics. 2019;16:915.

EXTENDED-RELEASE VILOXAZINE (SPN-812) FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN CHILDREN: TOPLINE RESULTS OF A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (P303).

Nasser A, Hull JT, Chowdhry FA, et al.

SPN-812, a structurally distinct, bicyclic norepinephrine reuptake inhibitor with selective serotonergic activity, is in development for ADHD treatment in children/adolescents. Here we present results of the second Phase 3 study evaluating the efficacy and safety of 2 SPN-812 doses for ADHD treatment in children. P303 was a randomized, double-blind, placebo-controlled, study of once-daily SPN-812 monotherapy dosed at 200mg

or 400mg in children ages 6-11 with ADHD. Key inclusion criteria were DSM-5 diagnosis of ADHD confirmed with the MINIKID, ADHD-RS-5 score ΓëÑ28, CGI-S score ΓëÑ4, and free from ADHD medication ΓëÑ1 week before randomization. Subjects were randomized 1:1:1 to placebo:200mg SPN-812:400mg SPN-812. The treatment period included up to 3 weeks of titration and 5 weeks of maintenance. The primary efficacy endpoint was change from baseline (CFB) to end of study (EOS) in ADHD-RS-5 total score. Selected secondary endpoints included ADHD-RS-5 hyperactivity/ impulsivity and inattention subscales and the CGI-I. Safety and tolerability were assessed using AEs, laboratory tests, vital signs, physical examinations, electrocardiograms, and the C-SSRS. The ITT population included 301 subjects (N=97, placebo; N=107, 200mg; N=97, 400mg). CFB to EOS in ADHD-RS-5 scores were -11.7 (placebo), -17.6 (200mg, p=0.0038), and -17.5 (400mg, p=0.0063). Both SPN-812 400mg and 200mg showed statistically significant differences from placebo starting at week 5 and continuing through week 8. CFB to EOS on the ADHD-RS-5 hyperactivity/impulsivity and inattention subscales were statistically significant vs. placebo in both SPN-812 groups, with p-values of 0.0020 (200mg) and 0.0039 (400mg), and 0.0087 (200mg) and 0.0248 (400mg), respectively. CGI-I scores at EOS were 3.1 (placebo), 2.6 (200mg, p=0.0028), and 2.6 (400mg, p=0.0099). Treatment-related AEs reported in Γ ëÑ5% of SPN-812 subjects were somnolence, decreased appetite, fatigue, headache, and upper abdominal pain. This Phase 3 study of 200mg and 400mg SPN-812 met the primary endpoint with robust statistical significance. SPN-812 exhibited a broad spectrum of efficacy across both the hyperactivity/impulsivity and inattention subscales of the ADHDRS-5. In this study, SPN-812 was efficacious, well tolerated, and associated with low discontinuation rates

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Nutr Health. 2018 Dec;24:279-84.

SUPPLEMENTATION WITH POLYUNSATURATED FATTY ACIDS (PUFAS) IN THE MANAGEMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Banaschewski T, Belsham B, Bloch MH, et al.

While pharmacotherapy and psychosocial interventions are recommended as the primary frontline treatment for attention deficit hyperactivity disorder (ADHD), alternative approaches to managing ADHD are becoming increasingly popular among patients and their families. Supplementation with polyunsaturated fatty acids (PUFAs) is an example of this. PUFA supplementation is not recommended by guidelines for managing ADHD; however, patients may still decide to use it. To provide direction to healthcare professionals (HCPs) managing ADHD, eight international experts in the field of adult and child ADHD came together for the Continuum Education Board: Omega Supplements in ADHD meeting. This commentary summarises the panel's consensus that current evidence suggests PUFA supplementation has a small beneficial effect on behaviour in children with ADHD, and that further high-quality research is needed to clearly evaluate and define its role in the management of ADHD of children, adolescents and adults. The panel concluded that in cases where patients use PUFA supplementation, HCPs should be comfortable explaining the potential gains that they may have and their possible side effects. The panel also concluded HCPs should not reinforce the idea that PUFA supplementation should replace treatment approaches with a more robust evidence base for managing ADHD

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Nutrients. 2020;12.

USE OF NON-PHARMACOLOGICAL SUPPLEMENTATIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A CRITICAL REVIEW.

Rosi E, Grazioli S, Villa FM, et al.

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents, with environmental and biological causal influences. Pharmacological medication is the first choice in ADHD treatment; recently, many studies have concentrated on dietary supplementation approaches to address nutritional deficiencies, to which part of non-responses to medications have been imputed. This review aims to evaluate the efficacy of non-pharmacological supplementations in children or adolescents with ADHD. We reviewed 42 randomized controlled trials comprised of the following

supplementation categories: polyunsaturated fatty acids (PUFAs), peptides and amino acids derivatives, single micronutrients, micronutrients mix, plant extracts and herbal supplementations, and probiotics. The reviewed studies applied heterogeneous methodologies, thus making it arduous to depict a systematic overview. No clear effect on single cognitive, affective, or behavioral domain was found for any supplementation category. Studies on PUFAs and micronutrients found symptomatology improvements. Peptides and amino acids derivatives, plant extracts, herbal supplementation, and probiotics represent innovative research fields and preliminary results may be promising. In conclusion, such findings, if confirmed through future research, should represent evidence for the efficacy of dietary supplementation as a support to standard pharmacological and psychological therapies in children and adolescents with ADHD

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Placenta. 2019 Aug;83:17-25.

PRETERM BIRTH SUBTYPES, PLACENTAL PATHOLOGY FINDINGS, AND RISK OF NEURODEVELOPMENTAL DISABILITIES DURING CHILDHOOD.

Raghavan R, Helfrich BB, Cerda SR, et al.

INTRODUCTION: Preterm birth (PTB) and in-utero inflammation are recognized risk factors of neurodevelopmental disabilities (NDDs); however, their combined role in NDDs is unknown. We examined the independent and joint association of PTB and placental histological findings with the childhood risk of NDDs (overall and by subgroups including autism spectrum disorder (ASD) and ADHD).

METHODS: We analyzed data from the Boston Birth Cohort, where mother-infant pairs were enrolled at birth and followed from birth onwards. Birth outcomes, placental pathology and NDDs were obtained from electronic medical records. Placental pathology was categorized using a standardized classification system proposed by the Amsterdam Placental Workshop Group.

RESULTS: PTB (all, including spontaneous, medically indicated) was an independent risk factor for NDDs. Placental histological chorioamnionitis (CA) and PTB additively increased the odds of NDDs (aOR: 2.16, 95% CI: 1.37, 3.39), as well as ADHD (aOR: 2.75, 95% CI: 1.55, 4.90), other developmental disabilities (aOR: 1.96, 95% CI: 1.18, 3.25) and possibly ASD (aOR: 2.31, 95% CI: 0.99, 5.39). The above associations were more pronounced in spontaneous than medically indicated PTB. PTB alone in the absence of CA only had a moderate association with ASD and ADHD. Placental maternal vascular malperfusion alone or in combination with PTB was not associated with the risk of NDDs.

DISCUSSION: Our study provided new insights on PTB and NDDs by further considering preterm subtypes and placental histology. We revealed that children of spontaneous PTB along with histological CA were at the highest risk for a spectrum of NDDs

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PLoS ONE. 2020;15.

EXECUTIVE FUNCTIONS, PERSONALITY TRAITS AND ADHD SYMPTOMS IN ADOLESCENTS: A MEDIATION ANALYSIS.

Krieger V, Amador-Campos JA, Gu+árdia-Olmos J.

Certain personality traits and cognitive domains of executive functions (EF) are differentially related to attention deficit hyperactivity disorder (ADHD) symptoms in adolescents. This study aimed to analyze the five-factor model (FFM) personality characteristics in adolescents with ADHD, and to examine whether EF mediate the relationships between FFM personality traits and ADHD symptoms. A comprehensive diagnostic assessment, including ADHD clinical interviews, ADHD rating scales, neuropsychological EF testing (i.e., working memory, flexibility and inhibition) and a personality assessment was carried out in a sample of 118 adolescents (75 ADHD and 43 control participants, 68% males), aged 12 to 16 years, and their parents and teachers. Adolescents with ADHD had lower scores than control participants on Conscientiousness and Agreeableness, and higher scores on Neuroticism. Structural equation models (SEM) showed that Conscientiousness directly influenced inattentive and hyperactive-impulsive symptoms, while Neuroticism, Agreeableness, and Extraversion directly affected hyperactive-impulsive symptoms. Only Conscientiousness exerted indirect effects on inattention, but not on hyperactivity-impulsivity symptoms, via EF; higher scores on Conscientiousness were related to higher scores on EF, which in turn were related to

lower scores on inattentive symptoms. These findings corroborate the relationships between ADHD symptoms, FFM personality traits and EF and indicate the mediating effect of EF on the relationship between Conscientiousness and inattention

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Psychiatry Clin Neurosci. 2019 Dec;73:762-63.

COMBINATION TREATMENT WITH GUANFACINE EXTENDED RELEASE AND BLONANSERIN FOR TOURETTE'S SYNDROME COMORBID WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kawabe K, Horiuchi F, Ueno SI.

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Psychiatr Invest. 2020;17:444-51.

WISC-IV INTELLECTUAL PROFILES IN KOREAN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Kim Y, Koh MK, Park KJ, et al.

Objective This study aimed to compare the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) profiles of children with attention deficit/hyperactivity disorder (ADHD) and typically-developing children (TC) in Korea. Methods The Korean version of the WISC-IV and the Advanced Test of Attention (ATA) were administered to 377 children and ado-lescents: 224 with ADHD (age 8.2-¦2.1 years, 182 boys) and 153 TC (age 8.7-¦2.4 years, 68 boys). Partial correlation and an analysis of covariance were used to investigate the relationship between the scores of the WISC-IV and the ATA. Results The mean score of the full-scale intelligence quotient was lower in ADHD children than in TC ($p<0.001$). In analyses control-ling for gender and with the full-scale intelligence quotient as a covariate, the working memory index (WMI) ($p<0.001$) and values of the Digit span subtest ($p=0.001$) of the WISC-IV were lower in the ADHD group than in TC. The WMI ($r=-0.26$, $p<0.001$) and its subtest Arithmetic scores ($r=-0.25$, $p<0.001$) were negatively correlated with Commission errors on the auditory ATA. Conclusion Children with ADHD have significantly lower WMI scores, which were clinically correlated with Commission errors on the auditory task of the ATA. Thus, the WMI is an indicator of attention deficit in children with ADHD

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Psychiatry Res. 2020;290.

BENEFIT OF METHYLPHENIDATE USE IN A PATIENT WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND HEART DISEASE: A CASE REPORT AND LITERATURE REVIEW.

Machado YDC, Lopes GDA, Souza TT, et al.

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Psychol Med. 2019 Aug;49:1841-49.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND CLINICALLY DIAGNOSED OBESITY IN ADOLESCENCE AND YOUNG ADULTHOOD: A REGISTER-BASED STUDY IN SWEDEN.

Chen Q, Hartman CA, Kuja-Halkola R, et al.

BACKGROUND: A recent family study of young adult males suggests a shared familial liability between attention-deficit/hyperactivity disorder (ADHD) and high body mass index (BMI), and a genome-wide meta-analysis reported a genetic correlation of 0.26 between ADHD and BMI. To date, it is unclear whether these findings generalize to the relationship between ADHD and clinically diagnosed obesity.

METHOD: By linking the Swedish national registers, we identified 25 38 127 individuals born between 1973 and 2000, together with their siblings and cousins. The risk of clinical obesity in individuals with ADHD was compared with the risk in those without ADHD. The relative contributions of genetic and environmental factors

to the association between ADHD and clinical obesity were examined via assessment of the familial co-aggregation of the two conditions and quantitative genetic analysis.
RESULTS: Individuals with ADHD were at an increased risk of clinical obesity compared with those without (risk difference 3.73%, 95% confidence interval (CI) 3.55-3.90%; risk ratio 3.05, 95% CI 2.95-3.15). Familial co-aggregation of ADHD and clinical obesity was detected and the strength of the co-aggregation decreased by decreasing genetic relatedness. The correlation between the liabilities to ADHD and clinical obesity can be entirely attributed to their genetic correlation (rg 0.30, 95% CI 0.17-0.44).
CONCLUSION: The association between ADHD and clinical obesity in adolescence and young adulthood can be entirely attributed to genetic underpinnings shared by the two conditions. Children with ADHD should be monitored for weight gain so that preventive measures can be taken for those on a suboptimal trajectory

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Psychol Med. 2019 Aug;49:1914-22.
TRAJECTORIES OF PSYCHIATRIC DIAGNOSES AND MEDICATION USAGE IN YOUTH WITH 22Q11.2 DELETION SYNDROME: A 9-YEAR LONGITUDINAL STUDY.
Kates WR, Mariano MA, Antshel KM, et al.
BACKGROUND: Chromosome 22q11.2 deletion syndrome (22q11DS) is associated with high rates of psychiatric disorders, including schizophrenia in up to 30% of individuals with the syndrome. Despite this, we know relatively little about trajectories and predictors of persistence of psychiatric disorders from middle childhood to early adulthood. Accordingly, we followed youth over four timepoints, every 3 years, to assess long-term trajectories of attention-deficit hyperactivity disorder (ADHD), anxiety, mood, and psychosis-spectrum disorders (PSDs), as well as medication usage.
METHODS: Eighty-seven youth with 22q11DS and 65 controls between the ages of 9 and 15 years at the first timepoint (T1; mean age 11.88 +/- 2.1) were followed for 9 years (mean age of 21.22 +/- 2.01 years at T4). Baseline cognitive, clinical, and familial predictors of persistence were identified for each class of psychiatric disorders.
RESULTS: Baseline age and parent-rated hyperactivity scores predicted ADHD persistence [area under curve (AUC) = 0.81]. The presence of family conflict predicted persistence of anxiety disorders (ADs) whereas parent ratings of child internalizing symptoms predicted persistence of both anxiety and mood disorders (MDs) (AUC = 0.84 and 0.83, respectively). Baseline prodromal symptoms predicted persistent and emergent PSDs (AUC = 0.83). Parent-reported use of anti-depressants/anxiolytics increased significantly from T1 to T4.
CONCLUSIONS: Psychiatric, behavioral, and cognitive functioning during late childhood and early adolescence successfully predicted children with 22q11DS who were at highest risk for persistent psychiatric illness in young adulthood. These findings emphasize the critical importance of early assessments and interventions in youth with 22q11DS

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Psychol Med. 2020 May;50:1203-13.
WHITE MATTER ENDOPHENOTYPE CANDIDATES FOR ADHD: A DIFFUSION IMAGING TRACTOGRAPHY STUDY WITH SIBLING DESIGN.
Chiang HL, Hsu YC, Shang CY, et al.
Background: Brain structural alterations are frequently observed in probands with attention-deficit/hyperactivity disorder (ADHD). Here we examined the microstructural integrity of 76 white matter tracts among unaffected siblings of patients with ADHD to evaluate the potential familial risk and its association with clinical and neuropsychological manifestations.
Methods: The comparison groups included medication-naÃ¯ve ADHD probands (n = 50), their unaffected siblings (n = 50) and typically developing controls (n = 50, age-and-sex matched with ADHD probands). Whole brain tractography was reconstructed automatically by tract-based analysis of diffusion spectrum imaging (DSI). Microstructural properties of white matter tracts were represented by the values of generalized

fractional anisotropy (GFA), fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD).
Results: Compared to the control group, ADHD probands showed higher AD values in the perpendicular fasciculus, superior longitudinal fasciculus I, corticospinal tract, and corpus callosum. The AD values of unaffected siblings were in the intermediate position between those of the ADHD and control groups. These AD values were significantly associated with ADHD symptoms, sustained attention and working memory, for all white matter tracks evaluated except for the perpendicular fasciculus. Higher FA and lower RD values in the right frontostriatal tract connecting ventrolateral prefrontal cortex (FS-VLPFC) were associated with better performance in spatial span only in the unaffected sibling group.
Conclusions: Abnormal AD values of specific white matter tracts among unaffected siblings of ADHD probands suggest the presence of familial risk in this population. The right FS-VLPFC may have a role in preventing the expression of the ADHD-related behavioral phenotype

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Psychophysiology. 2019 Sep;56:e13392.
REDUCED PREMOVEMENT POSITIVITY DURING THE STIMULUS-RESPONSE INTERVAL PRECEDES ERRORS: USING SINGLE-TRIAL AND REGRESSION ERPS TO UNDERSTAND PERFORMANCE DEFICITS IN ADHD.
Burwell SJ, Makeig S, Iacono WG, et al.
Brain mechanisms linked to incorrect response selections made under time pressure during cognitive task performance are poorly understood, particularly in adolescents with attention-deficit hyperactivity disorder (ADHD). Using subject-specific multimodal imaging (electroencephalogram, magnetic resonance imaging, behavior) during flanker task performance by a sample of 94 human adolescents (mean age = 15.5 years, 50% female) with varying degrees of ADHD symptomatology, we examined the degree to which amplitude features of source-resolved event-related potentials (ERPs) from brain-independent component processes within a critical (but often ignored) period in the action selection process, the stimulus-response interval, were associated with motor response errors (across trials) and error rates (across individuals). Response errors were typically preceded by two smaller peaks in both trial-level and trial-averaged ERP projections from posterior medial frontal cortex (pMFC): a frontocentral P3 peaking about 390 ms after stimulus onset, and a premovement positivity (PMP) peaking about 110 ms before the motor response. Separating overlapping stimulus-locked and response-locked ERP contributions using a "regression ERP" approach showed that trial errors and participant error rates were primarily associated with smaller PMP, and not with frontocentral P3. Moreover, smaller PMP mediated the association between larger numbers of errors and ADHD symptoms, suggesting the possible value of using PMP as an intervention target to remediate performance deficits in ADHD

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Psychosom Med. 2019 Sep;81:629-40.
MENTAL HEALTH OF A LARGE GROUP OF ADULTS WITH DISORDERS OF SEX DEVELOPMENT IN SIX EUROPEAN COUNTRIES.
de Vries ALC, Roehle R, Marshall L, et al.
OBJECTIVE: The aim of the study was to evaluate psychiatric symptoms among 1022 persons with various disorders of sex development (DSDs).
METHODS: The study was a European multicenter cross-sectional clinical evaluation in six countries. The mean (SD) age of participants was 32.1 (13.4) years. The cohort consisted of 325 individuals with Turner syndrome, 219 individuals with Klinefelter syndrome (KS), female individuals with various XY-DSD conditions (107 with and 67 without androgenization), 87 male individuals with XY-DSD conditions, and 221 female individuals with congenital adrenal hyperplasia. The Hospital Anxiety and Depression Scale, the Short Autism Spectrum Quotient, the Adult Attention-Deficit/Hyperactivity Disorder Self-Report Scale, and self-reported mental health history were used to assess psychiatric symptoms.
RESULTS: Across the six DSD diagnostic groups, clinical cutoff symptom scores were reached in 19.5% of participants for anxiety, in 7.1% for depression, in 4.1% for attention-deficit/hyperactivity disorder, and in

9.1% for autism. The mean depression and anxiety scores were higher compared with population norms in men with KS and men with XY-DSD. Compared with participants with other DSD conditions, men with KS reported significantly more mental health symptoms. Self-esteem, satisfaction with care, body dissatisfaction, and experiences of shame were associated with psychiatric symptoms in many DSD conditions.
CONCLUSIONS: A substantial minority of adults with DSD, with KS in particular, experience psychiatric morbidity. Across DSD conditions, adults may share feelings of shame. Developing a positive self-esteem and body image may be challenging. Multidisciplinary DSD care that involves specialized mental health support can be of important value.
TRIAL REGISTRATION: German Clinical Trials Register DRKS00006072

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Res Dev Disabil. 2020;104.

DISENTANGLING AUTISM SPECTRUM AND ATTENTION-DEFICIT/HYPERACTIVITY SYMPTOMS OVER DEVELOPMENT IN FRAGILE X SYNDROME.

Doherty BR, Longhi E, Cole V, et al.

Even genetic disorders associated with monogenic aetiologies are characterized by complex and variable risk for poor outcomes, highlighting the need to follow trajectories longitudinally. Here, we investigated the longitudinal relationships between attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) symptoms in a population at high risk for both: boys with fragile X syndrome. 59 boys with fragile X syndrome aged 3ΓÇô10 years old at entry participated in this study, and were followed up one and two years after their first visit. As expected, we found strong relationships over three timepoints for ADHD symptoms (as measured by the parent-rated Conners scale) and ASD symptoms (as measured by the Social Communication Questionnaire [SCQ]). In addition, using structural equation modeling (SEM) we found that ADHD symptoms at time 2 predicted ASD symptoms at time 3, suggestive of a causal relationship. Importantly, these relationships hold when including chronological age at entry to the study, as well as when including severity of impairment as measured by IQ, and their effects on both ASD and ADHD symptoms do not reach significance. This result highlights the need to study outcomes longitudinally and it informs the comorbidity of the two symptom domains in FXS as well as their potential directionality, both of which have been little researched. In addition, our findings may suggest a future need to study how ADHD symptoms and their treatment impact individuals with ASD

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Soc Work Health Care. 2019 Sep;58:807-24.

CHARACTERIZING BEHAVIORAL HEALTH-RELATED EMERGENCY DEPARTMENT UTILIZATION AMONG CHILDREN WITH MEDICAID: COMPARING HIGH AND LOW FREQUENCY UTILIZERS.

Lynch S, Pines J, Mutter R, et al.

While the frequency of children's behavioral health (BH)-related visits to the emergency department (ED) is rising nationwide, few studies have examined predictors of high rates of ED use. This study examines Florida Medicaid claims (2011-2012) for children age 0-18 who were seen in an emergency department (ED) for behavioral health (BH) conditions. A logistic regression model was used to explore factors associated with frequent ED use and patterns of psychotropic medication utilization. The majority (95%) of patients with at least one BH-related ED visit had three or fewer of these visits, but 5% had four or more. Seventy-four percent of ED visits were not associated with psychotropic medication, including over half (54%) of visits for attention deficit hyperactivity disorder (ADHD). Frequent ED use was higher among older children and those with substance use disorders. The implementation of interventions that reduce non-emergent ED visits through the provision of care coordination, social work services, and/or the use of community health workers as care navigators may address these findings

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Stem Cell Res. 2019 Dec;41:101635.

AN INDUCED PLURIPOTENT STEM CELLS LINE (SDQLCHI014-A) DERIVED FROM URINE CELLS OF A PATIENT WITH ASD AND HYPERACTIVITY CARRYING A 303KB DE NOVO DELETION AT CHR3P26.1 IMPLICATING GRM7 GENE.

Yang X, Liu Y, Zhou T, et al.

Autism spectrum disorder (ASD) is a childhood-onset neurodevelopmental disorder challenged in social reciprocity and restrictive repetitive behaviors. Here, we generated an induced pluripotent stem cell (iPSC) line SDQLCHi014-A from a patient with ASD and hyperactivity, carrying a 303kb de novo deletion at chr3p26.1 implicating GRM7 gene by reprogramming urine cells with non-integrating vectors. SDQLCHi014-A have shown full pluripotency, differentiation capacity and genetic stability. This iPSC line provides a valuable resource to study the molecular mechanisms underlying ASD

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The Lancet Child and Adolescent Health. 2020;4:435-43.

ASSOCIATION BETWEEN METHYLPHENIDATE TREATMENT AND RISK OF SEIZURE: A POPULATION-BASED, SELF-CONTROLLED CASE-SERIES STUDY.

Man KKC, Lau WCY, Coghill D, et al.

BACKGROUND: Individuals with attention-deficit hyperactivity disorder (ADHD) are at increased risk of seizures. Stimulant medications such as methylphenidate are the most commonly prescribed treatment for ADHD, but the association between their therapeutic use and the risk of seizures is unclear. We aimed to investigate the association between methylphenidate treatment and the risk of seizure.

METHODS: For this population-based observational study, we used the electronic medical record database of the Hong Kong Clinical Data Analysis And Reporting System to identify individuals aged 6-25 years who received at least one methylphenidate prescription during the study period. Individuals with records of seizure or epilepsy before the study period were excluded. Individuals treated with methylphenidate who had seizures during the study period were included in the subsequent analyses, and a self-controlled case-series design was used to control for time-invariant individual characteristics. We did additional analyses using skin infection as a negative control outcome. We compared relative incidence of seizure during periods when individuals were exposed to methylphenidate with that during non-exposed periods.

FINDINGS: Of 29 604 individuals prescribed methylphenidate between Jan 1, 2001, and Dec 31, 2017, 269 (199 males and 70 females) had incident seizures. The mean age at baseline was 6·66 years (SD 2·01) and the median age at the incident seizure was 9·69 years (IQR 7·62-12·99). The overall incidence of seizure during methylphenidate treatment was 4·4 per 10 000 patient-years. We detected an increased risk of seizure during the first 30 days of methylphenidate treatment compared with that during non-exposed periods, with an incidence rate ratio of 4·01 (95% CI 2·09-7·68). No increase in risk was identified during the following 31-180 days of treatment (1·13, 0·56-2·25) or during subsequent treatment (1·38, 0·92-2·07). We did not identify an increased risk in any risk window for the negative control outcome analysis. No individuals died because of a seizure during the study period.

INTERPRETATION: The incidence of seizures was higher in the period immediately after the start of methylphenidate treatment than in the non-exposed period. No increased risk was observed during continuation of methylphenidate treatment. The association between methylphenidate treatment and seizures immediately after initiation of medication can be seen as a potential safety signal. Monitoring of neurological outcomes in individuals with ADHD is recommended when they first start methylphenidate treatment.

FUNDING: Hong Kong Research Grants Council

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World J Biol Psychiatry. 2020.

NOVEL PLASMA METABOLITE MARKERS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IDENTIFIED USING HIGH-PERFORMANCE CHEMICAL ISOTOPE LABELLING-BASED LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY.

Wang L-J, Chou W-J, Tsai C-S, et al.

Objectives: Metabolites are the intermediate and final products of biological processes and ultimately reflect the responses of these processes to genetic regulation and environmental perturbations, including those involved in attention deficit/hyperactivity disorder (ADHD).

Methods: We identified a quantitative profile of plasma metabolites in 58 ADHD patients (mean age 9.0 years, 77.6% males) and 38 healthy control subjects (mean age 10.2 years, 55.3% males) using the high-performance chemical isotope labelling (CIL)-based liquid chromatography-mass spectrometry (LC-MS). Using a volcano plot and orthogonal projections to latent structure-discriminant analysis (OPLS-DA), we determined nine metabolites with differentially expressed levels in ADHD plasma samples.

Results: Compared to the control group, the plasma levels of guanosine, O-phosphoethanolamine, phenyl-leucine, hypoxanthine, 4-aminohippuric acid, 5-hydroxylysine, and L-cystine appeared increased in the ADHD patients, whilegentisic acid and tryptophyl-phenylalanine were down-regulated in the patients with ADHD. We found that the plasma levels of all nine metabolites were able to discriminate the ADHD group from the control group. Levels of O-phosphoethanolamine, 4-aminohippuric acid, 5-hydroxylysine, L-cystine, tryptophyl-phenylalanine, and gentisic acid were significantly correlated with clinical ADHD symptoms.

Conclusions: This study is the first to use the CIL-based LC-MS to profile ADHD plasma metabolites, and we identified nine novel metabolite biomarkers of ADHD

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PATHOPHYSIOLOGICAL MECHANISMS OF AUTISM IN CHILDREN .

Chernov AN.

Based on the analysis of literature, the authors describe the neuropathophysiological mechanism of the formation of synapses, synaptic transmission and plasticity, which may underlie the pathogenesis of autism. The results of some studies confirm the involvement of aberrant expression of genes and proteins of synaptic contacts, cell adhesion molecules p120ctn, CNTN5, CNTN6, activation of NMDA glutamate, TrkB, p75 receptors, Ca2+-input, BDNF, serotonin and testosterone. This leads to an imbalance in the exciting, inhibitory synaptic transmission and forms of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) at the level of individual neurons and their chains due to suppression of GABA synthesis, expression of its ionotropic and metabotropic receptors, G proteins, NGF, TrkA receptors, a reduction in the number of GABAergic neurons, their contacts and disruption of differentiation. The pathology of the nuclei of the thalamus, especially the reticular nucleus (RN), is associated with a disturbance of the expression of the subunits of metabotropic GABA+¦ receptors, Ca2+ channels, GABA excretion and the work of chlorine transmitters. These failures do not ensure the inhibitory effect of OC on the exciting associative and ventral nuclei of the thalamus, nor modify the incoming information to the cerebral cortex (CC) from these thalamus nuclei, the dentate gyrus of the hippocampus and the nuclei of the reticular formation. Information propagating into the somatosensory and associative regions of CC is not modified by mirror neurons (MN) when performing arbitrary actions, which prevents the formation of an adequate image in the neural networks of the associative cortex and promotes the development of hyperexcitability, irritability, increased visual and auditory sensitivity, anxiety, and the ability to form a holistic image based on the actions of other people

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RESEARCH ARTICLE Open Access

Emergency department attendance for injury and behaviours suggestive of attention deficit hyperactivity disorder (ADHD): a cross-sectional study

Ester Conversano[1*], Alice Tassinari[1], Lorenzo Monasta[2], Aldo Skabar[3], Matteo Pavan[3], Alessandra Maestro[4], Egidio Barbi[1,3] and Giorgio Cozzi[3]

Abstract

Background: The study aimed to investigate if the behaviours suggestive of ADHD were more frequent in a population of children attending the Emergency Department (ED) for injuries, rather than for other causes.

Methods: A cross-sectional study was carried out. Patients, aged 6 to 17 years, attending the ED for acute injuries and other causes were considered cases and controls, respectively. We used a questionnaire, which investigates the presence in the child of inattention, hyperactivity, and impulsivity. The primary outcome was the number of children with behaviours suggestive of ADHD in cases and controls.

Results: Five hundred forty-five children were enrolled, 251 with injuries and 294 with other complains. Twenty two out of two hundred fifty one (9%) children visited for injuries, and 30 out of 294 (10%) visited for other causes had behaviours suggestive of ADHD ($p = 0.661$). Among these cases, children with evocative ADHD scores had a higher probability (OR 4.52; 95% CI 1.45–14.04; $p = 0.009$) of having had more than five previous ED accesses due to injury, compared to the others.

Conclusions: This study did non shown a difference in behaviours suggestive of ADHD between cases and controls, but identified a population of children with behaviours suggestive of ADHD who more frequently access the ED for injuries.

Keywords: Screening, Treatment, Neurodevelopmental disorders, Inattentiveness, Impulsiveness, Trauma

What is already known?

- During their life, patients with ADHD are at risk of repeated injuries.
- The number of injuries could be decreased by an early diagnosis and appropriate treatment, but there is no agreement about a screening for ADHD in children accessing the ED for injuries

What is new?

- There is a population of children with behaviours suggestive of ADHD with a history of repeated ED accesses for injuries.
- Addressing this population of children, the development of a specific screening tool for behaviours suggestive of ADHD could be considered.

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Background

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children

and adolescents, with a prevalence that varies between 3 and 5% [1]. It is characterised by inattention, hyperactivity and impulsivity, causing impairment of daily activities [2–5].

Accidents in children and adolescents are the most common cause of visits to the emergency department (ED) and among the leading causes of morbidity and mortality in Europe [3]. Previous studies suggest that children affected by ADHD are exposed to a higher risk of severe accidental injuries due to hyperactivity and decreased vigilance [6–13]. Moreover, evidence shows that early diagnosis and treatment significantly reduces ADHD related comorbidity [14, 15]. However, no current indication exists to identify the presence of ADHD in patients who are admitted to EDs for repeated or severe traumas.

Previous studies performed in a paediatric ED setting did not reach a decisive verdict regarding any increased risk of injuries in children affected by ADHD [16, 17]. This study aimed to assess whether the frequency of visits to our paediatric ED due to trauma or injury was higher than the frequency of those who accessed the service for other causes among subjects with inattention and hyperactivity behaviours. The primary study outcome was to determine the number of patients with behaviours suggestive of ADHD in cases and controls. The second was to compare the rate of past injuries reported by parents among children with positive and negative scores for ADHD behaviours in all the cases examined in our ED.

Methods

A cross-sectional study was carried out from May to September 2017 at the paediatric ED of the tertiary care children's hospital Institute for Maternal and Child Health – IRCCS "Burlo Garofolo" of Trieste, Italy. The study protocol received approval from the Bioethics Committee of Friuli Venezia Giulia (CEUR-2017-Os-124-BURLO).

Patients eligible for the study were children attending the ED aged from 6 to 17 years old. The exclusion criteria were non-Italian speakers, patients with reported developmental delay, irreparable hearing, visual or intellectual delay, musculoskeletal or neurological diseases and non-self-caused-injury. Enrolment was carried out for approximately 6 hours per day, in the presence of a specially trained research assistant.

Children attending the ED for acute injuries, defined as trauma, wounds or burns, were included in the study group. Children attending the ED for causes other than injuries were included in the control group.

After the usual ED care and before the hospital discharge, the research assistant approached the parents of the injured and non-injured children for the enrolment. All children's parents signed informed consent to participate in this study. We collected data on age, sex and nursing triage category of each patient using the Italian national triage category system consisting of four priority levels with increasing severity [from white (not urgent), to green (minor urgencies), yellow (urgent) and red (emerging/resuscitation)]. Parents were asked to complete the SCOD-Parent Rating Scales-Revised questionnaire for ADHD symptoms [17]. Parents were also asked how many times their child had visited the ED or been admitted to hospital for treatment of trauma, fractures and/or wounds needing suturing previously, and if the child was previously diagnosed with ADHD or was treated for ADHD.

The SCOD-Parent Rating Scale is a revision of the Disruptive Behaviour Disorder Rating Scale translated and adapted into Italian, and extensively tested and implemented in the Italian population. The SCOD-Parent Rating Scale questionnaire consists of 42 items following the criteria of the Attention Deficit Hyperactivity Disorder of the Diagnostic and Statistical Manual of Mental Disorders. The answers to each question are based on a rating scale from "0 = never", "1 = occasionally", "2 = often", or "3 = very often" [17, 18]. As the aim of the study was not to diagnose ADHD in an ED setting, but rather to assess the presence of inattention and impulsivity as behaviours suggestive of ADHD, we requested answers to only nine of the SCOD questions related to these two symptoms. The behaviours suggestive of ADHD were defined by a score higher than the threshold of the inattention (≥14 points, range 0–27) and impulsivity / hyperactivity (≥12 points, range 0–27). These cut-offs represent the fifth percentile for these symptoms for males. Females have lower cut-off scores, 11 and 9 respectively, but we decided to use the cut-off for males for the entire population, in order to include only females with highly suggestive symptoms.

Statistical analysis

Data were described as frequencies and percentages, and as medians and interquartile ranges (IQR). Statistical significance ($p < 0.05$) was calculated according to the two-tailed exact Fisher test for contingency tables and using a Mann-Whitney rank sum test for the comparison between cases and controls in the case of continuous variables. To study the association between having had or not more than 5 previous ED visits for injuries and having or not having symptoms suggestive of ADHD, we conducted a bivariate (thus unadjusted) logistic regression analysis. All analyses were done using Stata/IC 14.2 (StataCorp LLC, College Station, USA).

Results

During the study period, 642 eligible children were approached. Fifty-six of them declined to participate and

41 patients were excluded from the study (16 did not complete the questionnaire, seven were unable to communicate in Italian, five left the ED without returning the questionnaire, nine presented intellectual delay, four had non-self-caused-injuries) (Fig. 1). We enrolled 545 children aged between 6 and 17 years. Among these, 251 patients visited the ED for injuries (46%), and 294 visited for other causes (54%).

The characteristics of the enrolled patients are described in Table 1. Cases and controls did not differ significantly regarding age. However, the number of males was significantly higher in the case group. The 294 patients enrolled in the control group attended our ED for the following reasons: 176 for infections, 31 for gastrointestinal diseases excluding infection, 27 for dermatological problems, 24 for neurological diseases, 14 for cardiological diseases, 11 patients for orthopaedic reasons other than trauma, eight for gynaecological diseases, and three for endocrinological and haematological diseases.

Among all patients, 37 children (7%) obtained a score higher than or equal to 14 in the questions related to inattention, and 28 children (5%) obtained a score higher than or equal to 12 in the hyperactivity/impulsivity questions.

Among the children who participated in our ED due to injury, 22 showed behaviours suggestive of ADHD, while in the control group, there were 30 without statistically significant differences between the groups ($p = 0.661$) (Table 2).

Children with scores evocative of ADHD ($n = 22$) showed a probability four and a half times higher (OR 4.52; 95% CI 1.45–14.04; $P = 0.009$) of having had more than 5 previous ED visits for injuries, compared to the children of the same group without ADHD behaviours ($n = 229$). On the other hand, there was no difference in the frequency of past fractures, the need for previous suturing or antecedent injury-related hospitalisations in children with scores suggestive of ADHD (Table 3).

Discussion

This study did not show any differences in behaviours suggestive of ADHD in children and adolescents visiting the ED for injuries compared to other causes. Nevertheless, we detected a population of patients with

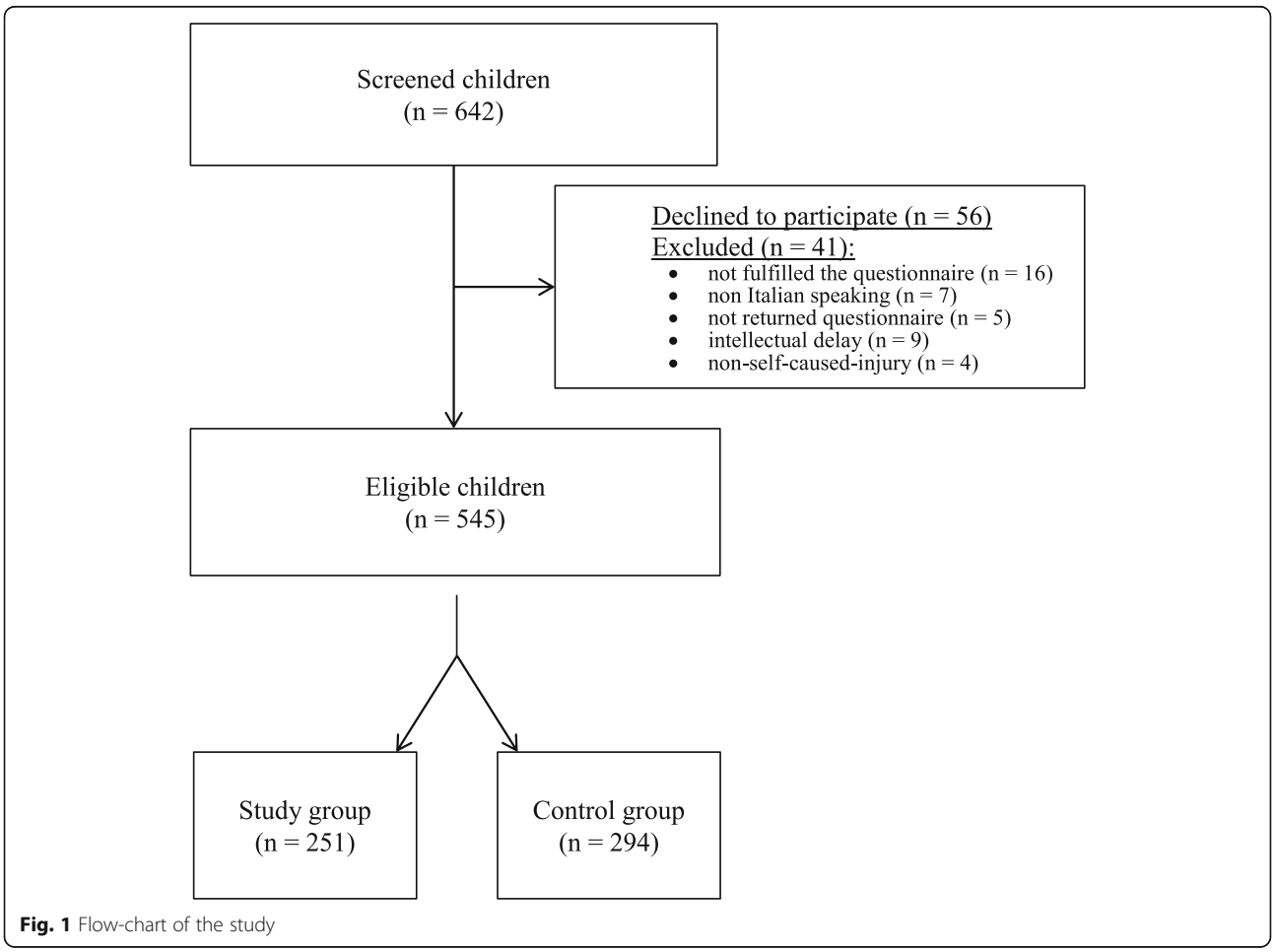

Fig. 1 Flow-chart of the study

Table 1 Description of cases (patients attending the emergency department for injuries) and controls (patients attending for other causes but injuries). Numbers in the table are frequencies and percentages or medians and interquartile ranges. *P*-values are the result of two-tailed Fisher exact tests for categorical variables and Mann-Whitney rank-sum tests for continuous variables

	Cases (251)	Controls (294)	*p*-value
Sex	Males = 164 (65%)	Males = 139 (47%)	$p = 0.000$
Age (years)	11.4 (8.6–13.8)	10.6 (8.1–14.3)	$p = 0.424$
Triage code	White, 46 (18%) Green, 187 (75%) Yellow, 18 (7%)	White, 97 (33%) Green, 175 (60%) Yellow, 22 (7%)	$p = 0.000$
For cases: type of injury For controls: main diagnoses	Trauma, 143 (57%) Minor wound, 29 (12%) Major wound, 26 (10%) Compound fracture, 42 (17%) Displaced fracture, 11 (4%)	Infection, 176 (60%) Gastrointestinal excluding infection, 31 (10%) Dermatologic, 27 (9%) Neurologic, 24 (8%) Cardiologic, 14 (5%) Ortopedics excluding trauma, 11 (4%) Ginecologic, 8 (3%) Endocrinologic/hematologic, 3 (1%)	

behaviours suggestive of ADHD whose history was remarkable for numerous injury-related ED visits.

Previously published evidence is discordant about the effects of ADHD on children attending the ED because of trauma: one study showed a 3-fold higher risk of being affected by ADHD than controls. Another similarly found a double risk of having higher scores on the Conners' scale [8, 19]. However, these results were challenged by another report, which showed that children visiting the ED with injuries were no more likely than non-injured children to have unrecognised ADHD, based on parental screening [9].

It is not possible to diagnose ADHD within the ED setting, and nor was this the aim of this study. Nevertheless, this report shows that the core behaviours of ADHD, such as inattention and hyperactivity/impulsivity, could be explored with a brief and focused questionnaire. Surprisingly, we found a population of children with behaviours suggestive of ADHD who had numerous previous injury-related ED visits. This finding supports previous studies that show that a history of repeated traumas, head injuries, or burns are potential indicators of ADHD [20, 21].

Injuries are the most common complication due to the hyperactivity and inattention, and children with ADHD have double the risk of dying compared to peers without ADHD. This increased risk is related to accidents, and it rises to five times by adulthood [14]. Specific treatment for ADHD reduces comorbidities such as injury rate and trauma-related ED visits by up to 43%, as well as substance use disorders, behavioural impairments and severe traffic accidents [22]. The authors underline that specific therapy appears to be more effective the sooner it is started [23]. With specific treatment, we are able to reduce the risk of injury and death; therefore, we should consider the implementation of effective screening strategies to detect ADHD in the ED. Future studies should investigate the efficacy of a questionnaire used in the ED for patients with a history of repeated injuries, to maximise the chances of early detection of children with behaviours suggestive of ADHD. These measures may allow early diagnosis, preventing severe ADHD-related impairments, which could occur from childhood to adulthood.

This study presents some limitations. First of all, the limited sample size and the lack of red codes may have conditioned the results of the primary outcome. We decided to exclude children with developmental delay, as a category of patients at higher risk for symptoms of

Table 2 Differences between cases and controls for SCOD scores and ADHD related items. Numbers in the table are frequencies and percentages or median and interquartile ranges. *P*-values are the result of two-tailed Fisher exact tests for categorical variables and Mann-Whitney rank-sum tests for continuous variables

	Cases (251)	Controls (294)	*P*-value
Previous ADHD diagnosis	10 (4%)	4 (1%)	$p = 0.061$
Inattention score (items 1 to 9)	4 (1–8)	4 (1–7)	$p = 0.395$
Inattention score ≥ 14	15 (6%)	22 (7%)	$p = 0.501$
Impulsivity/hyperactivity score (items 10 to 18)	2 (1–5)	3 (0–5)	$p = 0.859$
Impulsivity/hyperactivity score ≥ 12	13 (5%)	15 (5%)	$p = 1.000$
ADHD suggestive symptoms (positivity to SCOD-G questionnaire)	22 (9%)	30 (10%)	$p = 0.661$

Table 3 Patients attending the emergency department for injuries (cases): differences between patients with positivity vs. negativity to ADHD suggestive symptoms. *P*-values are the result of two-tailed Fisher exact tests for categorical variables and Mann-Whitney rank-sum tests for continuous variables

	P-SCOD (22)	N-SCOD (229)	TOTAL (251)	*p*-value
Sex				***P = 1.000***
Females	7 (32%)	80 (35%)	87 (35%)	
Males	15 (68%)	149 (65%)	164 (65%)	
Age	10.3 (8.3–13.0)	11.5 (8.7–13.9)	11.4 (8.6–13.8)	***P = 0.426***
Triage code				***P = 0.389***
white	4 (18%)	42 (18%)	46 (18%)	
green	15 (68%)	172 (75%)	187 (75%)	
yellow	3 (14%)	15 (7%)	18 (7%)	
red	0	0	0	
N. of previous ED accesses				***P = 0.017***
≤ 5	17 (77%)	215 (94%)	232 (92%)	
> 5	5 (23%)	14 (6%)	19 (8%)	
Previous sutures				***P = 0.268***
None	10 (45%)	133 (58%)	143 (57%)	
1–5	12 (55%)	96 (42%)	108 (43%)	
Previous fractures				***P = 0.230***
None	18 (82%)	155 (68%)	173 (70%)	
1–9	4 (18%)	73 (32%)	77 (30%)	
Previous hospitalizations related to injuries				***P = 0.071***
none	17 (77%)	207 (90%)	214 (85%)	
1–5	5 (23%)	22 (10%)	27 (10%)	

ADHD. Moreover, we were not able to enrol patients 24 h a day, so it can be a possible bias. We also took into consideration only one part of the SCOD questionnaire, intending to focus only on behaviours considered highly suggestive of ADHD. Moreover, our cut-off scores suggestive of ADHD were based on symptoms in males, thus only including females with high scores. We did not perform a separate analysis for already diagnosed ADHD patients in which the treatment may have influenced the symptoms' scores. Finally, we used rating scales based exclusively on subjective observations of parents and we therefore cannot exclude some recall bias regarding the secondary outcomes.

Conclusion

In this series, the behaviours suggestive of ADHD were not presented more frequently in patients who visited the ED for lesions compared to other causes, so our results do not support a screening for ADHD symptoms in the ED. Nevertheless, we found a population of patients with behaviours suggestive of ADHD and an unusual history of injury-related ED visits. This specific population of children may benefit from a tool to identify ADHD suggestive symptoms in the ED. Future studies could be aimed at developing and validating a specific questionnaire and better identifying children who could benefit from this screening.

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder; ED: Emergency department; IQR: Interquartile ranges; SCOD: Scala di valutazione dei Comportamenti Dirompenti, i.e. Evaluation Scale of Disruptive Behaviour

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Authors' contributions

GC, EB, AS contributed in the conceptualization and design of the study. AT collected data from participants of the study. LM contributed in statistical analysis and data curation.EC, GC, MP, LM wrote the draft of the manuscript. EB, AM, GC contributed review and editing the manuscript. The authors have read and approved the manuscript; all the authors gave final approval of the version to be published.

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Availability of data and materials

The datasets used and analyzed during the current study are not publicly available due to their containing information that could compromise the

privacy of study participants, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study protocol received approval from the Bioethics Committee of Friuli Venezia Giulia (CEUR-2017-Os-124-BURLO).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Publisher's Note

Working Memory and Decision making in children with ADHD: an analysis of delay discounting with the use of the dual-task paradigm

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SUBJECT AREAS
Psychiatry

KEYWORDS
ADHD, decision-making, delayed discounting, working memory load, digit span

Abstract

Objective

Deficits in working memory tasks have been widely documented in Attention Deficit Hyperactivity Disorder (ADHD) studies. The aim of this study is to evaluate the effects of working memory load in impulsivity during decision-making processes. A delayed discounting (DD) paradigm was used, comparing children with ADHD and age matched controls.

Method

Thirty-two children equally divided with typical development or ADHD between 8 and 10 years of age were assigned to sessions of a dual-task paradigm. The first task was a forced dual choice between different amount of moneys at different time delay, while the second task was the repetition of a random series of digits with different lengths.

Results

Compared to peers with typical development, delayed discounting was significantly stronger in children with ADHD and for heavier memory load conditions. Furthermore, the memory load impact was stronger in children with ADHD compared to children with typical development.

Discussion

Results are discussed in terms of the relation between working memory load and decision-making processes.

Introduction

Psychological and economic studies consider ways in which gain, losses and probabilities are associated and combined to generate informed choices. In such studies, the attention has been focused on determine whether the promptness with which a reward is obtained is an important factor in the process of decision-making [2][14][21][31][42][43]. Delay discounting (DD), which underlies decision-making, is the cognitive process that allows the individual to compare values between the immediate and delayed consumption of a determined commodity. In other words, DD is the depreciation of the value of a reward related to the time that it takes to be released [40].

The process of decision-making is based on the idea of choosing between alternative behaviours that

may involve a short-term sacrifice for long-term gain. In the same way, the DD task performed in this study implies a series of choices between receiving a small but faster (usually immediate) reward or a larger but delayed reward (DR) [29].

The DD task, in which one chooses between sooner/smaller or later/larger rewards, has proven useful in revealing deficits in executive functioning in various clinical groups [6][48]. Individual differences that are likely to occur in DD explain important functional differences in decision-making. For example, some people are likely to engage in temporary “myopic decisions” defined as the inability of individuals to realise that their action might implicate consequences [34][35]. Such decisions facilitate immediate choices but are impulsive or better only in the short period, as the immediate results they lead to are overestimated compared to those deferred. Temporarily myopic decision-making (impulsivity), characterizes many people and DD methods have been used to study their decision-making skills.

Most studies using the DD paradigm characterize an individual's choice, by generating a discount function, that models the effect of delay on subjective value of later rewards [33][53]. The subjective value V of a reward can be estimated using the present value of the delayed reward and is described mathematically as a hyperbolic curve with the following equation:

$$V = A / 1 + k * D$$

where D is the delay in delivery of the reward, and k is a free parameter that describes the rate of discounting [35]. Smaller values of k indicate a lack of discounting and a preference for delayed rewards, while higher values indicate strong discounting and a preference for immediate rewards. The parameter k is the rate at which an individual disregards future rewards, with a larger k suggesting a greater DD.

Higher rates of DD are found in subjects who are willing to decline greater rewards available in the near future, and who show a preference for smaller rewards that are available immediately [53]. Greater willingness to wait for larger but delayed rewards (usually indicator of a lower DD), has been associated with less impulsivity [1], better cognition and executive function [9][49]. Thus, higher values

of *k* are indicative of high levels of impulsivity [54].

Studies have demonstrated a developmental progression of DD: children show very high values of *k*, instead, adults are more tolerant with delays and show relatively low *k* values [50][51]. However, subjects with ADHD may have higher indices of DD. Garon, Waschbüsch and Moore[27] showed that decision making in people with ADHD is less effective than the one in people without ADHD. People with ADHD may lack focus in decision-making processes, and this can lead them to wrong choices [4] [23][2].

Some aspects of the cognitive components of temporarily myopic decisions can be explained in terms of the extent of working memory (WM) [1][25][55]. The WM is a brain system that supports temporary storage and manipulation of the information necessary for complex cognitive tasks, such as language comprehension, learning and reasoning [7] [8]. WM involves subsystems to store and manipulate visual images or verbal information and contains a temporary representation of the flow of information into and out of memory [47]. WM tasks monitor the completion of goal-directed actions during distractions. WM processes include executive and attention control of short-term memory to integrate, process, dispose and retrieve information [13].

The multicomponent model of WM theory proposes a central executive that directs attention to relevant information, suppresses irrelevant information and inappropriate actions and coordinates cognitive processes when more than one task is carried out at the same time [7].

Some studies showed that WM deficits are associated with ADHD and impulsivity [15][36][41][45]. For example, individuals with low WM capacity are more susceptible to increased impulsive behaviour due to a lower capacity of working memory to modulate response inhibition [26]. Moreover, impulsive behaviour reflects a deficit on inhibition of control of immediate behaviour, planning and evaluation of future options [44].

In accordance with the results of Hinson, Jameson and Whitney [30] this study analyses the association between the executive control system, responsible for coordination between information used to

perform tasks of planning and decision making, and impulsivity [7]. Moreover, the influence of cognitive load on DD will be considered. A load of work memory in a dual-task paradigm will be used to determine the amplitude of the WM in the processes of thought and language [5][32]. In a typical dual-task, the participant will be asked to keep a series of numbers or letters in memory while performing the task of primary interest. This load occupies the verbal buffer and, also, it disrupts the attentional resources of the WM central executive component [8]. The manipulation of memory load will be used to interfere directly with the WM and to determine whether this interference has an impact on performance in the DD. Further, the dual-task paradigm will be used. The performance of the primary task (i.e. decision making) with the secondary task will be compared with a control condition that has a similar response to requests but does not require the maintenance of information in WM. Hypotheses of this study are as follows: (1) Children with ADHD in the Experimental Group (EG) find more difficult than control group (CG) to defer a reward; (2) once the memory load increases the deferment of rewards becomes increasingly hard for all participants (both EG and CG) and (3) the increase of memory load have a larger impact on the performance of EG than CG.

Methods

Recruited Population

N= 414 Italian children, aged 8 to 10 years old, attending 4th or 5th grade of public primary school in Lombardy, Northern Italy, were recruited. Referrals were obtained from professionals taking part in an ongoing research and placement training programmes. A first screening, administered by teachers, based on the Italian versions of the ADHD Rating Scale for Teachers (SDAI)[10][39] and the Disruptive Behavior Disorders Rating Scale (DBDRS)[38] were used to assess ADHD traits in the participants prior the beginning of the study.

Inclusion Criteria

Inclusion criteria for all participants were as follows: (1) had to be between 8 and 10 years of age, (2) have a score above 70 in the verbal and performance IQ on the Wechsler Intelligence Scale for

Children - IV Edition (WISC-IV), and (3) have no history of brain damage, epilepsy, psychosis, autism spectrum disorder, bipolar disorders (early-onset bipolar disorder), Tourette's syndrome, childhood depression, oppositional defiant disorder; (4) have no current aggressive behaviour or severe oppositional tendency; (5) have no hearing, visual, or physical disabilities, and (6) not being under psychiatric medication.

Furthermore, all participants had to show good understanding of the concepts of time and money. The Concepts of Time and Money Questionnaire (CTMQ) was developed for this study and is reported in the supplementary materials. The cut-off was set to 15 correct answers among 16 questions in both time and money.

Participants included in the EG also have a cut-off severity scores of 14 or higher in both ADHD-I (inattentive subgroup) and ADHD-H (hyperactive subgroups) subscales, i.e. ADHD-C criteria (combined inattentive and hyperactive subgroups) on SDAI and a clinical diagnosis of ADHD based on DSM-5[3] criteria obtained from a licensed clinical child psychiatrist. The diagnosis was further confirmed through an additional assessment by the consensus of experienced clinicians in the research team (i.e. child psychiatrists and clinical psychologists).

Measures

The SDAI is an ADHD questionnaire widely used in Italy, validated and standardized for the Italian population [11][46]. It is composed by eighteen items matching the symptom domain of ADHD as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3]. It has a reliability of 0.80 (Inattentive subscale) and 0.74 (Hyperactive/Impulsive), optimal discriminatory power and concurrent validity ($r > 0.95$;[39]. Its test-–retest reliability is respectively 0.83 and 0.81 for Inattentive and Hyperactive/Impulsive [37]. The DBDRS is a 45-question screening measure, completed by either parents or teachers, designed to identify symptoms of ADHD, oppositional defiant disorder, and conduct disorder in children and adolescents.

Participants

Teachers were asked to observe the recruited children for two weeks and to complete SDAI and DBDRS for each child. Subsequently, they had to report the frequency of any problematic behaviour according to a Likert scale from 0 (problematic behaviour never presents) to 3 scores (very often present) for each questionnaire.

Thirty children were eligible for the EG according to the ADHD-C criteria on SDAI and were further assessed. Subsequently, the research team administered to the eligible children the CTMQ. Each participant was asked to answer 16 open-ended questions on knowledge regarding the values of money and time. Based on the results, N=22 children were eligible for the EG.

WISC-IV [52], DBDRS and the Parent Interview for children Symptoms (PICS-IV) scales were administered. These scales aimed to identify disruptive behaviours disorders or other psychiatric disorders, together with getting information about school achievement from parents, teachers, and students themselves. After this test, N=6 children were excluded because diagnosed with oppositional defiant disorders (figure 1).

The selected children were individually examined by experienced professionals of the research team and parents were interviewed to confirm their authorisation to be part of the EG.

---------- Insert Figure 1 here ----------

N=16 children (11M:5F; mean age in years = 8.75; SD = .48) fully met the inclusion criteria and were enrolled as EG in the present study. A randomized block selection among other children eligible for the CG was used to ensure that CG was balanced for number of children and gender. N=16 children (11M:5F; mean age in years = 8.62; SD = .62) were randomly assigned to the CG. Demographic data for both experimental and control groups are summarised in Table 1.

The EG displayed significantly higher scores than CG on both SDAI hyperactivity, $t(22.4) = 38.5$, $p < .001$, SDAI inattention subscales, $t(15.0) = 70.5$, $p < .001$, while there were no significant statistical differences in IQ, $t(30) = 1.29$, $p = .208$.

---------- Insert Table 1 here ----------

Experimental Design

Each of the N=32 participant was asked to engage in an individual assessment where the dual-task paradigm was administered. The digit span of each participant was assessed before starting the individual assessment using the digit span forward in the WISC-IV [52]. Assessments' data are reported in the Supplementary Materials, sheet S1.

The first task consisted on a series of choices between a small monetary reward obtained after a shorter time and a larger monetary reward obtained after a longer time. The delayed reward option task comprised a series of 16 trials. In each trial, the participant was asked to select between two options e.g. the first option was always a smaller amount of money the same day, whilst the second option was a larger amount of money deferred in different periods of time. Each participant knew that there was no right or wrong choices. Trials comprises 4 possible rewards combinations: €1-€11, €2-€12, €3-€13 and €4-€14, with a reward difference always set to €10; and 4 possible time delays of 1 week, 1 month, 6 months and 1 year. The full set of results from the money/time option task is reported in the Supplementary Materials, sheet S2. An algorithm specifically designed for the test had select the order of the 16 trials randomly and balanced them among participants.

The second task was the memory load task. It consisted in memorising and repeating a series of random numbers using the same structure of the digit span forward in the WISC-IV [52]. In the digits forward task, the participant is required to listen and repeat the assigned sequence of numbers. Starting from a total of 3 digits, the number of digits to repeat would increase if the participants successfully manages to repeat all of them. A new number sequence was randomly generated before each trial.

If an error in repeating the digits is made, another series of the same digits is presented; if the participant fails also to repeat the second series, the task is stopped and the number of correct digits is recorded as the maximum digit span of the participant for that specific trial (see Supplementary

Materials, sheet S2).

A dedicated application was developed for the administration of the individual sessions. All sessions were administered in a quiet classroom of the school, equipped with computers, monitors, chairs and desks. Each session lasted 20 minutes and all participants were asked to sit in front of a monitor in order to complete the tasks. Three different conditions were tested in the same order for each participant: (1) delayed reward option task without the memory load task; (2) dual-task with delayed reward option task and the memory load task administered together, with half memory load and (3) dual task with full memory load.

Statistical analysis

All statistical analysis was run through SPSS software (v. 23, IBM Corporation, Armonk, NY, USA). The descriptive statistics of the dependent variables were examined. The dependent variable (the value of *k*) were submitted to repeated measure ANOVA with one between-subject factor (group), and two within-subject factors: (1) three memory load conditions (zero load, half load, full load) and (2) four time delays (1 week, 1 month, 6 months and 1 year); trials within the same condition but different monetary rewards were averaged together. The alpha-level was set to .05 for all statistical tests. All effect size and post-hoc tests' power are reported in sheet S3 of Supplementary Materials. The effect sizes were computed using partial eta-squared. Omnibus tests were evaluated with two-tailed alpha-level = .05. Planned pairwise comparisons were performed among groups using *t*-test and ANOVA, alpha-level was Sidak's corrected. Greenhouse-Geisser correction was used for effects failing the Mauchly's test of sphericity.

The initial full load was set to the maximum digit span forward minus one (*n*-1) that was preliminary assessed, while the half load was set to *n*/2 if *n* was even and (*n*-1)/2 if *n* was odd.

With reference to the primary task parameter, the inverse formula of was calculated: . *k* is a parameter that measures the decrease rapidity in subjective value over time. A *k* value of zero shows a certain preference for delayed choice, while higher *k* values show an increase in DD. In our analysis we will use euros for *A* and *V* and weeks for *D* (setting a month to 4 weeks) as units. The specific units

of measurement that have been chosen change the result only by a multiplicative factor, the choice is therefore irrelevant for the purposes of statistical analysis.

Preliminary ANOVA was carried out to examine the secondary task performance, assuming digit span as the dependent variable to ensure that the relevant variable was the memory load and not the memory span.

Ethics, consent and permissions

The study was conducted in accordance with the American Psychological Association's (APA) ethical standards. The study design was approved by the Human Ethics Committee of Cognitive Science, Psychological, Educational and Cultural Studies of the University of Messina approved the study protocol (Protocol n. 20015_34). All the parents of the children who took part in the study signed a written consent form.

Results

The Experimental and the Control Group performed equally well in the Digit Span Forward task, $t(30) = .582$, $p = .565$. Furthermore, there were no difference in time and money understanding on CTMQ: Time scale, $t(28.7) = 1.17$, $p = .253$, Money scale, $t(22.6) = 1.85$.

Assessment data for both experimental and control groups are summarised in Table 2.

---------- Insert Table 2 here ----------

For both groups of participants, the percentage of errors on the memory load task was 0% in the half load condition and 15% in the full load condition.

The preliminary analysis revealed no effects of Digit Span on the primary task results (see sheet S4 of Supplementary Materials).

In the primary analysis, both memory load, $F(2,29) = 33.8$, $p < .001$, $\eta^2 = .700$, and time delay, $F(3,28) = 110$, $p < .001$, $\eta^2 = .922$, were significant main effect on k in the multivariate test.

ANOVA revealed also a significant main effect of Group $F(1,30) = 228$, $p < .001$, $\eta^2 = .884$, post-hoc

comparison showed that EG>CG, with M = 1.04, S.E. = .041 for EG and M = .150, S.E. = .041 for CG, indicating that the EG showed higher DD value than CG. Furthermore, a significant Group × Memory Load interaction effect was found, F (2,29) = 17.2, $p < .001$, $\eta^2 = .543$, post-hoc comparison showed that DD became higher in EG when the memory load was heavier.

---------- Insert Figure 2 here ----------

All the other 2-ways and the 3-ways interaction were also significant. Group × Time interaction effect, F (3,28) = 75.3, $p < .001$, $\eta^2 = .890$, post-hoc comparison showed a larger decrease of k with time in the EG compared to CG, and a larger difference for shorter reward delays. We also found a Memory Load × Time interaction effect, F (6,25) = 11.8, $p < .001$, $\eta^2 = .740$. A post-hoc comparison showed a larger effect of memory load for shorter reward delays.

Finally, we found the 3-ways interaction effect among Memory Load, Time and Diagnosis, F (6,25) = 5.69, $p = .001$, $\eta^2 = .577$, revealed that the heightened effect of memory load for shorter reward delays was more accentuated for the EG. Group comparison for each condition is reported in table 3 and the difference in effect size is depicted in figure 3. The full analysis is reported in sheet S5 of Supplementary Materials.

---------- Insert Table 3 here ----------

---------- Insert Figure 3 here ----------

To test the robustness of the results we ran two ancillary analysis: in the first one we used a simple ranking for the delays (1, 2, 3, 4) instead of the number of weeks (1, 4, 26, 52); in the second one we used the number of delayed responses as a dependent variable instead of k. In both analyses the effects where significant and in the same direction as the primary analysis. Hence, the effect is not an

artefact of the specific formula used to study DD. The two ancillary analyses are reported in the supplementary materials in sheets S6 and S7.

Limitations

We chose a restricted range of age (8 to 10 years old) in order to focus the study on a specific age frame, this impacts on the generalisability of the study. Moreover, although the selection process adopted by this study made possible to create a detailed assessment of the participants, it reduced considerably the number of final participants, lowering the power of the study even if the results were statistically significant.

A school setting has been chosen for this study for practical reasons. However, the children had to drop out of class to do the assessment. Thus, the actual attention of the child while performing the tasks cannot be assured. In addition, as the children were from different schools and there were different examiners, the settings were the assessments were carried out and the examiners that assessed the children differed. That might have reduced the controllability of the experiment. However, for each school/setting the number of children in the EG and in the CG were the same, therefore confounding factors linked to the specific setting should be negligible in the group comparison.

Furthermore, one limitation of this study is given by the specific formula used to compute the parameter *k*, which is supposed to be a constant, and that has been found to vary in relation to different temporal intervals. Meaning that the equation chosen to define DD might be too simplistic. However, the supplementary analysis employed to double-check the results using different formulae showed that the behavioural results are robust enough to remain statistically significant regardless of the specific equation used to compute the values of *k*.

Discussion

All hypotheses of the study have been confirmed: (1) children with ADHD show higher levels of DD than control subjects, (2) once the memory load increases, deferring a reward becomes harder for

both children with ADHD and with typical development, and (3) the performances of children with ADHD are significantly worsened by the addition of a memory load.

The analysis of the results also confirmed that the number of delayed choices decreases in ratio with the increasing of the time gap between immediate and delayed options. This data confirms that the value that the individual attributes to the different choices decreases as the reward become more distant in time [28][29]. The present study provided the evidence to support such a conclusion by indicating further corroboration of the DD.

The findings of this experiment are consistent with the literature of the discounting parameter *k*, influenced by the chosen behaviours of the subject. As Green et al. [28][29] stated, the impulsivity pushes the individual to make suboptimal choices, as immediate reward is overvalued compared to those deferred. Under the conditions of the full memory load used in this study, CG reported higher *k* values. This indicates that the effort in sustaining the attention on stimuli forces the subject to choose the first option presented, strengthening the hypothesis of a relationship among impulsivity and working memory [30].

The results we presented shown a variability of *k* with time. According to Body, Bradshaw and Szabadi [56] time delays have a non-linear scaling following a power law that takes into account the contraction of perceived time, Our results can be viewed as a starting point to create a larger dataset and find an empirical formula aimed to describe *k* in a more precise way using generalized hyperbolic functions instead of the standard model.

The ADHD-C group have levels of *k* significantly higher than their peers, and their performances are significantly more impaired by the memory load. In this group (EG), the decreasing of the subjective value over time is faster than the one in CG. As Ernst et al. [16] argued, at the moment of choosing, subjects with WM deficits or a higher memory load carry out inadequate choices. Therefore, when many factors are involved at the moment of a decision, the *k* value increases. In spite the fact that the delayed reward is more rewarding, the subject has difficulties in waiting, revealing a greater impulsivity.

Thus, we suggest that the WM has a significant role in the decision-making and DD processes in children with ADHD. Further, this paper invites future research to focus on replicating those findings with the aid of a different time and age frame, to explore if the time of the day in which the tasks are performed impacts on the children's scores and, if there are changes during the child's development.

Declarations

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

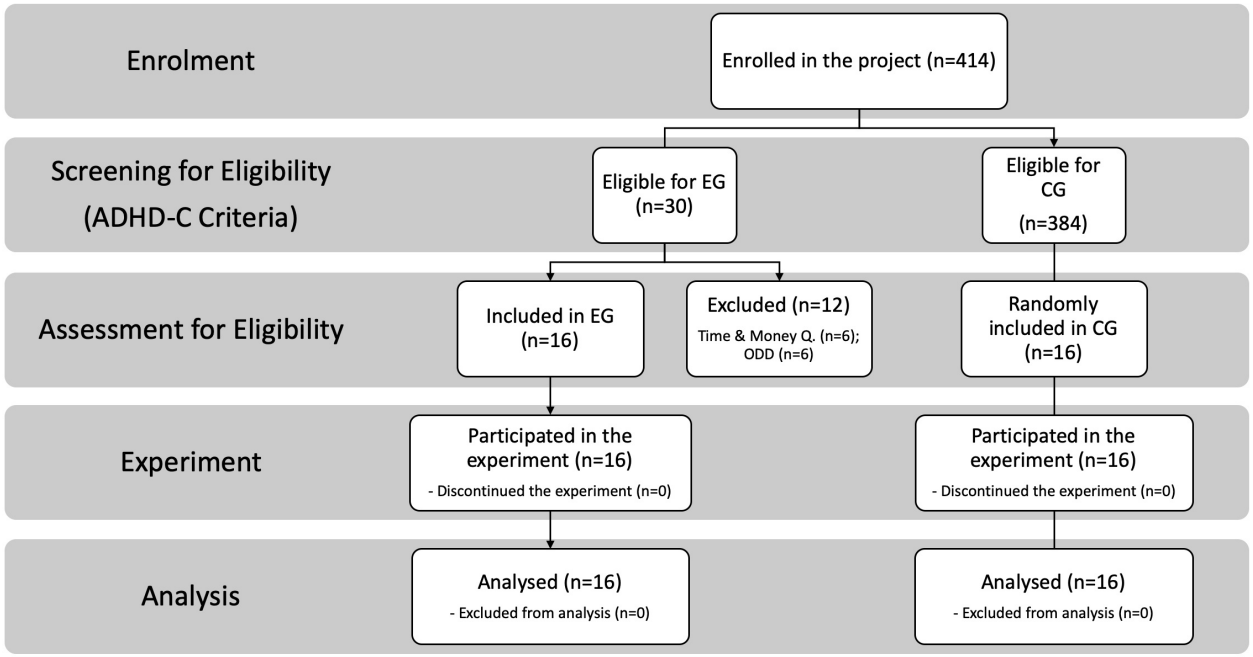

Figure 1

Subjects Recruitment, Assignment, and Assessment Procedures

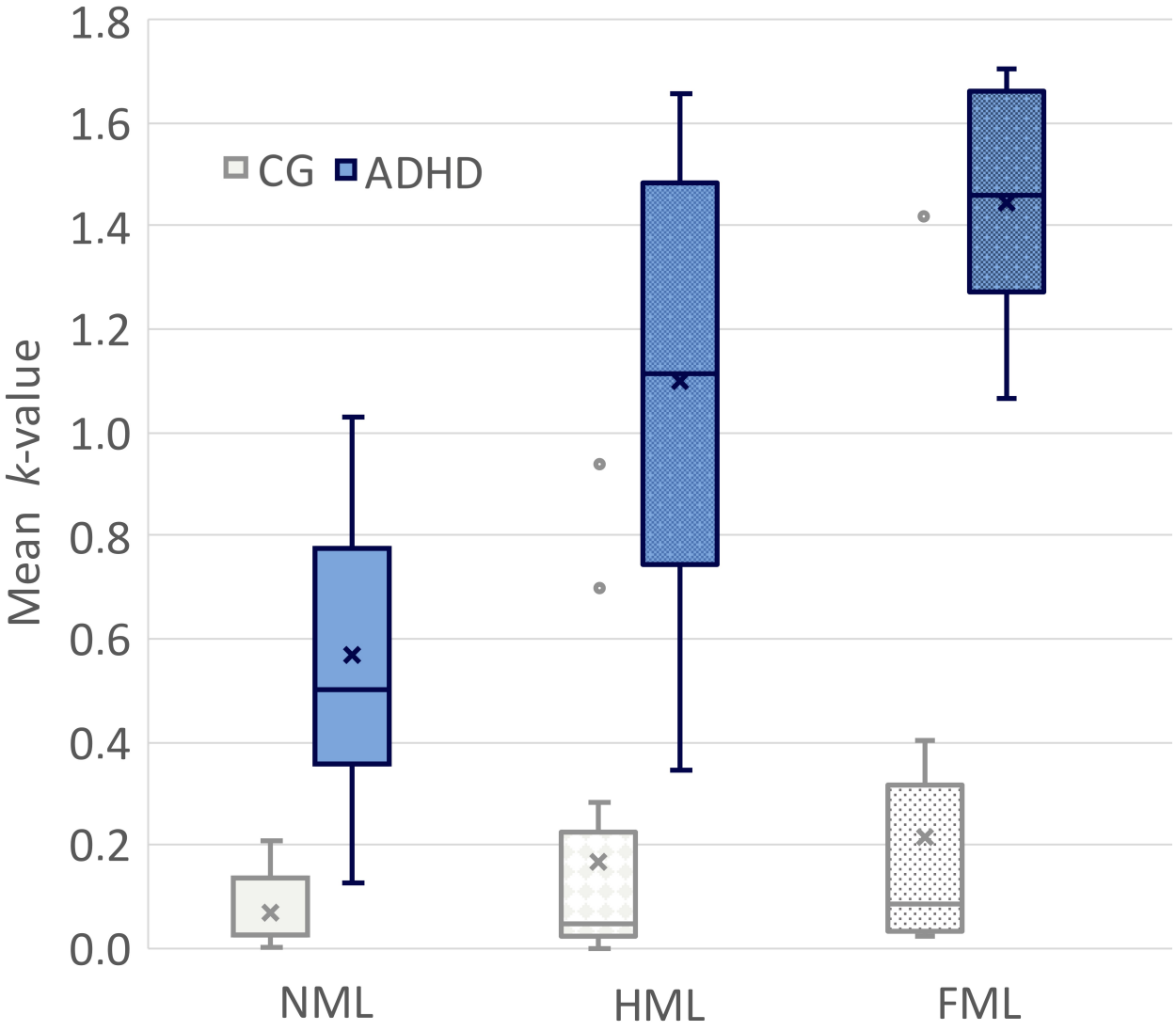

Figure 2

k-value Comparison Between Control and Experimental (ADHD) Group for Different Memory Load Conditions Footnote: In the Box and Whisker Plot a box is drawn from the first quartile to the third quartile, while a line is drawn at the median and the cross is the mean value. The whiskers extend from each quartile to the minimum or maximum. Outliers are depicted as dots.

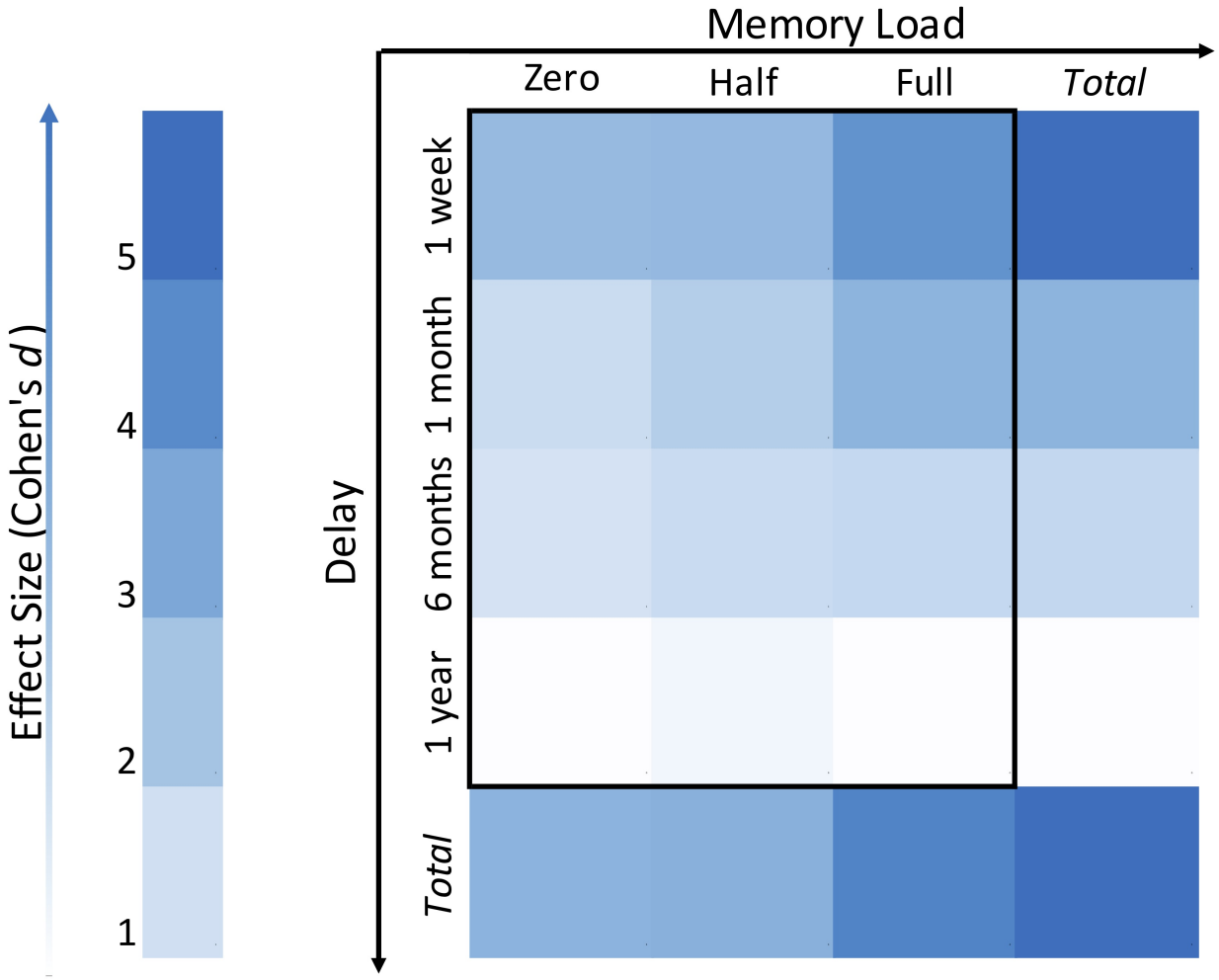

Figure 3

Effect Size Matrix of The Difference Between ADHD and Control Groups for Different Delays and Memory Loads

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Characterization of Clinical Manifestations in the Co-occurring Phenotype of Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder

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Comorbidity between attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) is a frequently reported condition. However, the clinical overlaps between the two disorders are not well characterized. The Child Behavior Checklist (CBCL) is a well-documented measure of emotional and behavioral problems in children and adolescents. The aim of the present study was to evaluate whether CBCL scales were able to detect psychopathological comorbidities as well as emotional and behavioral profiles across three groups of children with ASD, ADHD, and with the co-occurrence of both disorders. The results show that around 30% of participants with ASD exhibited internalizing problems, which was in line with previous findings. Co-occurrence condition showed a clinical intermediate phenotype: relative to ADHD and ASD, youths with co-occurrence of ADHD and ASD phenotype showed respectively lower ($p < 0.000$) and higher externalizing problems ($p < 0.000$). No differences emerged in internalizing problems ($p > 0.05$) across groups. CBCL is a useful measure to study the psychopathological conditions as well as emotional and behavioral profiles associated with ASD, ADHD, and the co-occurrence of ADHD and ASD. The identification of psychopathological and behavioral profiles associated with ASD and ADHD is crucial to perform specific and individualized treatments. Our preliminary findings suggested the existence of an intermediate and independent phenotype between ADHD and ASD that seems to be defined by the externalizing problems. Internalizing problems do not significantly differ between the combined phenotype and the two groups.

Keywords: neurodevelopmental disorders, psychopathological profile, behavioral problems, autism spectrum disorder, attention deficit hyperactivity/impulsivity disorder, externalizing problems, internalizing problems

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are common neurodevelopmental disorders (American Psychiatric Association [APA], 2013) that frequently co-occur (Lai et al., 2019).

Attention deficit/hyperactivity disorder is a prevalent and persistent psychiatric disorder that emerges in childhood as a complex of symptoms characterized by developmentally inappropriate and impairing levels of hyperactivity, impulsivity, and/or inattention (American Psychiatric Association [APA], 2013). Polanczyk et al. (2015) estimated that the worldwide prevalence in childhood population studies is around 5%. This result is in line with all previously reported systematic reviews, which estimated the prevalence of ADHD in the pediatric population as 3.4% (95% CI 2.6–4.5), with heterogeneity in methods between studies cited as a reason for different prevalences shown (Polanczyk et al., 2015).

Autism spectrum disorder is characterized by persistent deficits in social communication and social interaction across multiple contexts as well as restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association [APA], 2013). The last reported prevalence based on The Autism and Developmental Disabilities Monitoring (ADDM) Network (Christensen et al., 2018) estimated that ASD prevalence is around 1:59 children. European studies vary between 1 and 2% of the childhood population. Differences in prevalence estimates vary by methodological approach, demographic factors, geographical area, and time (Lyall et al., 2017).

Both conditions are characterized by a high rate of psychiatric comorbidities. These affect around 80% of youth with ADHD (Banaschewski et al., 2011), and approximately two-thirds of patients with ASD are indeed reported to have at least one associated mental health condition (Simonoff et al., 2008; Lai et al., 2014). ADHD and ASD show an overlap in symptoms, such as inattention and hyperactivity/impulsivity (Taylor et al., 2015; Ghirardi et al., 2019), and ADHD has been found to be the most frequently diagnosed disorder in co-occurrence with ASD (Lai et al., 2019).

Despite significant overlap in symptoms, the previous diagnostic criteria [Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR); American Psychiatric Association [APA], 1994] prohibited the simultaneous diagnosis of both disorders. In the context of revised criteria in the Diagnostic Statistical Manual of Mental Disorders Fifth Edition (DSM-5), a combined diagnosis is allowed (American Psychiatric Association [APA], 2013). Consequently, a growing interest in an in-depth characterization of the co-occurring phenotype has been observed. Indeed, co-occurred diagnosis of ADHD and ASD has been frequently described in several previous studies. Autistic symptoms co-occurred in 20–63% of children with ADHD (Ronald et al., 2008; Simonoff et al., 2008; Banaschewski et al., 2011; Lecavalier et al., 2019) and attention deficit and hyperactivity-impulsivity symptoms in a range between 22 and 83% of children among those with ASD (Ronald et al., 2008; Simonoff et al., 2008; Lai et al., 2014). Symptoms of ASD may frequently be misdiagnosed with a sole diagnosis of ADHD and vice versa in young children (Matson et al., 2013).

In one study, Sikora et al. (2012), looking at the ADHD symptoms in children with ASD, aged between 2 and 17.9years, divided the participants into groups based on whether their parents rated them as having clinically significant scores on ADHD problems subscales from the CBCL. The authors showed that those with ASD + ADHD symptoms had lower scores in several symptom scales: psychosocial health summary, school functioning, physical functioning, and emotional and social functioning scores were all lower than those of the children with ASD alone (Sikora et al., 2012).

In a more recent study, Lai et al. (2019) included 96 studies in a meta-analysis with the aim to evaluate the heterogeneity of ASD samples in terms of associated comorbidity diagnosis and symptoms. The authors found a pooled prevalence of ADHD comorbidity in ASD population of the 28%. Individuals with co-occurring ADHD and ASD are reported to show a range of other associated psychiatric and behavioral problems. The cumulative effects of the two disorders seem to lead to more severe impairments (Simonoff et al., 2008; Banaschewski et al., 2011; Lai et al., 2014) and poorer health-related quality of life (Lai et al., 2019) than those having ASD or ADHD alone.

An increased interest has been shown in the overlapping features between these disorders, including adaptive behaviors in children with ASD and ADHD co-occurrence. Mattard-Labrecque et al. (2013) investigated adaptive behaviors in children with overlap between ASD and ADHD compared to children with ADHD or ASD alone. The authors found that children with ASD and ADHD co-occurrence had lower adaptive behavior levels in all domains than children with ADHD or ASD alone, except in home/school domains, than children with ADHD (Mattard-Labrecque et al., 2013). In another study, no statistically significant differences emerged in adaptive functions between the ASD and ADHD group compared to the ASD group alone. However, the ASD and ADHD co-occurring phenotype shares inattention and hyperactivity deficit symptoms as well as emotional and behavior problems with the ADHD phenotype (Craig et al., 2015).

Moreover, according to the DSM-5 (American Psychiatric Association [APA], 2013), additional neurodevelopmental, mental, or behavioral conditions should be specified both in ADHD and in ASD, raising the need for a behavioral, emotional, and psychiatric evaluation. Furthermore, the elevated rate of medical disorders in children and adolescents with ASD and/or ADHD is associated with higher somatic problems (Muskens et al., 2017). The evaluation of psychological and medical conditions during the diagnostic assessment of children with ADHD, ASD, or the co-occurring phenotype, and follow-up examinations are then recommended to help determine risk factors and the most appropriate treatment.

However, although a large number of studies showed a high rate of ADHD and ASD combined diagnosis (Simonoff et al., 2008; Matson et al., 2013), few authors (McClain et al., 2017; Sokolova et al., 2017) have characterized the clinical features of a group with the co-occurrence diagnosis compared to ADHD or

ASD groups separately in terms of associated psychopathological and behavioral profile. Sokolova et al. (2017), using a statistical causal model in a population of children with ASD and/or ADHD, found a significant and positive association between both inattention and impulsivity symptoms and difficulties in understanding social information, between hyperactivity symptoms and stereotypic and repetitive behaviors, and between both inattention symptoms and difficulties with understanding social information and verbal intelligence quotient (IQ). Other authors have confirmed that poor social skills in females with ADHD are comparable to those in children with ASD (Ohan and Johnston, 2011).

McClain et al. (2017) found that children with ASD, ADHD, and co-occurring ASD/ADHD exhibit similar inattention and hyperactivity/impulsivity levels conversely to previous findings that demonstrated that a dual diagnosis of ASD/ADHD is associated with more severe ADHD symptoms (Jang et al., 2013).

The Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001) is a well-established and widely used parent-completed measure of emotional and behavioral symptoms in children and adolescents aged 1.5–18 years (Sokolova et al., 2017; Guerrera et al., 2019). The CBCL results in a guided description of the child by the parents, whose fidelity in reporting symptoms is also widely recognized for psychopathological conditions and behavioral problems associated with ADHD and ASD, as recently shown by Guerrera et al. (2019).

To the best of our knowledge, no study has focused on studying the differences between the ADHD, ASD, and co-occurrence ADHD–ASD groups in terms of psychopathological and behavioral-associated symptoms using the CBCL scales. Furthermore, we found few previous studies that analyzed the differences between groups of children with ASD or ADHD only compared to those with the co-occurrence of ADHD and ASD. Finally, we have also found some inconsistencies in the results of these previous studies.

The main aim of this study was to try to better characterize a psychopathological and behavioral profile of the co-occurring phenotype of ADHD and ASD.

MATERIALS AND METHODS

The Child and Adolescent Neuropsychiatry Unit of Bambino Gesù Children's Hospital, under the direction of the last author, upholds a comprehensive database made of several hundred patients. This database includes a wide range of information: anamnesis, family history, results from genetic analyses where available, information about past and current treatments (pharmacological and psychological treatments, speech therapy, etc. . .) and results from psychological and neuropsychological comprehensive evaluations, performed according to the good clinical practice recommended by international guidelines for neurodevelopmental disorder assessment.

Consistently with the aim of the current project, the patients who met our established inclusion criteria (described below) were retrospectively selected from this database. Our study is a retrospective observational study, and our institutional Ethic Committee has been notified according to the AIFA National Guidelines for Observational Study, in which retrospective studies do not require formal approval by the Ethics Committee.

Patients' confidentiality was protected.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from parents or legal guardians of each participant included in the study.

Participants

The inclusion criteria comprised: the age between 6.0 and 16.11 (included); a diagnosis of ASD, ADHD, ASD + ADHD (primary diagnosis of ASD), or ADHD + ASD (primary diagnosis of ADHD); available results from a psychological evaluation, including a measure of cognitive level and at least one "golden standard" to support clinical diagnosis, the Autism Diagnostic Observation Schedule 2 (ADOS-2) for ASD and Conners' Parent Rating Scale: Long Edition (CPRS) for ADHD diagnoses. Patients with suspected or ascertained genetic syndrome were excluded from the study.

In the period between September 2018 and June 2019, the Child and Adolescent Neuropsychiatry Unit of Bambino Gesù Children Hospital collected high-quality phenotype data of children who received a diagnosis of ADHD and/or ASD from two large datasets of 250 youths with ADHD and 250 youths with ASD (6–18 years of age). We included in the study 82 IQ- and age-matched individuals: 26 children with ADHD diagnosis, 30 with ASD diagnosis, and 26 with ADHD–ASD co-occurrence.

All the participants included in the database were previously assessed by an experienced multidisciplinary team, who performed an investigation of medical and developmental histories, as well as behavioral and diagnostic evaluations. The diagnoses of ASD and ADHD were based on the fifth version of the DSM; in addition to clinical assessment, ASD diagnoses were supported by the ADOS-2 (Lord et al., 2012). ADHD diagnosis was based on developmental history and extensive clinical examination and further supported by the evaluation of ADHD-related behaviors through the CPRS (Conners, 1997).

Measures

Cognitive Measures

Cognitive development was preferably assessed by Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003). WISC-IV administration provides four different indexes: Verbal Comprehension Index (subtests: similarities, vocabulary, and comprehension); Perceptual Reasoning Index (subtests: block design, picture concepts, and matrix reasoning); Working Memory Index (subtests: digit span and letter–number sequencing); and Processing Speed Index (subtests: coding and symbol search).

In cases of failures in the completion of the WISC-IV for inadequacy of the language, mainly children with ASD, or for lack in attention, mainly children with ADHD, we administered

Leiter-3 (Roid et al., 2013) or Colored Progressive Matrices (CPM; Raven et al., 1984), respectively.

The Leiter-3 offers a non-verbal measure of intelligence and evaluates the ability to reason by analogy and by matching and perceptual reasoning in general, irrespective of language and formal schooling. The non-verbal IQ obtained from the Leiter-3 is based on four subtests: Figure Ground, Form Completion, Classification and Analogies, and Sequential Order. CPM is a non-verbal assessment of intelligence. CPM is made up of 36 items appearing as a matrix reasoning test with a piece missing, which reduces the necessity for task instructions, for culture- or experience-dependent abilities, and for other specific abilities as fine motor or speech skills. The individual is asked to identify the correct response that completes the pattern, choosing from six alternative possible response options.

The Griffiths III (Green et al., 2016) was administered in only a few cases, when the child failed to complete the other cognitive scales because of his/her reduced attentional resources. The developmental quotient (DQ) obtained from Griffiths III is based on five subscales: Language and Communication Subscale, Eye and Hand Coordination Subscale, Personal, Social Emotional Subscale, and Gross Motor Subscale. Assessing proficiency in the activities of daily living, level of independence, and interaction with other children were employed as outcome measures.

ADOS-2 (Lord et al., 2012) is a semi-structured assessment tool allowing a systematic and standardized evaluation of the presence of ASD symptoms. It is considered a "gold standard" for collecting standardized and objective information about social communication skills, restricted interests, and repetitive behaviors, although it is insufficient on its own for a diagnosis. ADOS-2 comprises five modules: the Toddler Module for children aged 12–30 months without phrase speech, Module 1 for children aged 31 months and older without phrase speech, Module 2 for children with phrase speech but not verbally fluent, Module 3 for children and young adolescents with fluent language, and Module 4 for older adolescents and adults with fluent language.

Conners' Parent Rating Scales-Long Version, Revised (Conners, 1997), are broadly used instruments for diagnostic and research purposes in the ADHD field, which can be administered to both parents and teachers. They assess core symptoms as well as symptoms of other behavioral and emotional disorders commonly associated with ADHD (e.g., oppositional behavior) based on DSM-IV-TR (American Psychiatric Association [APA], 1994) criteria (Sparrow, 2010).

The CBCL, Ages 6–18 (Achenbach and Rescorla, 2001) was used to assess comorbid psychiatric symptomatology using parents' ratings. CBCL items investigate emotional and behavioral problems over the previous 6 months, with three response options (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true).

The CBCL 6–18 questionnaire consists of two parts: one addressing social competence and the other for assessing emotional and behavioral problems in children aged 4–18 years. In the study, only the latter part was used. The questionnaire includes a 118-item scale yielding several subscales, including syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior and Aggressive Behavior, a Total Problem Score) and two broadband scores, Internalizing Problems and Externalizing Problems.

The Internalizing domain incorporates three syndrome scales: Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints. The Externalizing domain incorporates the Rule-Breaking Behavior and Aggressive Behavior syndrome scales. The Total Problems scale is based on responses to all CBCL items, including Social Problems, Thought Problems, and Attention Problems scales. DSM-oriented scales included affective, somatic, and anxiety problems; ADHD; oppositional/defiant problems; and conduct problem. CBCL also includes three additional scales, the 2007 scales, namely, Sluggish Cognitive Tempo, Obsessive-Compulsive, and Post-Traumatic Stress Disorder scales.

All scales have a t-score mean of 50 and a standard deviation of 10, and different norms are provided for gender across age groups. According to the normative data of the CBCL, a *t*-score $\leq$64 indicates non-clinical symptoms, a *t*-score between 65 and 69 indicates problems rated high enough to be of concern but not overtly deviant, and a *t*-score $\geq$70 indicates clinical symptoms. For the subscales "internalizing," "externalizing," and "total" problems, a *t*-score $\leq$59 indicates non-clinical symptoms, a t-score between 60 and 64 indicates that the child is at risk for problem behaviors, and a *t*-score $\geq$65 indicates clinical symptoms.

Statistical Methods

Demographic Variables

Analyses of variances (ANOVAs) were used for group comparisons between the ASD, the ADHD, and the

TABLE 1 | Demographic characteristics and cognitive and psychopathological measures of children and adolescents included.

	ADHD (*n* = 26)	ASD (*n* = 30)	Co-occurrence ADHD-ASD (*n* = 26)	*p*-values
Age (mean and SD)	9.6 (3)	9.1 (2.6)	9.5 (3.1)	0.800
Sex (M/F)	19/7	24/6	22/4	0.586
IQ or DQ (mean and SD)	91.5 (19.5)	82.3 (20.6)	82.8 (22.1)	0.194
ADOS-2 (mean and SD)	–	6.8 (0.9)	6.2 (1.5)	0.088
CPRS – ADHD scale (mean and SD)	84 (6.4)	–	73.6 (11.9)	0.0003

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; co-occurrence ADHD–ASD; DQ, developmental quotient; IQ, intelligence quotient; ADOS-2, Autism Diagnostic Observation Schedule-2 Comparative Score; CPRS, Conners' Parent Rating Scales-ADHD scale. ANOVAs indicated that the cohorts had similar population characteristics regarding age at evaluation, sex, and IQ ($p > 0.05$). ASD and co-occurrence ADHD–ASD groups did not significantly differ on ADOS-2 comparative scores ($p > 0.05$). ADHD scale of CPRS was used to compare ADHD severity in ADHD and co-occurrence ADHD–ASD groups: a statistically significant difference emerged ($p < 0.001$).

ASD + ADHD groups (age and IQ). The chi-squared test was performed on categorical variables. ADOS-2 comparative scores of ASD and comorbidity groups, as well as CPRS scores of ADHD and comorbidity groups, were compared by means of *t*-tests.

The following analyses were conducted: descriptive statistics (mean and standard deviations; percentage of non-clinical, borderline, and clinical scores) for 17 CBCL subscales separated for diagnostic group (ASD, ADHD, co-occurrence ADHD and ASD); multivariate analysis of variance (MANOVA) to evaluate the impact of diagnosis on CBCL subscales' scores, with group (ASD, ADHD, comorbidity) as a between-subject factor and 17 CBCL subscale T-scores as within-subject factors: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, internalizing problems, externalizing problems, total problems, affective problems, anxiety problems, somatic problems, ADHD, oppositional/defiant, conduct problems; Bonferroni *post hoc* analyses were conducted; and comparisons across all groups were made. Finally, for the examination of the relationship between age, sex,

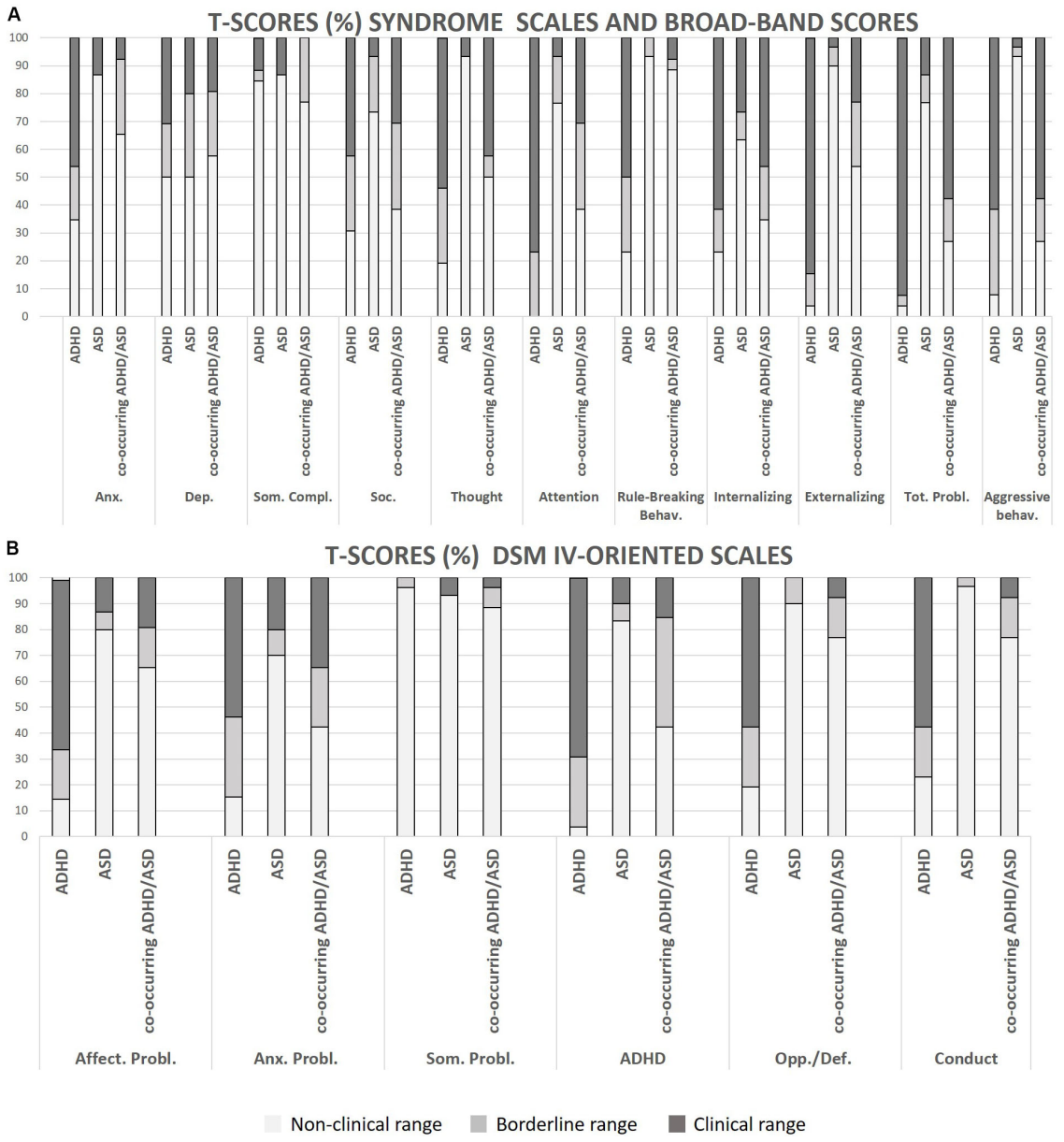

FIGURE 1 | (A,B) Representations of the distributions of CBCL scores (clinical, borderline and non-clinical). *Anx.*, Anxious/depressed; *Dep.*, withdrawn/depression; *Soc.*, social problems; *Thought*, thought problems; *Tot. Probl.*, Total Problems; *Affect. Probl.*, affective problems; *Anx. Probl.*, anxiety problems; *Som. Probl.*, somatic problems; *Opp./Def.*, oppositional/defiant; *Conduct*, conduct problems.

and T-scores on internalizing and externalizing problems in CBCL subscales, additional Pearson and Spearman correlations were applied.

All statistical tests were based on a significance level of $p < 0.05$.

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 13.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Demographic and Clinical Features

Demographic features of the sample are summarized in **Table 1**. As concerns the cognitive measures used for the assessment of the ADHD group, 14 out of 26 youths (54%) were evaluated by means of the WISC-IV, seven (27%) by means of CPM, and the remaining five (19%) by means of Leiter-3, whereas 23 out of 30 youths (77%) belonging to the ASD groups were evaluated by means of Leiter-3, five (17%) were evaluated by means of WISC-IV, and only two children were evaluated through CPM and Griffiths III. Finally, as concerns the ADHD and ASD co-occurrence group, 13 out of 26 youths (50%) were evaluated by means of Leiter-3, eight (31%) were evaluated through WISC-IV, three (11.5%) were assessed through CPM, and two (7%) were assessed by Griffith III.

Psychopathological Profile: Child Behavior Checklist Scores Across Diagnoses

Qualitative representations of the distributions of CBCL in clinical, borderline, and non-clinical scores for each group are provided in **Figures 1A,B**. Means and standard deviations of the scores in the selected CBCL subscales were calculated for each group (**Table 2**).

Bonferroni *post hoc* analyses were conducted; comparisons across all groups were made. As expected, comparisons between ADHD and ASD groups were statistically significant ($p \leq 0.001$) for all the considered CBCL scales. Depression, Somatic Problems and Somatic Complaints scales did not significantly differ between the two groups ($p > 0.05$). Comparisons between the ADHD and the co-occurrence ADHD-ASD groups revealed statistically significant differences in the following scales: Anxiety ($p = 0.006$), Attention ($p = 0.029$), Rule-Breaking Behavior ($p < 0.000$), Aggressive Behavior ($p < 0.000$), Externalising Problems ($p < 0.000$), Total Problems ($p < 0.000$), Affective Problems ($p = 0.001$), ADHD ($p < 0.000$), Oppositional/Defiant ($p < 0.000$), and Conduct Problems ($p < 0.000$). Comparisons between co-occurrence ADHD–ASD and ASD groups revealed statistically significant differences in the following scales: Thought Problems ($p = 0.003$), Attention ($p = 0.008$), Aggressive Behavior ($p = 0.047$), Externalising Problems ($p < 0.000$), Total Problems ($p = 0.001$), ADHD ($p < 0.000$), and Conduct Problems ($p = 0.016$).

DISCUSSION

The main aim of the present study was to characterize a psychopathological and behavioral profile of the co-occurring ADHD–ASD phenotype.

We analyzed three subgroups of a large dataset of outpatients diagnosed for ADHD, ASD, and the ADHD–ASD co-occurrence groups at the Child and Adolescents Psychiatric Unit at the Bambino Gesù Children's Hospital in Rome.

The new DSM-5 (American Psychiatric Association [APA], 2013), allowing for a dual diagnosis, has contributed to the increasing interest of clinical researchers studying the comorbid phenotype. We learned by several previously reported authors (Ronald et al., 2008; Simonoff et al., 2008; Banaschewski et al., 2011; Lai et al., 2014; Lecavalier et al., 2019) that ADHD and ASD frequently co-occur.

Our results showed that in the co-occurrence ADHD–ASD phenotype, the externalizing dimensions, obtained from the CBCL Externalizing Problems scales, as well as Thought Problems, Attention scores, Aggressive Behaviors, ADHD scores, and Conduct Problems are higher than those in the ASD group but lower than those in the ADHD group. Our preliminary findings revealed that the externalizing symptom scales of the CBCL scores significantly differed between the co-occurring ADHD–ASD group and the other two groups. This finding supports the hypothesis of the existence of an intermediate and independent phenotype between ADHD and ASD, which seems to be defined by the externalizing problems dimension.

Furthermore, we found that a representative prevalence of the internalizing problems, as well as Depression, Somatic

TABLE 2 | Group differences on CBCL scales (means and standard deviations).

	ADHD	ASD	Co-occurrence ADHD–ASD	*p*-values
Anxious/Depressed	66.9 (8.1)	56.3 (8.3)	59.8 (7.5)	<0.000
Withdrawn/Depressed	65.1 (9.8)	61.7 (8.3)	63.1 (10.4)	0.416
Somatic Complaints	58.8 (6.3)	55.1 (7.9)	56.5 (7.1)	0.151
Social Problems	69.5 (9.8)	60.3 (5.9)	64.7 (7.9)	<0.000
Thought Problems	68.6 (8.1)	59.1 (7.9)	66.3 (7.7)	<0.000
Attention Problems	74.5 (6)	61.2 (10.11)	68.3 (8.4)	<0.000
Rule-Breaking Behavior	68 (8.1)	54.5 (4.8)	56 (11.6)	<0.000
Aggressive Behavior	75.9 (10.7)	53.9 (5.2)	59.1 (6.7)	<0.000
Internalizing Problems	65.6 (7.3)	56.4 (10.2)	60.1 (9.3)	0.002
Externalizing Problems	71.8 (8)	51.2 (7.7)	59.1 (6.6)	<0.000
Total Problems	72.7 (5.2)	56.5 (7.9)	63.9 (7.4)	<0.000
Affective problems	70.4 (6.9)	57.7 (9.4)	61.8 (7.5)	<0.000
Anxiety Problems	68.6 (7.1)	59.8 (8.2)	64.6 (7.6)	<0.000
Somatic problems	56.1 (5.4)	54.2 (7.9)	55 (6.9)	0.607
ADHD Problems	72.4 (5.1)	57.5 (7)	64.5 (6.6)	<0.000
Oppositional/Defiant Problems	69.2 (7.5)	53.8 (4.9)	57 (7.1)	<0.000
Conduct Problems	69.4 (9.1)	53.1 (4.1)	58.3 (6.5)	<0.000

The comparison of the ADHD, ASD and co-occurrence ADHD–ASD samples applying a MANOVA with group as the between-subject factor, revealed significant group differences for almost all scores of the considered CBCL scales. Results are summarized in ***Table 2****.*

Complaints, and Somatic Problems scales obtained from the CBCL, does not significantly differ between the co-occurring ADHD–ASD phenotype and the other two groups. This finding means that internalizing problems may overlap across the three groups.

Our findings also confirm the high sensitivity of the CBCL for the internalizing symptoms previously described around 30%, in line with Guerrera et al. (2019). This result confirms that CBCL is a specific instrument to measure internalizing symptoms in ASD.

Our study has some limitations. First, our analyses examined a limited number of children and adolescents with the co-occurring ADHD–ASD phenotype. Therefore, we look at our results as preliminary findings, and we are working to expand the size of each group. Furthermore, in this study, we evaluated the differences across groups. Thus, future studies using dimensional analyses focused on internalizing and externalizing symptom dimensions and in groups with a bigger sample size are needed. Moreover, this is a retrospective study using diagnostic tools according to parental judgment. So, future studies will have perspective designed with a consistent long-term follow-up. Finally, parents alone completed CBCL, while collecting reports from both parents and teachers may be more informative. Also, in the current study, we did not have any report about the adaptive behaviors nor interviews led by clinicians [i.e., Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)] which may explain what symptom associated with ASD and ADHD is the most disabling. In the next studies, reports from teachers and interviews led by clinicians will be included to integrate parent's reports and as a measure of the adaptive behaviors.

CONCLUSION

In summary, results suggested that CBCL has been confirmed to be a very accurate instrument to detect the psychopathological, symptoms, and emotional and behavioral profile of the associated comorbidities in children and adolescents with ASD, ADHD, and the co-occurrence condition.

Our preliminary findings suggested the existence of an intermediate and independent phenotype between ADHD and ASD that seems to be defined through the externalizing symptom dimensions.

Further studies are needed to analyze the overlap of symptoms in the three groups with dimensional analyses and in order to reinforce the current results.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the IRCCS Bambino Gesù Children's Hospital of Rome. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AC participated the design, coordination of the study and interpretation of the data, performed the measurement, drafted, and revised the manuscript. EF conceived the study, participated in its design and interpretation of the data, performed the statistical analysis, and helped to draft and revise the manuscript. SG, EN, and GV participated in the design of the study, performed the measurement, and helped to draft and revise the manuscript. SV participated in the design of the study and coordination, interpretation of the data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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A Cooperative Learning Classroom Intervention for Increasing Peer's Acceptance of Children With ADHD

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Abstract

Objective: The hypothesis behind this study was that trained teachers using cooperative learning procedures with children in their classroom (aged from 6 to 10 years) can influence the social skills of children with ADHD symptoms and their acceptance by their peers. **Method:** The study involved 30 children with ADHD symptoms attending 12 different classes, where cooperative learning was adopted in some, and standard practices in others. ADHD children's symptoms, social skills, and cooperative behavior were assessed by means of a teacher's questionnaire, and the social preferences of the children in their class were collected. **Results:** Changes emerged in teachers' assessments of the children's cooperative behavior in the experimental classes. Improvements in the sociometric status of children with ADHD symptoms were only seen in the cooperative learning classes. **Conclusion:** These results show the importance of well-structured intervention in classes that include children with ADHD symptoms. Implications of these findings for future intervention are discussed. *(J. of Att. Dis. 2019; 23(3) 282-292)*

Keywords

ADHD, cooperative learning, peer acceptance, social preferences

ADHD is a neurobiological developmental disorder characterized by a persistent inattention and/or hyperactivity-impulsivity that interfere with the normal psychological development of children and hinder their performance in common daily activities, making them unable to adjust their behavior to the expectations of outside word (Capodieci & Cornoldi, 2013). In particular, symptoms of ADHD tend, by their very nature, to prevent successful interaction with peers (Mrug, Hoza, Pelham, Gnagy, & Greiner, 2007). Specifically, children with such symptoms are often rejected because of their inclination to be domineering, tactless, unyielding, disturbing, touchy, careless, and heedless of the rules in organized games. The classroom behavior of children with ADHD that is associated with their rejection by their peers includes being off-task, troublesome, rude, and incapable of self-control (Rich, Loo, Yang, Dang, & Smalley, 2009). Little attention has been paid to the issue of how to contain this problem.

Reported prevalence rates of ADHD among schoolchildren of all ages in Europe and worldwide are typically high (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Wittchen et al., 2011), meaning that nearly every classroom may include a child with symptoms of ADHD. The classroom is a very important place for all children because it is where they learn how to relate to others, as well as gaining academic skills. Relationships in the classroom represent a primary setting in which children learn to cooperate, negotiate, solve conflicts—skills crucial to effective social functioning throughout life (Hoza, 2007). The troubled social relationships of children with ADHD are associated with numerous negative longitudinal outcomes, including serious conduct problems (Bagwell, Molina, Pelham, & Hoza, 2001). High negative sociometric nomination rates may anticipate subsequent psychopathology (Mikami et al., 2015). For example, boys with ADHD and difficult relationships with their peers in childhood are associated with more criminality, depression, and substance use in adolescence than boys with ADHD but no social problems with their peers (Greene, Biederman, Faraone, Sienna, & Garcia-Jetton, 1997). In a sample of girls with ADHD, rejection by peers in childhood significantly contributed to academic disappointment in adolescent, disruptive behavior, and internalizing symptoms (Mikami & Hinshaw, 2006).

Given their importance, social aspects and peer acceptance have been taken into account in intervention programs for ADHD. Stimulant medication and behavioral management

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can reduce the core symptoms of ADHD and may improve parents' and teachers' ratings of the affected children's social skills (Swanson et al., 2001), but there is no evidence of any improvement in their sociometric status, that is, of their peers' attitudes toward them (Mrug, Hoza, & Gerdes, 2001). Training for children with ADHD to improve their social skills has produced unclear results, when assessed with sociometric measures (Abikoff et al., 2004), prompting pessimistic conclusions on the feasibility of including peer problems in the treatment of this population (Hoza et al., 2005).

There is a potential weakness in the literature, however, concerning intervention on the social skills and peer relations of children with ADHD. The social aspects of children, including peer acceptance and rejection, have often been measured by means of class nominations, but social skills programs for children with ADHD have often considered these particular children from an individual point of view and outside the normal classroom setting. It is worth nothing that changes in the behavior of children with ADHD may not necessarily induce changes in the attitude to their behavior taken by their peers. It has been demonstrated, for instance, that the same behavior is interpreted differently depending on whether the child concerned has a high or low social preference rating (Peets, Hodges, & Salmivalli, 2008). Peers are willing to give the benefit of the doubt to children they already like, whereas a child they dislike behaving in the same way may be judged negatively. In other words, peers are unlikely to change their opinions of their classmates with ADHD even when the latter's behavior improves (Mikami, Lerner, & Lun, 2010).

Although it is generally assumed that the classroom is one of the most important social settings for children with ADHD to develop and maintain positive social relationships with others, this important social environment has seldom been considered in investigations and interventions (Chang, 2004). Furthermore, not enough importance has been attributed to the role of teachers (Mikami, Griggs, Reuland, & Gregory, 2012) despite the fact that teacher's behavior is known to influence children's social preferences (Mikami et al., 2012). Teachers who personally like and accept children with behavioral problems have been shown to attenuate the typically strong correlation between such children's behavior and their sociometric status. Likewise, the extent to which a teacher exhibits frustration with such children or criticizes their behavior mediates the association between these children's behavior and their rejection by peers (McAuliffe, Hubbard, & Romano, 2009). This evidence goes to show that the classroom should be seen as the main setting for intervention on the social aspects of children with ADHD, as it is the primary environment for their social interactions. This is confirmed by the use commonly made of class nominations as the main measure of students' peer relations in social behavior studies. The solidity of social preference is usually conceptualized as resulting from children's steady behavior over time, and especially from consistency in the troublesome conduct of unpopular children. Strong social inclination may also be propagated by subjective predispositions held by the peer group, however, and appropriate educational strategies might be able to influence such predisposition.

Educational practices may have a key impact on such aspects of classroom life. To give an example, children who watched a video in which a teacher delivered experimentally manipulated feedback to a child with a negative reputation, altered their perception accordingly (White & Jones, 2000). As suggested by Mikami and colleagues (2013), training regular classroom teachers to make the peer group more inclusive may have a positive effect on the children with ADHD in these teachers' classroom. A durable change in teacher' practices may also prevent children with ADHD enrolling in their future classes from being rejected by their peers.

Cooperative Learning (CL) appears to be particularly relevant among the educational practices in the classroom that could have positive implications for the child with ADHD. CL involves students working in small, organized groups to reach shared objectives. It is broadly recognized as a teaching strategy that promotes learning and socialization among students of all ages and across various subject domains. It has been used successfully to promote academic achievement, upgrade students' willingness to work cooperatively and productively with others who have different learning levels and needs, and improve intergroup relations with children from different backgrounds. It has been argued that CL experiences are crucial to avoiding and mitigating many of the social problems related to children, adolescents, and young adults (for a review, see Gillies, 2014).

CL has been widely accepted as a teaching strategy obtaining documented improvements in achievement, applications of knowledge, and motivation (across subject areas and grades) by comparison with traditional teaching methods (Emmer & Gerwels, 2002; Gillies, 2003). CL has a wide base of support among educators and researchers, who have documented increased motivation and academic gains in every academic subject area, grade level, and type of school, especially when it includes certain elements (e.g., individual accountability, positive interdependence, group rewards, structure; Antil, Jenkins, Wayne, & Vadasy, 1998; McMaster & Fuchs, 2002).

Positive effects of CL have been documented in whole-classroom observational research. For example, it generated fewer off-task verbalizations and more positive verbal interactions (in groups of typical eighth graders) at schools defined as being scarce and inexpert users of CL (Beyda, Zentall, & Ferko, 2002; Gillies, 2003). It has to be said that, because it is difficult to randomly assign conditions in naturalistic whole-classroom research, the effects obtained might be attributable to previous differences between

teachers, classrooms, or schools (e.g., teachers choosing to adopt these practices may have other teacher variables that contribute to these gains). A completely random assignment to a CL condition would contrast with the ethical standards typically required for school-based studies in which participants are properly informed volunteers. Overall, the findings of research using different designs, types of participant, and definitions of CL suggest that the CL approach warrants more systematic study. A first step would probably involve establishing clear definitions and crucial variables (Kuester & Zentall, 2012).

There are some important elements to consider when organizing lessons to be conducted according to the CL method (as done in the present study) given their demonstrated importance (Johnson, Johnson, & Smith, 2007): (a) Positive interdependence: when people see that they can achieve their objectives if and only if the other individuals with whom they are cooperatively linked reach their goals too and therefore endorse each other's efforts to achieve the result. (b) Individual accountability: This exists when the performance of each single child is monitored and the outcomes are offered back to the individual and the group. Each member is held responsible by the other member of the group contributing to the group's success. (c) Enhanced interaction: To encourage each other's success, group members help and support each other, exchange the necessary resources such as information and materials, offer each other feedback, challenge each other's conclusions and reasoning, and act in trusting and responsible ways. (d) Use of social skills: Some skills like decision making, communication management, and conflict resolution have to be taught just as carefully as academic skills. (e) Group processing: Effective group work is influenced by whether or not groups periodically reflect on how well they are functioning and how they may improve their learning processes. Teachers need to give the class time for group processing and show students how to examine their processes efficiently.

Although CL has been widely and sometimes even too enthusiastically and generically accepted as a teaching strategy, educators' perceptions of the difficulties involved in adopting this approach might clarify their inclination to exclude scholars with hyperactivity or inattention from group experiences. This would also help to explain why educators use cooperative practices less frequently than they think would be desirable (Lopata, Miller, & Miller, 2003), especially with children in Grades 3 to 8 (Race & Powell, 2000).

In addition, despite the potential importance of CL in the case of ADHD, only a few studies have analyzed the effects of CL on children with this disorder (Kuester & Zentall, 2012; Mikami et al., 2013; Zentall, Kuester, & Craig, 2011). They generally found that the social interactive rules that CL entails reduced the negative verbal and off-task behavior and improved the proportion of problems solved by all children but sociometric measures did not change significantly. This could be due partly to the different places being used to conduct the CL intervention and to record the sociometric measures and partially to the limited importance attributed to the teacher's preparation and role in influencing social preferences of the children in their classrooms.

The aim of our research was to draw on the strengths of previous studies on CL, and to overcome their weaknesses, by proposing a CL intervention in normal classroom with well-trained teachers. CL sessions were organized in classes where children with ADHD-related problems interacted with typically developing children (TD) supervised by teachers specifically trained to teach children with symptoms of ADHD. Adequately trained teachers, reportedly consider CL an effective and useful strategy to use with students who have been diagnosed with (or have symptoms of) ADHD (Garcia, 2013).

The main purpose of the present study was to test the hypothesis that teaching through CL can help children with symptoms of ADHD to become better integrated in class and more appreciated by their peers, improving their social and collaborative skills as a result. These aspects were measured on the basis of both teachers' ratings and children's sociometric choices. Although the teachers' ratings might be biased by the presence among the raters of the same teachers who conducted the classroom activities, such ratings were the only procedure practicable and permitted by schools participating in this study, thus replicating the methods adopted in previous research on similar issues (e.g., Kuester & Zentall, 2012).

Method

Participants

The study involved 30 children (aged between 6 and 9.8 years) attending 12 classes (Grades 1 to 5) that included one or more children with symptoms of ADHD, at nine different schools in northeastern Italy. All the teachers of the 12 classes were part of a group that had received information on ADHD and on the nature of the project, and they were being trained (on a voluntary basis) on how to teach children with ADHD. Six classes adopted the CL teaching method (number of students = 132, number of students with ADHD symptoms = 16) while the other six classes, with similar characteristics in terms of size, location, teachers' age, and positive attitude toward CL (number of students = 121; number of students with ADHD symptoms = 14) taught the same content as the CL classes but using standard teaching methods. The inclusion of a class in the experimental (CL) group could not be completely randomized because it was also affected by the teachers' and their school administrations' willingness to fulfill all the requirements of the study. The two groups of children with ADHD were

Table 1. Characteristics (*M* and *SD* in parenthesis) of Children With Symptoms of ADHD in the CL Group and the Standard Learning (Control) Group.

	CL group (n = 16)	Control group (n = 14)	χ^2		p
Male (%)	87.5	85.7	.54		.44
	M (*SD*)	*M* (*SD*)	Range[a]	$t(28)$	p
Age (months)	97.94 (14.87)	98.14 (15.32)	72-118	0.04	.97
Disadvantaged family environment (COM)	1.00 (.89)	.71 (1.07)	0-3	−0.80	.43
Cognitive abilities (COM)	4.45 (2.66)	5.21 (3.40)	0-10	0.62	.54
Inattention (SDAI)	18.13 (5.01)	16.57 (5.27)	0-27	−0.83	.42
Hyperactivity (SDAI)	12.88 (8.37)	12.21 (5.89)	0-27	−0.25	.81
CD symptoms (COM)	1.88 (2.28)	2.43 (2.85)	0-12	0.59	.56
ODD symptoms (COM)	3.30 (3.51)	4.00 (4.26)	0-15	0.53	.60
Internalizing symptoms (COM)	3.19 (4.17)	3.07 (3.29)	0-15	−0.08	.93
Social skills (COM)	3.94 (2.70)	3.71 (3.32)	0-12	−0.20	.84
Cooperation (COM)	6.44 (2.61)	7.64 (3.75)	0-18	1.03	.31

Note. CL = cooperative learning; CD symptoms = minor symptoms of conduct disorder; ODD symptoms = minor symptoms of oppositional defiant disorder; Internalizing symptoms = presence of minor symptoms of anxiety or depression. COM = comorbidity; SDAI = *Scala per i Disturbi di Attenzione/Iperattività per Insegnanti* [ADHD scale for teachers].
[a]Ranges for scores refer to the lowest and highest possible value considered by the measure.

comparable in terms of age, gender, rated intellectual ability, socioeconomic level, presence of concurrent minor psychopathological problems, and educational level (investigated by a questionnaire; see Table 1). The different subtypes of ADHD were also similarly represented in the CL and in the control groups, with, respectively, six and six inattentive children, three and two hyperactive/impulsive, and seven and six with the combined subtype.

As explicit diagnoses are infrequently made in Italy, the children with ADHD group were identified by the authors on the basis of a screening process that included interviews and a score of 14 or higher (the diagnostic cutoff given in the Manual) on one or both the subscales of the SDAI (*Scala per i Disturbi di Attenzione/Iperattività per Insegnanti* [ADHD scale for teachers]; Marzocchi & Cornoldi, 2000). This scale is widely used in Italy and has been validated for the Italian population, with high interjudge and test–retest reliabilities ($r > .8$ in both cases), discriminatory power, and concurrent validity obtained by correlating the scale with other scales ($r > .95$; Marzocchi, Re, & Cornoldi, 2010). The scale exactly reflects the 18 symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) for diagnosing ADHD and therefore includes two subscales, one for inattention (nine items) and one for hyperactivity/impulsivity (nine items). Teachers were asked to closely monitor a child's behavior for about 2 weeks and report the frequency of the types of symptomatic behavior described in each item. Scores for the items of the SDAI scale range from 0 (*problematic behavior never present*) to 3 (*very often present*). Teachers were also asked to answer the COM (comorbidity) questionnaire to identify any minor symptoms of other psychological and psychopathological problems, and to collect relevant information on the children (Marzocchi et al., 2010). In both the CL group and the control group, the children with ADHD symptoms had an average cognitive level, no other serious psychological problems (oppositional behavior or internalizing problems), and none of them were socioeconomically disadvantaged (see Table 1). Teachers and parents were interviewed informally to collect further evidence of the children's ADHD symptoms, not only at school but also in other settings to rule out children with other relevant difficulties. None of the children had a history of neurological or psychiatric problems. Written consent was obtained from children's parents before they participated in the experiment. The teachers taking part in the research were all female, with a mean age of 42.3 years, and with a lengthy teaching experience.

Material and Procedure

Teachers' ratings of children's social skills and cooperative practices. To investigate the children's social ability (four items) and cooperation (six items), we used the Social Questionnaire, a supplementary section of the COM scale (Rivetti & Capodieci, in press). The Social Questionnaire was completed by the group of teachers responsible for the class, including the teacher involved in the CL activities, among others. The social ability subscale identifies any social problems. On the basis of data collected from 907

primary school children, its mean score is 1.06 and Cronbach's alpha is .75. The cooperation subscale describes a child's cooperative skills, and the mean score and Cronbach's alpha (obtained with the same sample of 907 children) are 12.56 and .87, respectively.

To analyze children's social preferences (Elledge, Elledge, Newgent, & Cavell, 2016), we asked them to nominate three classmates with whom they most liked to play. As suggested by Asher and Dodge (1986), "liked-least" nominations were avoided. Instead, children rated how much they liked to play with each classmate on a 5-point scale, where 1 counted as *liked-least* nominations. Children were asked to write the names of their three favorite mates, and then to answer three questions for each classmate, on a scale from 1 = *not at all* to 5 = *very much*: "How much do you like to play with him/her?" "How much would you like him/her as a desk mate?" and "How much would you like him/her as a teammate?" As the number of classmates providing nominations varied between classrooms, scores were converted to *z* scores within each class—as is normal practice in sociometric research (e.g., Coie & Dodge, 1983)—to enable comparison between scores for students in class of different sizes.

Social preference scores were computed by subtracting "liked-least" ratings from "liked-most" nominations, then dividing this number by the number of student raters minus 1 (i.e., students could not rate or nominate themselves). Children were classified as "rejected" on the ground of the following three criteria (Coie, Dodge, & Coppotelli, 1982):

a. Standardized social preference scores < -1.0;
b. Standardized liked-least scores >0;
c. Standardized liked-most scores <0.

Social preference scores and rejected sociometric status were considered as separate indicators of children's social risk and were used to analyze changes.

Teacher training and CL activities. All six teachers involved in implementing CL attended a course on teaching methods and educational psychology for pupils with ADHD. The teachers received specific instructions on the use of CL and the experimental sessions started after the teachers and children had completed the questionnaires. During the training, teachers implemented a specific CL activity in class. A clinic psychologist expert in this field monitored the activities and suggested any necessary changes. The six subsequent sessions were held once a week and lasted 2 hr.

For each activity, teachers had to provide (a) general information on the class (number of children, number of males and females, children with a particular diagnosis or special educational needs), (b) learning objectives, (c) relational/social objectives, (d) timetable, (e) type of activity, (f) tools and materials, and (g) a final discussion and summary. In the relational and social objectives section, teachers were asked to specify which aspects of CL they have touched (positive interdependence, individual accountability, promotive interaction, use of social skills, group processing) and how.

The six sessions followed the procedure described in the *Manual for Personalized Cooperative Learning* (Rivetti & Capodieci, in press) and were completed in the months of November and December 2015, during the normal class time. The activities were organized so that the first two sessions were devoted to creating the class's climate and training the children's social abilities. They included play situations to help the children get to know each other better, trust each other, and learn to accept others and be part of a group. The next two sessions involved simple cooperative activities with children in small groups undertaking simple tasks, such as finding support for an explanation or an idea previously proposed by a teacher. The final two sessions involved complex learning activities. Children in groups of three to five had to follow specific rules (see the appendix for an example of the activities involved). Meanwhile, children in the classes forming the control group spent the same amount of time on their usual activities devoted to improving their academic learning. Teachers were asked to use similar contents and offer similar opportunities for the children to interact with their classmates as in the CL classes, but to avoid CL activities. Treatment fidelity was controlled both by receiving information and offering feedback before each activity and by meeting teachers. In particular, teachers' adherence to the program was tested by holding meetings with them during the formative lessons proposed, in the context of the master course every week. During these meetings, we also checked that the classes in the control group had not been involved in any CL activities. This careful monitoring ensured that there was no lack of adherence to the instructions. During the study period, the children with ADHD received no medical or psychological treatment. Approximately 1 week after the six sessions, the baseline study measures were collected again, that is, teachers completed the SDAI and the Social Questionnaire and the children reported their sociometric nominations.

The study was conducted in accordance with the ethical standards required by the Italian Scientific Community (Associazione Italiana di Psicologia, 2014) and had the approval of all the school authorities and parents involved.

Results

The children with symptoms of ADHD who attended the CL sessions were compared with the children with symptoms of ADHD attending normal classes, using a Group (CL vs. Control) × Time (pre- vs. post-CL) ANOVA for a mixed design.

Table 2. Mean Scores (*SD* in Parenthesis), Main Effect Size, and Interactions for the Two Groups of Children With Symptoms of ADHD (CL Group vs. Control Group) on Teachers' Ratings and Peers' Class Nominations.

	CL group (n = 16)		Control group (n = 14)		Time effect		Time × Group	
	Pre	Post	Pre	Post	$F(1, 28)$	p	$F(1, 28)$	p
Teachers' ratings								
SDAI inattention	18.13 (5.01)	15.88 (5.28)	16.57 (5.27)	15.27 (5.98)	12.45	.001	0.93	.34
SDAI hyperactivity	12.88 (8.37)	10.31 (7.78)	12.21 (5.89)	10.79 (6.10)	20.39	<.001	1.65	.21
COM sociality	3.94 (2.70)	3.06 (2.38)	3.71 (3.32)	3.07 (2.67)	11.21	.002	0.26	.61
COM cooperation	6.44 (2.61)	8.31 (2.85)	7.64 (3.75)	6.00 (3.74)	0.68	.80	15.68	<.001
Class nominations								
As a preferred playmate, Q1	−.29 (.24)	−.17 (.25)	−.26 (.31)	−.28 (.32)	2.83	.10	4.72	.04
As a preferred desk mate, Q2	−.31 (.29)	−.22 (.25)	−.33 (.35)	−.36 (.35)	1.04	.32	3.57	.07
As a preferred teammate, Q3	−.35 (.31)	−.22 (.23)	−.31 (.33)	−.31 (.34)	4.30	.05	5.07	.03

Note. Question (Q) 1: "How much do you like to play with him/her?" Q2: "How much would you like him/her as a desk mate?" Q3: "How much would you like him/her as a teammate?" CL = cooperative learning; SDAI = *Scala per i Disturbi di Attenzione/Iperattività per Insegnanti* [ADHD scale for teachers]; COM = comorbidity.

Table 2 presents the mean scores and standard deviations for the teachers' ratings and, in the last two columns of the table, the F values and the respective p values obtained for the main effect of time (indicating whether there were any general changes after 2 months of the study period), and the Pre–Post × Group interaction (which indicates whether one group changed to a different extent from the other).

Considering the teachers' questionnaire (Table 2), we found a significant main effect of time (with a medium effect size; Sullivan & Feinn, 2012) on the dimensions of inattention, $F(1, 28) = 12.45$, $p = .001$, $\eta_p^2 = .31$; hyperactivity, $F(1, 28) = 20.39$, $p < .001$, $\eta_p^2 = .42$; and sociability, $F(1, 28) = 11.21$, $p = .002$, $\eta_p^2 = .29$, but no significant Time × Group interaction. Table 2 shows that both groups scored lower in the teachers' perception of the children's inattentive, hyperactive, or socially problematic behavior. Considering the area of cooperation of teachers' questionnaire (where a higher average score means a higher level of cooperation), we found no significant main effect of Time ($F < 1$), but Time × Group interaction was significant, $F(1, 28) = 15.68$, $p < .001$, here again with a medium effect size, $\eta_p^2 = .36$ (Sullivan & Feinn, 2012). Only the CL group improved in the children's level of cooperation, and this improvement was significant, Student's $t(15) = 3.70$, $p = .002$

Concerning the results of peers' sociometric nominations, we analyzed the three questions ("How much do you like to play with him/her?" "How much would you like him/her as a desk mate?" "How much would you like him/her as a teammate?") separately. For the first question, we found no significant main effect of Time ($F < 1$), but the Time × Group interaction was significant, $F(1, 28) = 4.72$, $p = .04$, $\eta_p^2 = .14$. The interaction was due to the fact that only the children with ADHD symptoms in the CL group were judged more positive by their peers at the post-test, student's $t(15) = 2.77$, $p = .014$. In the question about how much the children wanted his or her peer as a desk mate, there was no main effect of Time ($F < 1$), and the Time × Group interaction only approached significance, $F(1, 28) = 3.57$, $p = .07$, $\eta_p^2 = .11$. In the third question, we found the main effect of Time, $F(1, 28) = 4.30$, $p = .05$, $\eta_p^2 = .13$, and a significant Time × Group interaction, $F(1, 28) = 5.07$, $p = .03$, $\eta_p^2 = .15$. Here again, only the children with ADHD symptoms in the CL group were judged more positively by their peers, Student's $t(15) = 3.01$, $p = .009$.

Then we analyzed whether the sociometric status of the children with symptoms of ADHD changed after the period of intervention in the three different areas (playmate, desk mate, and teammate) using the procedure described in the "Method" section (see also Coie et al., 1982), and we performed a chi-square test for dichotomous variables (rejected vs. accepted). Table 3 shows that there were no differences between the two groups before the intervention, whereas some differences were apparent afterwards. As regards playing together, we found a significant difference between the number of children with ADHD symptoms in the two groups who were rejected by their peers before and after the intervention $\chi^2(1) = 4.69$, $p = .03$. However, the difference only approached the significance for rejection as a desk mate and teammate, $\chi^2(1) = 3.21$, $p = .07$, but the data show that the switch from a rejected to an accepted status only occurred for the children attending CL lessons. These effects varied slightly by grade (and classes) involved in the CL project. For the first two questions, there was a change from pre-test to post-test among first graders from two rejected to one; in second grade, from three rejected to none; in third grade, from two rejected children to none; and in fourth grade from three rejected to two. For the third question, there was no change for one child in first grade, a change from two rejected children to none in second grade,

Table 3. Changes From Rejected to Accepted Children in the Two Groups of Children With Symptoms of ADHD (CL Group vs. Control Group).

	CL group (n = 16)		Control group (n = 14)			
	Pre	Post	Pre	Post	$\chi^2(1)$	p
Accepted as a playmate	6	12	6	5	0.09	.77
Rejected as a playmate	10	4	8	9	4.69	.03
Accepted as a desk mate	6	12	5	6	0.01	.91
Rejected as a desk mate	10	4	9	8	3.21	.07
Accepted as a teammate	8	12	6	6	0.15	.70
Rejected as a teammate	8	4	8	8	3.21	.07

Note. Peers were asked, "How much do you like to play with him/her?" "How much would you like him/her as a desk mate?" "How much would you like him/her as a teammate?" CL = cooperative learning.

from two rejected children to one in third grade, and from three rejected children to two in fourth grade. Should be noted, however, that one child in fifth grade changed status from accepted to rejected for the first two questions.

Discussion

Poor social skills prevent children with symptoms of ADHD from interacting successfully with their peers (Mrug et al., 2007). These problems lead to their rejection by their peers and have negative longitudinal outcomes in adolescence: These individuals are more likely to suffer from psychological or conduct problems (Bagwell et al., 2001).

The main context in which children refine their social skills is the classroom, where peers and teachers tend to give children with symptoms of ADHD a more or less constantly negative feedback about their social problems and the difficulty to control their behaviors. Some studies have investigated how to improve social skills in children with ADHD, focusing mainly on their social acceptance by peers by measuring changes in their class nominations (Kuester & Zentall, 2012; Mikami et al., 2013). In the past, the sociometric status of children with ADHD has proved refractory to treatment, but studies have failed to thoroughly analyze the importance of involving regular classroom teachers and pupils, despite the suggestion that improving inclusiveness could lead to improvements and changes in social preferences (Mikami et al., 2013). In the present study, we examined the implications of taking action on standard classroom interactions by using CL procedures. CL has shown positive effects in whole-classroom observational research (Beyda et al., 2002; Gillies, 2003), but more systematically and controlled studies are needed, and the particular case of children with ADHD has never been considered. Teachers who have children with ADHD in their classes are often reluctant to use CL because, although they think it would be useful and they would like to use it more (Garcia, 2013; Lopata et al., 2003), they perceived CL as a difficult method and too demanding for children with behavioral problems. Training teachers on how to manage children with symptoms of ADHD, and providing them with a basis for putting the CL method into practice would thus be the first step toward the success of an intervention to help children with ADHD symptoms improve socially and be reconsidered by their peers, giving them a chance to be accepted.

The aim of the present study was to analyze how the practice of teaching according to the CL method (in the hands of experienced and knowledgeable teachers) can help children with symptoms of ADHD to fit in the rest of the class, be more appreciated by their peers, and improve their social and cooperative skills.

Our results show that, after 2 months, teachers generally noticed an improvement and a reduction of some symptoms of inattention and hyperactivity in the children with ADHD symptoms in the CL group and the control group (classrooms conducting standard lessons). The children's scores relating to the presence of ADHD symptoms remained high, of course, but there was an important reduction with a good effect size. The improvement was general, however, and concerned both groups, so it may have been due not only to teachers' increased attention to ADHD but also to measurement artifacts, and in particular to a regression to the mean. Teachers noted an improvement in all the children's social abilities, but an improvement in the cooperation skills only in the children taking part in the CL activities (and there was even reportedly some deterioration in the other children's cooperation).

Concerning peer preferences based on class nominations, we found a specific improvement for children with ADHD symptoms who took part in the CL sessions. In particular, there was an increase in the number of their classmates who would choose to play with children with symptoms of ADHD, in those who would like them as a teammate, and also a trend toward an increase in the number of their peers who would want a child with ADHD symptoms as a desk mate. We compared the changes in sociometric status (rejected vs. accepted) of the children with symptoms of ADHD between the two groups. An

important change emerged for the playmate area, with the children in the CL group passing from a situation where six were accepted and 10 were rejected to a situation where 12 were accepted and only four were still rejected. Positive, but less evident changes were found for the desk mate and teammate areas too, where the number of accepted children being accepted increased only in the CL group and not at all for the control group.

To sum up, our study offers some new input on the importance of implementing CL in classrooms attended by children with symptoms of ADHD and TD. In our view, an important factor concerns the training and attitude of teachers, who needed to be sensitive and knowledgeable about ADHD and CL to be able to create an adequate setting (McAuliffe et al., 2009). It should be noted that the CL activities were proposed gradually in this study, enabling the children to learn some basic social abilities, practice communicating with others, and solving interpersonal problems, before working together toward academic goals (Johnson et al., 2007). The present study only involved six sessions (plus an initial practice session) and the effects of CL would probably be more substantial if a more prolonged CL educational program were implemented (and this could be done in a normal class).

A feature of the present project lay in that the students with symptoms of ADHD worked together with the other children in the classroom—unlike the case of other interventions to improve the social skills of children with ADHD (e.g., Abikoff et al., 2004; Mikami et al., 2013)—and this may have helped their peers to get to know them better and nurtured a mutual exchange of help and needs (Chew, Jensen, & Rosén, 2009). In fact, a study involving college students showed that more negative than positive adjectives were endorsed by college students in describing classmates with ADHD, but more frequent contact with individuals with ADHD was associated with more favorable ratings, suggesting the importance of facilitating peer normalization (Chew et al., 2009).

Despite the interest of the findings, the present study suffers from a number of limitations. In particular, our sample was relatively small and our results should be replicated with larger samples. Our study benefited from particular conditions that enabled us to involve expert teachers (who were also attending a course on the management of children with ADHD) and to give them training on the use of CL, but their timetable left us only 2 months for our classroom intervention and prevented any subsequent follow-up. Because the teachers were attending a course on ADHD and their selection for the study was not fully randomized, it is hard to say to what extent the improvements observed were due to the teachers being better prepared or more motivated rather than to the CL procedure. Another important limitation lies in that we were unable to collect organized information from parents (who were asked to complete a questionnaire, but only few did so). Another issue concerns the measures used in the study, which were based on teachers' subjective ratings or on children's feelings, with no observational measures or blind subjective ratings. Future research should include objective observations on the actual interactions between children with ADHD and their classmates, though it has to be said that the measures and method used in the present study are standard in this type of research because of the complexity of objective assessment. It was impossible for us to include a blind outside observer, but teachers made an effort to be as objective as possible, also basing their ratings on consultations with other members of teaching staff. The fact that their ratings were consistent in their differentiation between the areas offers some indication of their reliability. Concerning pupils' responses, it may be that they were also influenced by the more positive atmosphere created in the classroom. This atmosphere is a crucial factor in changing social interactions. It is worth nothing, however, that the children's class nominations differed for the three questions they were asked, indicating that they were not giving general responses, but were considering each question specifically.

To conclude, this study offers new important insight on the feasibility of developing situations for social interaction in a standard class for promoting the social skills and acceptance of children with ADHD. To the best of our knowledge, it is the first case study to report some positive changes being induced in the sociometric measures concerning children with ADHD. Given some skepticism in the literature on the effects of psychoeducational interventions on ADHD, and the scarcity of research on CL (partly due to the difficulty of conducting interventional research and controlling all the variables involved), the present study offers quite an optimistic view and should prompt further research and educational efforts in this area. It seems important for the future of children with symptoms of ADHD to prepare and train teachers to influence the social preferences of the children in their classes and to implement CL activities to help students to cooperate and appreciate one other.

Appendix

Example of a complex CL activity for second graders.

- **General information on the class:** 25 children, 13 males, and 12 females.
- **Learning objectives:** Listening to and understanding a story titled "Rainbow: The most beautiful fish of all the seas"; making a "book in a box" (i.e., making characters of the story with the materials available and decorating a box to contain them), and telling the same story to children in other classes with the help of the contents of their box.

- **Relational/social objectives:** Learning to work together, nurturing a positive interdependence (I need the group and the group needs me), solving conflicts, sharing the material, combining different opinions and ideas, and involving everyone in the activity. Assigned roles: materials manager (the only child given the materials); reporter (the child who asks the teacher questions and reports the information back to the group); voice controller (in charge of keeping the children's tone of voice at an appropriate level); reorganizer (the child responsible for keeping the desk tidy during and after the activity).
- **Timetable:** 4 hr (two 2-hr sessions).
- **Type of activity:** The teacher reads the story "Rainbow: The most beautiful fish of all the seas" to the class. The story is about a fish that learns to be generous, gives its colorful scales to other fish, and is surrounded by friends as a result. The teacher works orally on the comprehension of the text, by means of targeted questions. Then the teacher divides the students into two groups of four and three groups of three pupils according to the criteria of cognitive and relational heterogeneity and assigns each member of the group a task, as mentioned above. Each child uses the available material to make his or her own fish or other characters named in the story. The children take turns coloring the inside and outside of the box. They decide together how to complete the decoration of the box, for example, by writing the title of the story on the cover. Then the characters they have made are strung onto the thread attached to the edge of the box to obtain the effect of a diorama. When the book in the box is ready, each group chooses another class in the school where they go to tell their illustrated story.
- **Tools and materials:** A shoe box, tempera paints, crayons, markers, trimmings, seashells, sand, sticks, sequins, beads, tissue paper, crepe paper, colored paper, glue sticks, hot glue, transparent drool.
- **Final discussion:** Students are administered a questionnaire on their satisfaction with the proposed cooperative learning activity.

The activity was conducted briskly but was very productive. The children kept essentially to their assigned roles, the most problematic proving the voice controller because the children talked together while making their fish characters because they were not satisfied with each other's work.

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Research paper

Narcissistic traits as predictors of emotional problems in children with oppositional defiant disorder: A longitudinal study

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ABSTRACT

Background: Children's self-views encompass two independent dimensions: self-esteem and narcissism, which recently have received growing attention from researchers and clinicians. The current study sought to test whether these dimensions might predict the developmental course of children with Oppositional Defiant Disorder diagnosis.

Method: The sample (N = 64, M age = 10.1 years, 57 boys) included children with Oppositional Defiant Disorder diagnosis. We examined longitudinal relationships between self-views (both self-esteem and narcissism) and parent-reported internalizing and externalizing behavioral problems.

Results: The study spanned two time-points, spaced 12 months apart. None of the predictors were longitudinally associated with the levels of externalizing behavioral problems in children. However, narcissism predicted the levels of children's internalizing problems at the follow-up, whereas self-esteem did not.

Limitations: The relatively small sample and the lack of assessing causality limit the generalizability of the findings. Results need to be replicated in larger samples.

Conclusions: These findings illustrate the value of taking into account children's narcissistic traits in clinical assessment. By broadening knowledge of narcissistic traits in clinical samples of children, we hope to inform assessment procedures in standard clinical practice, as well as the development of tailored interventions to curb the emergence of later negative outcomes related to childhood narcissism, such as internalizing problems.

1. Introduction

Oppositional Defiant Disorder (ODD) is one of the most prevalent childhood psychiatric disorders, with prevalence estimates ranging from about 3% - 16% in community samples, and from 28% - 65% in clinical samples (Boylan et al., 2007). ODD is characterized by persistent angry and irritable mood (e.g., the child easily loses temper), argumentative and defiant behavior (e.g., the child refuses to comply with requests), or vindictiveness (American Psychiatric Association (APA), 2013). ODD contributes to poor psychosocial functioning during childhood, with echoes across the life course (Burke et al., 2014; Rowe et al., 2005).

Although research on how childhood ODD may predict the developmental course of psychopathology has focused mainly on externalizing behavior problems, some work has tested predictive associations between ODD and internalizing problems, too. One longitudinal study found, in an at risk sample of 510 children aged 2–5, that children with ODD were more likely to continue to exhibit disorder, and to develop comorbid internalizing (as well as externalizing) disorders, including anxiety and mood disorders, years later (Lavigne et al., 2001). Similarly, findings from the Great Smoky Mountains Study showed, in a community sample of children aged 9–16, that ODD was a significant risk factor for the emergence of later anxiety disorders and depression (Copeland et al., 2009), along with later conduct problems (Rowe et al., 2002).

What explains why ODD may foretell not just externalizing outcomes, but—in some children—internalizing outcomes as well? One plausible reason is that common risk factors, such as child characteristics known to be associated with broad and diverse indices of maladjustment, drive the emergence of (potentially comorbid)

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internalizing symptoms, along with externalizing symptoms, over time (Burke, 2012; Leadbeater and Homel, 2015; Mikolajewski et al., 2017). Among many factors, emotional dysregulation may help to explain this frequent association. A severe difficulty in emotion regulation is a pervasive and impairing characteristic of several disorders, including ODD. Children with ODD are frequently irritable, moody, and angry, and studies have widely shown that they exhibit a significant dysregulation of emotions, especially negative ones (e.g., sadness and anger; Tonacci et al., 2019). This is consistent with previous reports in individuals with two of the main internalizing disorders, namely depression and anxiety (Brody et al., 1999; Campbell-Sills et al., 2006; Tull et al., 2009). Moreover, among ODD children, those with higher levels of emotion dysregulation (e.g., severe irritability) are at higher risk of developing internalizing problems (Burke et al., 2010; Evans et al., 2017; Rowe et al., 2010; Stringaris and Goodman, 2009).

As it stands, little is known about whether or how children's self-views predict the developmental course of psychopathology, and especially of externalizing and internalizing symptoms, in children with ODD. Children's self-views encompass two core independent dimensions—i.e., self-esteem and narcissism—which recently have received growing attention from researchers and clinicians alike (e.g., Hiemstra et al., 2019; Muratori et al., 2018; Thomaes and Brummelman, 2016).

Self-esteem refers to one's global feelings of self-worth (Rosenberg, 2015), the extent to which someone likes oneself (Brown and Marshall, 2006). Self-esteem is central to people's well-being, and theoretical models have long associated low self-esteem with the development and expression of psychopathology. One example is the Vulnerability model (Beck, 1967). Briefly, it assumes that people with low levels of self-esteem possess fewer coping skills, and this, in turn, makes them more vulnerable to the effects of negative and stressful events. Instead, the Scar model suggests that low self-esteem might be a consequence of psychopathology. Low self-esteem would be caused by the impairment of psychological resources and interpersonal relationships, usually associated with psychological disorders.

Research on children's level of self-esteem as a correlate or longitudinal predictor of psychopathology has provided some inconsistent findings. For example, although low self-esteem is a common correlate of childhood internalizing disorders, including anxiety (Henning et al., 2007) and depression (Orth et al., 2009), it appears to be only a weak predictor of later internalizing problems (Keane and Loades, 2017). As to externalizing problems (e.g., aggression, conduct problems) research suggests a heterogeneous pattern of association as well (Denissen et al., 2018). While some studies have found that aggressive children tend to have high levels of self-esteem (Menon et al., 2007; Sandstrom and Jordan, 2008), other studies found no consistent link between self-esteem and aggression or externalizing problems (e.g., Hiemstra et al., 2019; Thomaes et al., 2008). Finally, other research in both community (e.g., Donnellan et al., 2005) and clinical samples (Muratori et al., 2018) of children suggests that low levels of self-esteem may increase the risk for aggression.

Narcissism involves an exaggerated need for attention and admiration, along with a sense of entitlement and grandiosity (Morf and Rhodewalt, 2010; Thomaes and Brummelman, 2016). As a dimensional trait, narcissism varies in the general population. Individual differences in narcissism emerge and can be assessed in children from about age 8 (Thomaes and Brummelman, 2016). The Dynamic Self-Regulatory Processing Model (Morf & Rhodewalt, 2001) argues that narcissism is a relentless personality process that revolves around the need to create and maintain a positive self-view. The instability of narcissists' self-view requires them to seek external validation, though, especially in the long term, it is an extremely difficult goal to reach. This may lead to anger, negative feelings, and potentially also aggressive behavior and interpersonal problems.

Some preliminary findings suggest that narcissism may place children at risk for developing internalizing problems. That is, research in community samples of children and young adolescents showed that narcissism predicts heightened internalizing symptoms, including depressive and anxious symptoms and fear of negative evaluation (Thomaes et al., 2008b; Washburn et al., 2004). Moreover, research in children with ODD showed that narcissism was associated with increased emotional symptoms, such as worry and psychosomatic complaints (Muratori et al., 2018). Besides the suggestive evidence that narcissism may predispose children to experience internalizing problems, narcissism has been established as a risk factor for youth aggression and conduct problems as well (Barry et al., 2007). Among clinical samples of children referred for disruptive behavioral problems or ODD, narcissism was found to be positively associated with self-reported aggression (Hiemstra et al., 2019) and parent-reported conduct problems (Muratori et al., 2018), although some inconsistencies across informants remain (Hiemstra et al., 2019).

Notwithstanding this emerging evidence, longitudinal research to examine how the self-views (i.e., self-esteem and narcissism) of children with ODD predict change in internalizing and externalizing problems over time is still lacking. We aimed to help fill this lacuna. Accordingly, we examined the prospective links among narcissism, self-esteem, and both internalizing and externalizing problems in a sample of ODD outpatients (ages 8 – 12), a different sample from the one we used in our previous research. This research may help to better understand heterogeneity in the developmental course of ODD and its associated pathology and may inform the development of more tailored interventions.

2. Method

2.1. Participants

The present study has been conducted in an outpatient hospital unit, working with children and adolescents with aggressive behavioral problems and/or ADHD. We asked all parents of children (age range 8–12 years) who were admitted to the hospital from May to October 2018 and received an ODD diagnosis, if they were interested in taking part in the study. Trained child psychiatrists provided the ODD diagnosis, using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). Participants were excluded from participation if (1) they suffered from autism spectrum disorder, (2) their IQ was below 80 (assessed with Wechsler Intelligence Scale for Children Fourth Edition [WISC-IV]; Wechsler et al., 2012), or (3), their parents did not give consent for them to take part in the study.

A sample of $N = 64$ children entered the study at T1 (consent rate = 87%). They were all Caucasian, and most of them (57, 90%) were boys. Parent-reported approximate annual household incomes ranged from < 15,000 to > 40,000 Euros. Most (75%) reported incomes ranged from 20,000 to 30,000 Euros, which is equivalent to an average household income in Italy. Mean IQ was 97.73 ($SD = 8.29$). Some children had comorbid ADHD (15, 24%), or were receiving pharmacological treatment at T1 (25, 38%). Baseline CBCL externalizing scores were 66.48 ($SD = 2.75$) and internalizing scores were 64.04 ($SD = 3.67$). Eight children dropped out of the study at follow-up. The baseline measures provided include the participants who left the study at T2.

We did a post-hoc power analysis (Faul et al., 2007) to determine the stastistical power associated with our sample size, which is 0.98 given an effect size of 0.40.

2.2. Procedure

The study spanned two time-points, spaced 12 months apart. At baseline (T1), children completed the self-view measures—i.e., the *Childhood Narcissism Scale* (CNS) (Thomaes et al., 2008b), and the *Multidimensional Self Concept Scale* (MSCS) (Bracken, 1992). A research

Table 1
Correlations among variables.

	1	2	3	4	5	6	7	8
1. Age	1	.047	-.024	.056	.081	.099	-.100	.110
2. Pharmacotherapy		1	-.110	-.086	.053	-.039	.059	.128
3. CNS_T1			1	-.030	.251*	-.019	.367*	-.195
4. MSCS_T1				1	-.085	-.242	.036	.118
5. CBCLINT_T1					1	.162	.397*	.158
6. CBCLEXT_T1						1	.112	.252*
7. CBCLINT_T2							1	.119
8. CBCLEXT_T2								1
Mean	123.80		9.89	419.62	64.06	66.48	63.82	64.42
SD	5.41		4.47	49.62	3.67	2.76	8.33	7.37

Note. False discovery rate (FDR; Benjamini and Hochberg, 1995) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied across all correlations.

* $p < .05$. CNS_T1 = Child Narcissism at T1; MSCS_T1 = Self-esteem at T1; CBCLINT_T1 = Internalizing Child Behavior Checklist at T1; CBCLEXT_T1 = Externalizing Child Behavior Checklist at T1; CBCLINT_T2 = Internalizing Child Behavior Checklist at T2; CBCLEXT_T2 = Externalizing Child Behavior Checklist at T2.

Age: months; CNS: raw scores (sum of items' scores); MSCS: raw scores (sum of items' scores); CBCLINT_T1/T2: T scores; CBCLEXT_T1/T2: T scores.

assistant introduced the study, emphasized the confidentiality of responses, and encouraged children to ask questions if they had difficulty in understanding any items. Also at T1, parents completed the *Child Behavior Checklist* (CBCL) (Achenbach and Rescorla, 2004). After 12 months (T2), parents completed the CBCL again. All children and parents gave written informed consent at both time points.

2.3. Measures

Child Behavior Checklist (Achenbach and Rescorla, 2004). The CBCL is a 118-item standardized behavioral checklist, completed by parents, to index behavioral problems and competencies in children ages 6 to 18. Items are rated along a 3-point scale ranging from 0 to 2. Items are aggregated in eight subscales, which, in turn, comprise Internalizing (sample items: "There is very little he/she enjoys", "Unhappy, sad, or depressed") or Externalizing (sample items: "Argues a lot", "Gets in many fights") domains. We used the domain T-scores at both time points in the current study. The CBCL domains have been shown to display good diagnostic efficiency for assessing common externalizing and internalizing problems in children (e.g., Hudziak, Copeland, Stanger, & Wadsworth, 2004). In the current sample, the reliability coefficients (Cronbach alpha) of the CBCL internalizing and externalizing domains at both time points ranged from 0.81 to 0.83.

Childhood Narcissism Scale (Thomaes et al., 2008b). The CNS is a 10-item self-report scale, which measures childhood narcissism as a dimensional trait. Items are positively worded, so children do not feel they are rating negative or socially undesirable (sample item: "Kids like me deserve something extra"). Responses are scored using a 4-point scale ranging from 0 (not at all true) to 3 (completely true). The CNS has been shown to be a one-dimensional measure of stable individual differences in childhood narcissism with good internal consistency. For the present study, we used the Italian version of the CNS, recently validated by Muratori et al. (2018), which showed similar psychometric properties as the original version.

Multidimensional Self Concept Scale (Bracken, 1992). The MSCS is a 150-item multidimensional measure of children's self-concept. The scale measures self-concept in six contextual domains: Social (e.g., "I am too shy"), Competence (e.g., "I am too lazy"), Affect (e.g., "I am not a happy person"), Academic (e.g., "I learn fairly easily"), Family (e.g., "My parents care about my future"), and Physical (e.g., "I feel good about how I look"). These domains are strongly related and jointly contribute to a general self-concept factor (i.e., self-concept total score). The MSCS domain scores are highly correlated with the scores of a self-esteem measure in samples of Italian children (Bracken, 1993). The current study used the total score of the MSCS as a measure of self-esteem, which showed good internal consistency (alpha 0.88).

3. Statistical analysis

We conducted a hierarchical regression analysis to examine how children's self-views (i.e., narcissism, self-esteem) predict the levels of the internalizing and externalizing problems of children with ODD. Specifically, we explored two regression models. In the first model, our dependent variable was the variance in T2 CBCL externalizing scores, which cannot be predicted from T1 CBCL externalizing score. In Step 1, we entered gender, age, pharmacotherapy (yes or no), and externalizing CBCL score at T1 as control variables. In Step 2, we entered narcissism and self-esteem at T1 as predictor variables. The second regression model was identical to the first, but we replaced the externalizing CBCL scores at T1 and T2 by its internalizing counterpart scores. All data were analyzed using the Statistical Package for Social Science (SPSS) 25.0 for Windows. The false discovery rate (FDR; Benjamini and Hochberg, 1995) correction of the *p*-values (implemented using the *p*.adjust function in R; R Core Team, 2018) was applied for all statistical analyses.

4. Results

Preliminary analyses. Eight children dropped out of the study at follow-up and they were not included in the analyses. Therefore, statistical analysis has been conducted on a sample of 56 children. Descriptive statistics and zero-order correlations for the main study variables are shown in Table 1. Narcissism, measured at T1, was positively associated with internalizing CBCL scores at both T1 and T2. The CBCL internalizing and externalizing scores were correlated over time.

Table 2 shows the results for the first regression model testing

Table 2
Linear regression analysis with Externalizing CBCL score at T2 as dependent variable (N = 56).

		Beta	Adjusted R2	p
Block 1			.091	
	Age	-.060		NS
	Gender	.078		NS
	Pharmacotherapy	.203		NS
	CBCLEXT_T1	.192		NS
Block 2			.112	
	MSCS_T1	.203		NS
	CNS_T1	-.175		NS

Note. False discovery rate (FDR; Benjamini and Hochberg, 1995) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied for all predictors. CNS_T1 = Child Narcissism at T1; MSCS_T1 = Self-esteem at T1; CBCLEXT_T1 = Externalizing Child Behavior Checklist at T1

Table 3
Linear regression analysis with Internalizing CBCL score at T2 as dependent variable (N = 56)

		Beta	Adjusted R^2	p
Block 1			.110	
	Age	-.149		NS
	Gender	-.014		NS
	Pharmacotherapy	.067		NS
	CBCLINT_T1	.374		.043
Block 2			.183	
	MSCS_T1	-.175		
	CNS_T1	.294		.043

Note. False discovery rate (FDR; Benjamini and Hochberg, 1995) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied for all predictors. CNS_T1 = Child Narcissism at T1; MSCS = Self-esteem at T1; CBCLINT_T1 = Internalizing Child Behavior Checklist at T1

predictive linkages between the self-view measures and externalizing problems. None of the predictors included in Step 1 of the model were associated with the levels of externalizing behavioral problems at T2. More importantly, neither narcissism nor self-esteem, which were entered in Step 2 of the model, were significant predictors of change in externalizing problems over time. The regression model explained around 11% of the variance. Variance inflation (VIF) in this regression was lower than 2.

Table 3 shows the results for the second regression model testing predictive linkages between the self-view measures and internalizing problems. The levels of the CBCL internalizing score at T1 predicted the levels of internalizing problems at T2. More importantly, we found that narcissism predicted the levels of children's internalizing problems at T2, accounting for their internalizing problems at T1. By contrast, self-esteem was not associated with such changes in internalizing problems over time. This regression model explained around 18% of the variance. Variance inflation (VIF) in this regression was lower than 1.

5. Discussion

Oppositional Defiant Disorder is characterized by dysregulation of emotion and behavior, and increased risk of developing further internalizing and externalizing problems over time (Lavigne et al., 2001). Both individual and environmental factors contribute to possible internalizing and externalizing outcomes in ODD children (REFS). Focusing on individual factors, we tested narcissism and self-esteem as possible predictors of internalizing and externalizing problems in a clinical sample of children with ODD.

We found associations between childhood narcissism and internalizing problems measured at baseline and after 12 months. In particular, narcissism (assessed at baseline) predicted children's levels of internalizing problems at the follow-up, after controlling for baseline levels of internalizing problems. This finding builds on and extends previous studies that found a cross-sectional link between childhood narcissism and anxiety and depressive symptoms in youth (Washburn et al., 2004), Moreover, it is consistent with prior work that suggested the presence of significant emotional symptoms in children with an ODD diagnosis and high narcissistic traits (Muratori et al., 2018).

The Dynamic Self-Regulatory Processing Model (Morf & Rhodewalt, 2001) casts narcissism as involving a self-concept that is both grandiose and vulnerable, along with a craving for external validation. Narcissists are relatively insensitive to others' concerns, and typically present themselves as arrogant, entitled, and dismissive. Consequently, they often leave other people feeling hurt, sad, or angry. In the long run, narcissists often fail to get the approval they seek, which leads them to seek further self-validation. Indeed, although children with narcissistic traits can make positive impressions on others in the short term, they often experience at least some level of rejection or criticism from peers over time (though see Poorthuis et al., 2019). While children with ODD often suffer interpersonal problems (REFS), the presence of co-occurring narcissistic traits may further exacerbate these problems. Peer relational problems (e.g., rejection, social isolation) are potent risk factors for internalizing problems (Laursen et al., 2007; Van Lier and Koot, 2010; Sentse et al., 2017). Thus, when the emotional instability and dysregulation that characterizes ODD co-occurs with the interpersonal sensitivity that characterizes narcissism, this may place children at increased risk of internalizing symptoms.

Narcissism (assessed at baseline) did not predict externalizing problems. This latter finding was unexpected, and different from prior cross-sectional studies—both in community and clinical samples of children—showing that narcissism does place children at risk of externalizing problems (Hiemstra et al., 2019; Muratori et al., 2018; Thomaes et al., 2008a). Our finding is not unprecedented, however. In a longitudinal study with adolescents, Wetzel et al. (2019) found that overall narcissism at 14 years of age failed to predict the later emergence of problem behaviors, including symptoms of Conduct Disorder and ODD. We speculate that in our sample of ODD children, other variables (that we did not assess) were more potent predictors of the development of externalizing problems—think of callous-unemotional (CU) traits (lack of guilt and remorse, superficial and shallow emotions, lack of empathy, Frick and White, 2008; Pisano et al., 2017) or contextual factors, such as parenting and parental psychopathology (Muratori et al., 2015; 2016). We emphasize that our sample consisted of severely impaired ODD children referred to a third level psychiatric hospital, who already showed very high levels of externalizing problems at the T1 assessment, leaving relatively little room for further symptomatic increases. Moreover, pharmacotherapy may have modified the longitudinal relationships between children's self-views and their later behavioral problems in a subset of our sample (Masi et al., 2016, 2017).

Finally, our results suggest that self-esteem is not a robust predictor of change in externalizing or internalizing problems in ODD children, a finding that is consistent with prior studies (e.g., Hiemstra et al., 2019; Keane and Loades, 2017). And yet, other work in general population samples of youth has found that low self-esteem is a risk factor for increased psychological symptoms, especially internalizing ones (Sowislo and Orth, 2013). Differences in sampled populations, along with those in study designs may explain some of these inconsistencies, and highlight the need for research to better understand this heterogeneity.

Our findings must be interpreted in light of some study limitations. We used a global measure of narcissistic traits, and did not assess the difference between grandiose and vulnerable narcissism. Initial findings highlighted that this distinction may have significant implications for children's adjustment and psychopathology (see for instance, Derry et al., 2019). We encourage future work to address this topic. Also, we assessed children's externalizing and internalizing psychopathology with parent-report measures (CBCL subscales) only. Multiple-informant assessments would have provided a more comprehensive view. While we focused on children's self-views as potential predictors of psychological problems, our design did not allow for testing possible joint or interactive effects of other candidate predictors—including other child characteristics (e.g., the presence of subclinical mood disorder, other personality or temperamental traits, intelligence) or environmental variables (e.g., parenting, parental psychopathology). Finally, our relatively small sample size did not allow us to test potential interactions between our self-views measures. Previous work has shown that narcissism can have differential effects on externalizing problems at high as compared to low levels of self-esteem (Thomaes and Brummelman, 2016), a possibility that we could not address here.

There is a growing body of literature that illustrates the value of taking youth narcissism into consideration in psychological assessment in clinical contexts. The present work contributes to this literature, and

shows how narcissism may influence the psychological adjustment of ODD children over time. In light of the current evidence, it would be premature to recommend targeting narcissism as treatment strategy for ODD children. Still, our results highlight the need to better understand children's narcissistic traits and how they are implicated in processes of psychological maladjustment.

CRediT authorship contribution statement

Pietro Muratori: Conceptualization, Writing - original draft. **Annarita Milone:** Conceptualization, Writing - original draft. **Valentina Levantini:** Writing - review & editing. **Simone Pisano:** Writing - review & editing. **Valentina Spensieri:** Formal analysis, Methodology. **Elena Valente:** Data curation. **Sander Thomaes:** Supervision, Writing - review & editing. **Gabriele Masi:** Conceptualization, Writing - original draft.

Declaration of Competing Interest

Dr. Masi was on the advisory boards for Eli Lilly, Shire and Angelini. He has received research grants from Eli Lilly and Shire, and has been speaker for Eli Lilly, Shire, Lundbeck, FB and Otsuka. None of the other authors have conflicts of interest to declare.

Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.075.

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Commentary

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Supplementation with polyunsaturated fatty acids (PUFAs) in the management of attention deficit hyperactivity disorder (ADHD)

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Abstract

While pharmacotherapy and psychosocial interventions are recommended as the primary frontline treatment for attention deficit hyperactivity disorder (ADHD), alternative approaches to managing ADHD are becoming increasingly popular among patients and their families. Supplementation with polyunsaturated fatty acids (PUFAs) is an example of this. PUFA supplementation is not recommended by guidelines for managing ADHD; however, patients may still decide to use it. To provide direction to healthcare professionals (HCPs) managing ADHD, eight international experts in the field of adult and child ADHD came together for the Continuum Education Board: Omega Supplements in ADHD meeting. This commentary summarises the panel's consensus that current evidence suggests PUFA supplementation has a small beneficial effect on behaviour in children with ADHD, and that further high-quality research is needed to clearly evaluate and define its role in the management of ADHD of children, adolescents and adults. The panel concluded that in cases where patients use PUFA supplementation, HCPs should be comfortable explaining the potential gains that they may have and their possible side effects. The panel also concluded HCPs should not reinforce the idea that PUFA supplementation should replace treatment approaches with a more robust evidence base for managing ADHD.

Keywords

Nutrition, ADHD, omega, health, supplements, attention deficit hyperactivity disorder, polyunsaturated fatty acids, PUFA

Introduction

Primary frontline treatments recommended for attention deficit hyperactivity disorder (ADHD) may make use of both pharmacotherapy and psychosocial interventions. However, alternative approaches to managing ADHD are becoming increasingly popular among patients and their families (Bos et al., 2015). Supplementation with polyunsaturated fatty acids (PUFAs) is one example of this; however, its use is not recommended by mainstream clinical guidelines, such as NICE guidelines (NICE guidelines, 2016), due to the relatively low effect size of meta-analyses' results. Important questions such as how PUFA supplements should be used, if patients decide to use them, remain unanswered, underscoring the need for well-designed clinical trials to support healthcare professionals (HCPs) to make confident recommendations to their patients (Gow et al., 2015).

In an attempt to provide direction to HCPs managing ADHD, on 29 August 2017, eight international experts in

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the field of both adult and child ADHD came together for the Continuum Education Board: Omega supplements in ADHD meeting. The meeting served as a forum in which a panel of experts could assess the current landscape of PUFA supplementation in light of accumulating data, and provide practical recommendations to help HCPs make evidence-based decisions for patients and their families seeking alternative treatments. Details from the panel's consensus are summarised here, along with recommendations for future research.

Mechanism of action and rationale for effect in ADHD

Omega-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential nutrients, and DHA is highly abundant in the mammalian brain (Bos et al., 2016). By altering cellular phospholipid membranes in the central nervous system, omega-3 PUFAs play an important role in different neural processes, some of which may be compromised in individuals with ADHD. Animal studies suggest effects on neurotransmission – via increased levels of serotonin and dopamine – and cell survival (Bazinet and Laye, 2014; Chalon, 2006). Omega-3 PUFAs might help minimise oxidative stress, which can be increased in individuals with ADHD (Bos et al., 2016).

Inflammation, which could be associated with neuropsychiatric disorders, might be reduced with EPA and DHA (Donev and Thome, 2010; Simopoulos, 2008). In contrast to omega-3 PUFAs, omega-6 PUFAs produce compounds that have pro-inflammatory properties (Königs and Kiliaan, 2016). Furthermore, a high omega-6/3 PUFA ratio is thought to have adverse health effects, including the development of some psychiatric disorders (Simopoulos, 2011). Indeed, Western diets show a trend towards higher omega-6/3 PUFA ratios, which has been posited to correlate with a higher rate of certain psychiatric conditions. The ratio between omega-3/6 PUFAs is important since omega-3 PUFAs competitively inhibit omega-6 PUFAs, causing a reduction in the synthesis of pro-inflammatory mediators (Ergas et al., 2002).

In line with these observations, recent findings have shown that some individuals with ADHD have low blood and plasma levels of omega-3 PUFAs (Bos et al., 2015; Chang et al., 2017; Parletta et al., 2016). Such a deficiency may have a significant and widespread impact on the function and development of the brain (Königs and Kiliaan, 2016). Therefore, increasing the intake of omega-3 PUFAs, through PUFA-rich diets or PUFA supplements, could be an appropriate strategy to address this potential deficiency and improve ADHD symptoms.

Efficacy

PUFAs have been assessed across many psychiatric conditions. Meta-analyses of omega-3 PUFA trials in patients with depression have resulted in inconsistent conclusions. One analysis concluded that omega-3 PUFA supplementation does not have a significant benefit on depressive symptoms (Bloch and Hannestad, 2012). Meanwhile, several others have found significant beneficial effects of EPA alone on depression (Hallahan et al., 2016; Martins et al., 2012; Mocking et al., 2016). In schizophrenia and other psychotic disorders, current data are inconclusive for omega-3 PUFAs. (Akter et al. 2012; Freeman et al., 2006; Fusar-Poli and Berger, 2012). Promising results from one study suggest omega-3 PUFA supplementation reduces the risk of progression to psychotic disorders and psychiatric morbidity (Amminger et al., 2015). Data from autism (van Elst et al., 2014), anxiety disorders (Ravindran and da Silva, 2013) and obsessive–compulsive disorder studies (Fux et al., 2004) are too sparse from which to draw conclusions.

In ADHD, clinically meaningful effect sizes have been observed in some studies using PUFA supplements. Several prospective, interventional studies have suggested that omega-3/6 PUFA supplements – either alone or in combination – offer improvement in cognitive performance (Sinn et al., 2008) and enhanced tolerability of the stimulant methylphenidate when prescribed as an add-on treatment (Barragán et al., 2017; Sinn et al., 2008). One report describes improvement in measures that include sleep quality and emotional functioning (Chen et al., 2004). In recent years, attempts to clarify the effect of PUFA supplementation in ADHD have culminated in the publication of several meta-analyses, all relating to children/adolescents (Bloch and Qawasmi, 2011; Chang et al., 2017; Gillies et al., 2012; Sonuga-Barke et al., 2013).

Meta-analyses mainly report a small effect size in ADHD (Table 1), although they differ in how the clinical benefit is interpreted. In the Cochrane review by Gillies et al. (2012), PUFA supplementation showed a small, non-significant impact on ADHD symptoms (parent-ratings: overall symptoms (standardised mean difference (SMD): 0.17); inattention (SMD: 0.04); hyperactivity/impulsivity (SMD: 0.04) and teacher-ratings: overall symptoms (SMD: –0.05); inattention (SMD: –0.26); hyperactivity/impulsivity (SMD: –0.10)). The authors concluded that, overall, there was no significant benefit for PUFA supplementation in children and adolescents with ADHD compared with placebo. Meanwhile, Bloch and Qawasmi (2011) found a small but statistically significant improvement on ADHD symptoms with omega-3 PUFA supplementation (particularly with EPA) compared with placebo (overall ADHD symptoms (SMD: 0.31); inattentive symptoms (SMD: 0.29); hyperactivity (SMD: 0.23)), equating to small efficacy compared with existing pharmacotherapies, such as psychostimulant medication (Bloch and Qawasmi, 2011). Sonuga-Barke et al. (2013) found that PUFA supplementation produced small but statistically significant reductions in overall ADHD symptoms (SMD: 0.21). When 'probably blinded' assessments were used, effects remained statistically significant for overall symptoms (SMD: 0.16); however, when stratified

Table 1. Summary of meta-analyses assessing efficacy of PUFA supplementation in children and adolescents with ADHD.

Study	*N*	Intervention	Studies included	Effect size (overall ADHD symptoms)
Chang et al.	534	Omega-3 PUFAs	Placebo-controlled	*g*: 0.38
Bloch and Qawasami	699	Omega-3, omega 3/6 PUFAs	Placebo-controlled	SMD: 0.31
Gillies et al.	1011	Omega-3/6 PUFAs	Placebo-controlled and cross-over	SMD: 0.17 (parent-rated) SMD: –0.05 (teacher-rated)
Sonuga-Barke et al.	890	Omega-3, omega-6, omega-3/6 PUFAs	Placebo-controlled and cross-over	SMD: 0.21 (m-proxy) SMD: 0.16 (p-blind)

ADHD: attention deficit hyperactivity disorder; *g*: Hedges' *g* effect size; PUFA: polyunsaturated fatty acid; SMD: standardised mean difference.

into specific aspects of ADHD, the effect sizes for each component were: inattention, SMD: 0.11; hyperactivity/impulsivity, SMD: 0.13. In a recent systematic review and meta-analysis, Chang et al. (2017) suggested that monotherapy with omega-3 PUFA supplementation does benefit children and adolescents with ADHD compared with placebo, and is associated with an improvement in both their clinical symptoms (Hedges' *g* effect size (*g*): 0.38, $p<0.0001$) and their cognitive performance (*g*: 1.09, $p=0.001$).[12]

Variations in the inclusion criteria for meta-analyses may account for these conflicting results in terms of significance or non-significance. It should be noted that Cochrane reviews are stricter in terms of what data they will typically include to calculate effect size, so fewer studies usually contribute to the meta-analysis. It should also be noted that studies included also vary in sample size, trial length, dosage, supplement composition and whether participants are concurrently taking stimulant medication. In summary, current evidence suggests that PUFA supplementation has a small beneficial effect on behaviour in children with ADHD.

Further considerations

Although effect sizes on ADHD symptoms are small compared with established stimulant treatments, research suggests there are virtually no severe side effects of PUFA supplements. The most frequently reported side effects are dyspepsia and incidental nosebleeds (Königs and Kiliaan, 2016).

In addition, there have been reports of PUFA supplement products being highly oxidised, with oxidation levels exceeding recommended averages (Albert et al., 2015). This is often not considered in trials and may account for their inconsistent results.

Research has also suggested that certain subsets of patients (possibly those with developmental disorders and other comorbid conditions, and patients with PUFA-poor diets) may stand to benefit more than other groups of patients (Chang et al., 2017; Parletta et al., 2016). It has been postulated that this may reflect the heterogeneity of the underlying causes of ADHD, for example, a deficiency in PUFAs or certain food intolerances (Chang et al., 2017).

Proposed future research

It is evident that further high-quality research is needed to clearly evaluate and define the role of PUFA supplementation in the management of ADHD for children, adolescents and adults (Gow et al., 2015). First, it is crucial that future trials should include larger samples. As the benefits of omega-3 PUFA supplements are likely to be small, larger samples will be needed to demonstrate a statistically significant effect. It is worth considering that even a small improvement from omega-3 PUFA supplements may be clinically useful given the absence of significant side effects and the growing evidence that they may be health-promoting in other areas of medical and psychiatric health (Amminger et al., 2015; Bos et al., 2016).

Blood PUFA levels should be routinely analysed and monitored in future trials as it would allow researchers to study compliance, likely responders, and correlations between PUFA blood levels and ADHD symptoms. Furthermore, circumstantial findings suggest that individuals with certain dietary deficiencies may stand to benefit more from PUFA supplementation, yet, to our knowledge, no prospective investigation has taken place to test this hypothesis, and it should be a focus of future research. This information may enable patient stratification in the future.

Additionally, future research should aim to clarify the difference in efficacy between omega-3 and omega-3/6 combination PUFA supplements. Future clinical trials should also include data on oxidation values as well as average measured contents of EPA and DHA in the supplements used in the studies.

Much interest has been generated in identifying patient populations more likely to respond to PUFA supplementation. One study has suggested that PUFA supplements might have a higher impact on a subgroup of patients with the inattentive presentation and other neurodevelopmental problems (Johnson et al., 2009). To this end, data collected from future trials should include information on concomitant use of other nutritional supplements that may have a masking effect on PUFAs, and also on comorbid conditions and the gender of the participants.

Other unanswered questions exist regarding the optimal age in which to use PUFA supplements. In animal studies,

where there is an existing omega-3 PUFA deficiency, it has been shown that maternal supplementation during the pre-/post-natal period restores processes affected by the deficiency if given prior to the 21st day of life (Kodas et al., 2004), suggesting an optimal time frame may exist in humans too. Thus, future studies should also focus on the prophylactic impact of PUFA supplementation in the prenatal and neonatal period. It is also crucial to encourage research on PUFA supplements in adults with ADHD as most research presently focuses on children and adolescents. Finally, more research should be carried out to assess the optimal duration of PUFA treatment.

Recommendations for HCPs communicating with ADHD patients and their families

Interest in PUFA supplementation as a possible treatment for a wide range of diseases and conditions has increased remarkably among the public and the media. Their growing popularity is likely attributable to their tolerable safety profile and concerns about the over-medicalisation of children.

As a result, HCPs are increasingly asked by patients and their families about the role of PUFA supplements in neurodevelopmental disorders, such as ADHD. Commonly, PUFA supplements are requested by those who are not keen to use, would like to delay using or have not tolerated more traditional pharmacological treatments for ADHD. Many of these patients and families want to try PUFA supplementation as a first step, before starting a stimulant or other ADHD treatments. Some individuals request to use them in combination with stimulant treatment, either because they believe this will enhance the therapeutic effect or improve tolerability.

In these scenarios, HCPs should ensure patients and their families are aware that, in all likelihood, PUFA supplements typically do not have as much effect on ADHD symptoms as stimulants but that they are generally well tolerated. HCPs should not necessarily advise patients and families against using PUFA supplements, so long as their use does not deter them from using first-line treatments which have a stronger evidence base. It is important to mention that PUFA supplements have been associated with minor dyspepsia.

HCPs should also advise patients and their families to try to find the purest source of PUFA supplements available, ensuring that the preparation contains EPA, DHA and vitamin E (added to prevent oxidation of fatty acids) and that, ideally, they contain no flavours or colours. In situations where a patient wishes to use a PUFA supplement instead of stimulant medication, HCPs should advise them to take at least 750 mg of both EPA and DHA per day for at least 12 weeks before evaluating the response (recommendation of the expert panel). HCPs should discuss with patients and their families the available clinical evidence for PUFA supplements and other treatments to ensure they are making an informed choice.

Conclusion

PUFA supplementation, in particular omega-3 PUFAs, may produce small but statistically significant reductions in ADHD symptoms while having a tolerable safety profile. Accumulating evidence suggests that they may offer benefits outside of ADHD symptom control, including improvements in sleep quality and cognitive function, but more research is needed to confirm these additional benefits. The variation in results from the meta-analyses conducted, however, highlights the need for caution when interpreting studies. Moreover, HCPs should consider each patient on an individual basis, taking into account individual preference, current ADHD severity and treatment history before discussing PUFA supplementation. In cases where PUFA supplements are used, HCPs should be comfortable explaining the potential gains that PUFA supplementation may have and its possible side effects. Furthermore, HCPs should not reinforce the idea that PUFA supplementation should replace treatment approaches with a more robust evidence base for managing ADHD.

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MDPI

Review

Use of Non-Pharmacological Supplementations in Children and Adolescents with Attention Deficit/Hyperactivity Disorder: A Critical Review

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents, with environmental and biological causal influences. Pharmacological medication is the first choice in ADHD treatment; recently, many studies have concentrated on dietary supplementation approaches to address nutritional deficiencies, to which part of non-responses to medications have been imputed. This review aims to evaluate the efficacy of non-pharmacological supplementations in children or adolescents with ADHD. We reviewed 42 randomized controlled trials comprised of the following supplementation categories: polyunsaturated fatty acids (PUFAs), peptides and amino acids derivatives, single micronutrients, micronutrients mix, plant extracts and herbal supplementations, and probiotics. The reviewed studies applied heterogeneous methodologies, thus making it arduous to depict a systematic overview. No clear effect on single cognitive, affective, or behavioral domain was found for any supplementation category. Studies on PUFAs and micronutrients found symptomatology improvements. Peptides and amino acids derivatives, plant extracts, herbal supplementation, and probiotics represent innovative research fields and preliminary results may be promising. In conclusion, such findings, if confirmed through future research, should represent evidence for the efficacy of dietary supplementation as a support to standard pharmacological and psychological therapies in children and adolescents with ADHD.

Keywords: dietary supplementations; non-pharmacological treatment; rehabilitation; neurodevelopment; attention deficit hyperactivity disorder (ADHD); children; adolescents

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting about 5% of children and 2.5% of adults worldwide. It is characterized by dysregulated cognition and behaviors, resulting in inattention, excessive motor activity, and impulsivity [1].

Drug treatments for ADHD mainly act to potentiate the action of catecholamines, which are neurotransmitters involved in the prefrontal cortex responsible for the maintenance of attention and cognitive control [2].

Stimulants, the first choice for ADHD drug treatment, include methylphenidate that inhibits dopamine reuptake and amphetamines that inhibit dopamine and noradrenaline reuptake and increase dopamine release. Atomoxetine is the most common non-stimulant medication for ADHD and acts by inhibiting norepinephrine reuptake [3].

The efficacy of stimulants and non-stimulants in reducing ADHD symptoms is well documented in children and adults [4,5]. However, the tolerability of these drugs can be scarce in some patients, warranting treatment interruption. At least 10–30% of children with ADHD may not benefit from these medications due to non-response or adverse effects [6,7] such as decreased appetite, insomnia, stomachache, headache, weight loss (potentially leading to growth retardation), tics, increases in blood pressure, and potential abuse or misuse [8]. Although less effective than stimulants, non-stimulant medication are first choice treatments for individuals with co-diagnoses including tic, mood, and anxiety disorders [3]. However, atomoxetine use has been associated with increased risk of suicidal behavior in youths [9].

ADHD is a multifactorial disorder, in which genetic and biological factors have important roles; ADHD symptomatology expression is also influenced by environmental factors, like nutrition [10]. To explain the role of nutritional deficiencies, to which part of non-responses to medications have been imputed, several studies focused on supplementation approaches, as alternative or additional therapies.

Within this research area, many studies have focused on macronutrient supplementations, mainly polyunsaturated fatty acids (PUFAs), that are precursors of eicosanoids and are relevant components of cell membranes and of phospholipids. PUFAs influence the quality of growth and development [11]. Research about PUFAs adjunctive treatments for ADHD did not produce convincing evidence, probably due to the heterogeneity of methods and doses administered [12,13].

Few studies have also examined the role of other macronutrients such as peptides and amino acids derivatives, which can act as metabolic adjuvants. In particular, there are experimental trials using Acetyl-L-carnitine (ALC) to optimize mitochondrial fatty acid oxidation. It has been reported that ALC treatment increased sodium levels in the cingulate cortex and the 5HIAA/5HT ratio in both cingulate cortex and medial frontal cortex in adolescent impulsive rats [14] and it could have a link with hyperactivity and impulsivity symptoms in children with ADHD [15]. L-carnosine (a dipeptide composed of β-alanine and l-histidine) is known as an antiaging antioxidant and neuroprotective compound, and it is found highly concentrated in brain tissues [16]. L-carnosine has also been associated to ADHD symptoms [17]: it accumulates in the subfrontal cortex and may enhance frontal lobe functions [18], interesting for ADHD research. Lastly, Phosphatidylserine (PS), a naturally occurring phospholipid, modulates the activity of receptors, enzymes, ion channels and signaling molecules, and contributes to regulate membrane fluidity [19]. PS has been shown to counteract the stress-induced activation of the hypothalamic-pituitary-adrenal axis [20]; it has been involved in ADHD symptomatology and short-term auditory memory [21].

Other studies have investigated the role of various micronutrients (e.g., oligoelements, vitamins, minerals) as alternative or supporting non-pharmacological treatment for ADHD.

Vitamin D deficiency is relevant in the pathogenesis of psychiatric disorders including autism, depression, schizophrenia, and ADHD [22–24]. Vitamin D can act on central dopamine levels via different mechanisms, including calcium transition, antioxidant properties and gene expression [25].

Another micronutrient linked to dopamine metabolism is zinc, a cofactor of many metalloenzymes and metal–enzyme complexes [26]. Studies conducted on animals and humans associated zinc deficiency and hyperactivity [27,28]. Researchers also focused on broad-spectrum supplementation approaches, highlighting the efficacy of minerals and vitamins combinations [29].

Complementary or alternative medicine approaches propose herbal extracts for children with ADHD. However, these studies have not yet produced structured evidence [30].

Lastly, an interesting hypothesis is that gut microbiota and probiotics could influence brain activity and behaviors and psychiatric symptoms [31]. In rodent studies, modifications of gut microbiota are associated with cerebral signals modification, in cortical and subcortical regions, linked to affective

and sensory functions [32]. Evidence in humans is preliminary; however, chronic intake of probiotics is associated in healthy adults with altered brain connectivity during affective and attentive tasks [32].

Given the number and heterogeneity of studies conducted on nutritional supplementation in ADHD, the present review aims at offering a systematization for the results of studies conducted from January 2010 to March 2020 and evaluating the efficacy of non-pharmacological dietary supplementations in ADHD.

We defined the present review as "critical" to highlight our aim to offer clinicians an analytical and up-to-date point of view in the clinical management of children and adolescents with ADHD, specifically in a nutritional supplementation framework alone or in combination with pharmacological treatment. Moreover, this review did not have a systematic or quantitative objective.

2. Materials and Methods

The present review is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [33]. We searched PubMed from January 2010 to March 2020 using the following string: (probiotic OR prebiotic OR vitamin OR mineral OR phytonutrient OR amino acid OR supplementation OR non-pharmacological) AND (ADHD OR attention deficit hyperactivity disorder) NOT review [All Fields] NOT adult NOT infant. The search manually completed with relevant articles. We included randomized controlled trials involving children and adolescents with ADHD receiving non-pharmacological supplementation. We focused on studies addressing cognitive or behavioral outcomes; we excluded papers not written in English, researches addressing other diagnoses than ADHD, studies with no administration of non-pharmacological supplementations, studies that did not report behavioral/cognitive outcomes, and studies on preschool or adult subjects. Specifically, our search did not include infants (<5 years) given ADHD onset which typically corresponds to school age [1]. Moreover, since this review aim was to offer evidences regarding clinical management of children and adolescents with ADHD, we decided to exclude adults in the PubMed search.

3. Results

Our search found 414 articles. After title and abstract screening, articles retained were 44; we excluded two articles after full text review. In total, 42 articles are included in the present review. The PRISMA flow chart is shown in Figure 1.

In the following text and tables, results are presented according to supplementation categories as follows:

a. PUFAs;
b. peptides and amino acids derivatives;
c. single micronutrient (Zinc or Vitamin D);
d. micronutrients mix;
e. plant extracts or herbal supplementations;
f. probiotics.

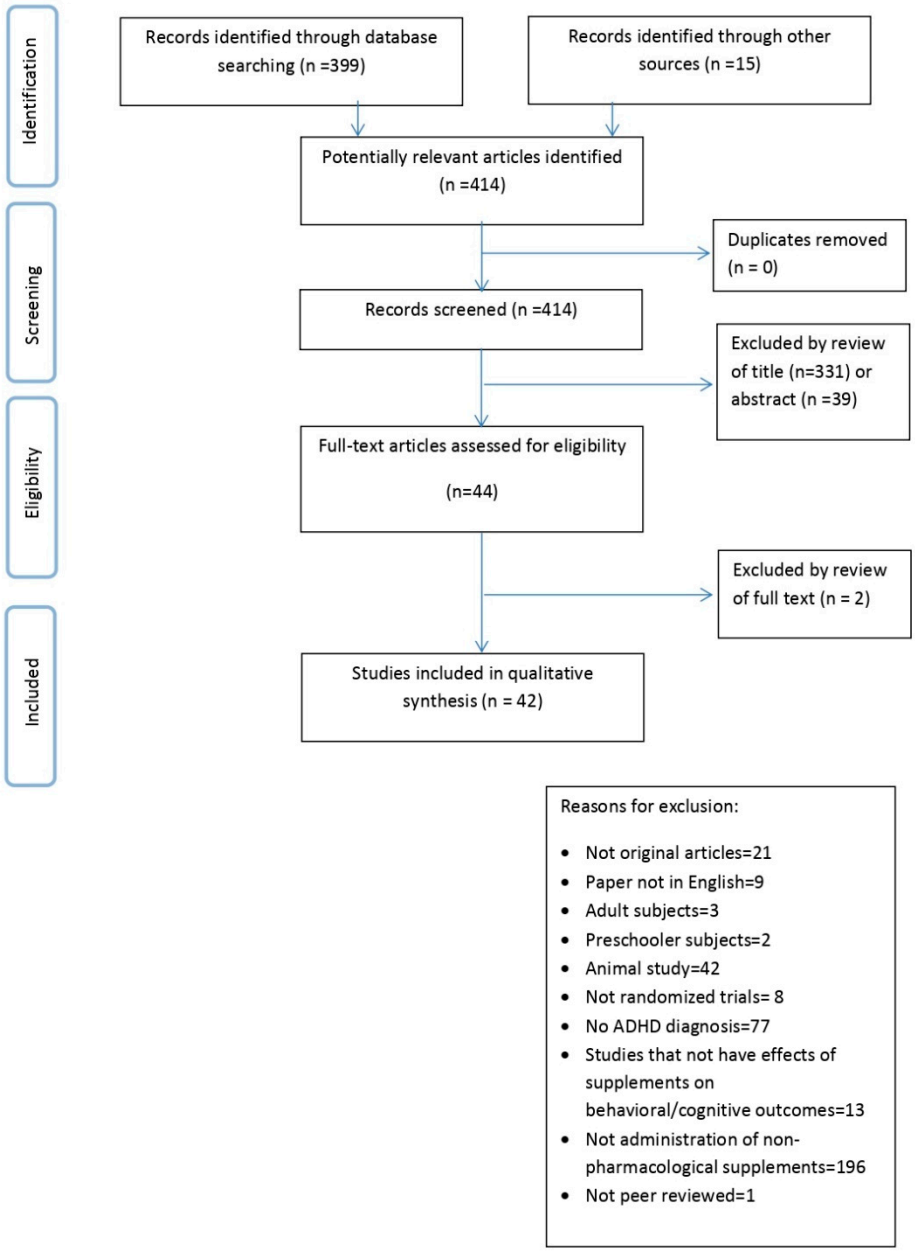

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA).Flow diagram of the study selection process.

3.1. PUFAs

3.1.1. Methodologies

In total, 20 studies focused on supplementation with PUFAs [34–53] (see Table 1a): fourteen were on patients without comorbidities [34,36–38,40–47,50,53], two with oppositional defiant disorder (ODD) [35,39], and four with various co-diagnoses, such as specific learning disorder, ODD, conduct disorder, tic disorder, anxiety, Tourette syndrome, or psychomotor difficulties [48,49,51,52]. Two researches [42,43] include very small samples.

Table 1. (**a**) Studies comprising supplementation with polyunsaturated fatty acids (PUFAs). (**b**) Studies comprising supplementation with peptides and amino acids derivatives. (**c**) Studies comprising supplementation with a single micronutrient. (**d**) Study comprising supplementation with micronutrients mix. (**e**) Studies comprising supplementation with plant or herbal extracts. (**f**) Study comprising supplementation with probiotics.

(a)

Authors, Year	Sample and Age	Methodology and Durations	Daily Doses	Outcome Measures	Main Results
Anand et al., 2016 [34]	50 ADHD (35 males), no other neuropsychiatric comorbidities. Age range: 4–11 years (6 ± 2.1 years).	4 months DBRCT 25 subjects taking ATX+ PUFA. 25 subjects taking ATX.	ATX: 0.5 mg/kg/day. PUFA: EPA 180 mg + DHA 120 mg/day.	CPRS-R: parent-rated behavioral indexes.	CPRS-R: Non significant trend: supplementation group improved in ADHD scores as compared to the control group. Improvement was more evident, although not significant, in males with combined type of ADHD.
Assareh et al., 2017 [35]	40 ADHD (30 males), ODD was present in 21 subjects. Age range: 6–12 (PUFA group: 9 ± 2 years; Placebo group 9.2 ± 2 years).	10 weeks DBRCT Unspecified subjects taking MPH +DHA + EPA+ Omega 6. Unspecified subjects taking MPH + Placebo.	MPH: 0.3 mg/kg/day (in 2 doses). Increased to 1 mg/kg/day for 2 weeks. EPA:33 mg/day. DHA: 241 mg/day. Omega 6: 180 mg/day. Placebo: similar to other capsules.	Parent rated ADHD-RS every two weeks.	ADHD-RS: Significant time effect: both groups showed an improvement in symptomatology over time.
Barragán et al., 2017 [36]	90 ADHD (60 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (8.27 ± 1.74 years).	12 months RPT 20 subjects taking MPH. 22 subjects taking Omega-3/6. 27 subjects taking MPH + Omega-3/6.	MPH: 0.3 mg/kg/ day, increased to 0.5 mg/kg/day after the first 2 weeks. The dose was increased to 1 mg/kg/day depending on response and tolerability. Omega-3/6: EPA: 558 mg\day. DHA: 174 mg\day. GLA: 60 mg\day.	Parent rated ADHD-RS. CGI-S: assessment of severity as reported by clinician and parents.	ADHD-RS and CGI-S: - Significant time x treatment effect: MPH + supplementation group showed greater improvements compared to supplementation alone. CGI-S: - Slow decrease in Omega-3/6 groups, compared with a rapid decrease and subsequent slight increase in the MPH-containing groups. - Adverse events were numerically less frequent with Omega-3/6 or MPH + Omega-3/6 than MPH alone.

Table 1. *Cont.*

Behdani et al., 2013 [37]	69 ADHD (55 males), no other neuropsychiatric comorbidities. Age range: 7–15 years (8.7 ± 1.7 years).	Eight weeks DBRCT 36 subjects taking MPH + Omega 3 33 subjects taking MPH + Placebo.	MPH: 2.5–5 mg/day. Increased 2.5–5 mg weekly, to attain a final dose of 1 mg/kg (in two or three doses). Omega-3:1000 mg\2 times a day (240 mg of DHA and 360 mg of EPA). Placebo: similar to Omega 3 capsules.	Parent and teacher rated ADHD-RS.	ADHD-RS: Significant time effect: reduction in both parent's and teacher's rating scores in both groups.
Bos et al., 2015 [38]	38 ADHD; 38 TD (76 males), no other neuropsychiatric comorbidities. Age range: 8–14 years (ADHD:10.3± 2.0 years; TD: 10.9 ± 2.0 years).	16 weeks DBRPCT 19 ADHD* taking Omega 3. 19 ADHD* taking Placebo. 20 TD taking Omega 3. 18 TD taking placebo. *subjects took MPH before trial.	Omega 3 fortified margarine: 10 g (650 mg DHA and 650 mg EPA). Placebo: 10 g of similar margarine.	CBCL (parent-rated) SWAN (parent-rated) fMRI with G/No-Go paradigm	CBCL: Significant main effect of treatment: supplementation group had less attention problems compared to placebo groups.
Pei-Chen Chang et al., 2019 [39]	92 ADHD (79 males), ODD was present in 51 subjects. Age range: 6–18 years (9.49 ± 3.05 years).	12 weeks DBRPCT 48 subjects taking PUFAs. 44 subjects taking Placebo.	PUFAs (EPA): 1.2 g/day. Placebo: 1.2 g/day soybean oil.	CPT: computerized continuous performance test to evaluate attention measures. Parent, teacher and self-rated SNAP IV: checklist of DSM-IV ADHD symptoms.	CPT: Significant time x treatment interaction effect: supplementation group showed greater improvement in focused attention compared to placebo group.
Cornu et al., 2018 [40]	162 ADHD (127 males), no other neuropsychiatric comorbidities. Age range 6–15 years (6.9 ± 2.9 years).	Three months DBRPCT 77 subjects taking Omega 3. 80 subjects taking Placebo.	Omega 3 for subjects aged 6–8: EPA 336 mg + DHA 84 mg/day. Omega 3 for subjects aged 9–11: EPA 504 mg + DHA 126 mg/day. Omega 3 for subjects aged 12–15: EPA 672 mg + DHA 168 mg/day. Supplementation capsules also contained 100 mg vitamin A + 1.25 mg vitamin D + 3.5 mg vitamin E. Placebo: similar to Omega 3.	Parent-rated ADHD-RS-IV: ADHD symptomatology as outlined in the DSM-IV-TR. CPRS-R: parent-rated behavioral indexes. "L'Alouette" test: french reading test. Attentional Performance Tests for Children. Children's Depression Inventory: self-rated depression symptomatology.	ADHD-RS: the severity score decreased in both groups. The decrease was significantly higher in the placebo group.

Table 1. *Cont.*

Crippa et al., 2019 [41]	50 ADHD (46 males), no other neuropsychiatric comorbidities. Age range: 7–14 years (Omega 3 group: 11.06 ± 1.85 years; Placebo group: 10.91 ± 1.42 years).	Six months DBRPCT 25 subjects taking Omega 3. 25 subjects taking Placebo.	Omega 3: DHA 500 mg/day. Placebo: similar to Omega 3.	Parent-rated ADHD-RS version IV: ADHD symptomatology as outlined in the DSM-IV-TR. CPRS-R: parent-rated behavioral indexes. SDQ: parent-rated emotional and behavioral indexes. CHQ: parent-rated measure of quality of life. CGI and C-GAS: assessment, severity and improvement of symptoms as reported by clinician.	A main amelioration effect over time was found in the following measures: ADHD-RS, CPRS-R ADHD index, CPRS-R Global Index restless – impulsive, CPRS-R Global Index total, DSM-IV hyperactive– impulsive scale and DSM-IV total, SDQ Hyperactivity scale and on SDQ total difficulties score, CGI severity, C-GAS. Children in the DHA group showed significantly higher amelioration effect compared to the placebo group in the CHQ. Psychosocial summary and emotional problems on SDQ.
Dean et al., 2014 [42]	16 ADHD, 11 CD (17 males), no other neuropsychiatric comorbidities. Age range: 7–14 years (10.3 ± 2.2 years).	Six weeks RPCCT+ Follow-up 12 subjects taking fish oil capsules for six weeks (Phase 1) followed by placebo capsules for six weeks (Phase II). Nine subjects taking placebo capsules for six weeks (Phase I) followed by fish oil for six weeks (Phase II).	Fish oil: 4 g/day, (400 mg EPA + 2000 mg DHA). Placebo: 4 g\day (low polyphenol, olive oil and 10 mg standard fish oil to assist in maintaining blinding).	Children's Aggression Scale – Parent Version. MOAS (parent-rated) SDQ (parent-rated) Family Assessment Device General Functioning Scale (FAD) ADHD-RS (parent-rated) Cognitive functioning: -Executive control trail-making task. -Response inhibition–stop signal task Cognitive control: -Eriksen flanker task.	Aggressive behaviour: No effect of fish oil treatment was observed on changes in total scores despite it increased serum concentrations of EPA and total omega-3 s. SDQ: Fish oil group worsened in Conduct Subscale but improved in Hyperactivity Subscale. No effect of fish oil supplementation was observed for other SDQ subscales or SDQ total score, the ADHD rating scale, or family functioning (FAD). Cognitive measures: Fish oil supplementation did not lead to any changes on the stop signal task, trail-making task, or flanker task.

Table 1. *Cont.*

Dubnov-Raz et al., 2014 [43]	17 drug naïve ADHD (10 males), no other neuropsychiatric comorbidities. Age range: 6–16 years (ALA group: 11.1 ± 3.00 years; Placebo group: 10.9 ± 2.30 years).	Two months DBRPCT Nine subjects taking Alpha-Linolenic Acid (ALA). Eight subjects taking Placebo.	ALA: 1 g/day. Placebo: similar to ALA.	MOXO-CPT: standardized computerized continuous performance test designed to evaluate ADHD-related symptoms. Four performance indices: attention, timing, impulsivity, and hyperactivity. CPRS-R: parent-rated behavioral indexes. CTRS-R: teacher-rated behavioral indexes.	No significant between-group difference was found in the changes of the various measures of ADHD symptoms throughout the study period.
Gustafsson et al., 2010 [44]	82 ADHD (number of males unspecified), no other neuropsychiatric comorbidities. Age range: 7–12 years (no mean age declared).	15 weeks DBRCT 40 subjects taking Omega 3. 42 subjects taking Placebo.	Omega 3: EPA 500 mg+ DHA 2.7 mg/day. Active capsules also contained 10 mg Vitamin E. Placebo: similar to Omega 3.	CPRS-R: parent-rated behavioral indexes. CTRS-R: teacher-rated behavioral indexes.	CTRS-inattention / cognitive subscale: children in supplementation group showed significant amelioration effect. CTRS total score: -48% of the children receiving supplementation vs. 9% of placebo improved ≥25%. -Among the less hyperactive/impulsive children, 36% of the ones receiving supplementation vs. 18% receiving placebo improved ≥25%. -Among the more hyperactive/impulsive children, 8/13 receiving supplementation vs. 1/9 receiving placebo improved ≥25%.
Hariri et al., 2012 [45]	103 ADHD (74 males), no other neuropsychiatric comorbidities. Age-range: 6–11. (Omega 3 group: 7.90 ± 1.53 years; Placebo group: 7.90 ± 1.45 years).	15 week DBRPCT 53 subjects taking Omega 3. 50 subjects taking Placebo.	Omega 3: EPA 635 mg+ DHA 195 mg/day day. Placebo: similar to Omega 3.	ASQ-P: parent-rated behavioral indexes.	ASQ-P: children in EPA + DHA group showed significant improvement.

Table 1. *Cont.*

Manor et al., 2012 [46]	147 ADHD (104 males), no other neuropsychiatric comorbidities. Age-range: 6–13 years (Supplementation group: 9.2 ± 2.0 years; Placebo group: 9.2 ± 1.8 years).	15 weeks DBRPCT + 15 weeks OL 100 subjects taking Phosphatidylserine (PS) + -Omega 3. 47 subjects taking Placebo.	PS: 300 mg/day. Omega 3: 120 mg/day (EPA/DHA ratio of 2:1). Placebo: similar to supplementation.	CPRS-R: parent-rated behavioral indexes. CTRS-R: teacher-rated behavioral indexes. SDQ: parent-rated emotional and behavioral indexes. CHQ: parent-rated measure of quality of life.	CPRS-R: -Significant reduction in the Global restless/impulsive subscale in supplementation group -Children with more severe symptomatology revealed a significant reduction in the ADHD-Index and hyperactive components. CPRS-R and CTRS-R: Children that switched to supplementation group from placebo showed a significant reduction in subscales severity scores compared to baseline. CHQ: significant improvement in Parent impact-emotional (PE) subscale in supplementation group.
Matsudaira et al., 2015 [47]	76 ADHD (76 males), no other neuropsychiatric comorbidities. Age-range: 12–16 years (LC-PUFA group: 13.7 ± 1.2 years; Placebo group: 13.7 ± 1.1 years).	Three months DBRPCT 38 subjects taking LC-PUFA 38 subjects taking Placebo.	LC-PUFA: EPA 558 mg + DHA 174 mg + CLA 60 mg + vitamin E 9.6 mg/day. Placebo: similar to LC-PUFA.	CTRS-R: teacher-rated behavioral indexes (specifically, the authors considered the ADHD index).	No between-group difference was found in the changes of the various measures of ADHD symptoms throughout the study period.

Table 1. *Cont.*

Milte et al., 2012 [48]	87 ADHD or parent-rated symptoms higher than the 90th percentile on the CPRS-R (67 males), including parent-reported learning difficulties. Age range: 6–13 years (EPA-rich group: 8.77 ± 1.76 years; DHA-rich group: 8.89 ± 1.60 years; LA-rich group: 9.14 ± 2.03 years).	Four months RCT 30 subjects taking EPA-rich oil. 28 subjects taking DHA-rich oil. 29 subjects taking LA oil.	EPA-rich oil: EPA 1109 mg+ DHA 108 mg/day. DHA-rich oil: DHA 1032 mg + EPA 264 mg/day. LA oil: 1467 mg/day. Each capsule also contained low concentration of vitamin E.	WIAT-III word reading and spelling subtests: literacy assessment. WISC-III vocabulary subtest: literacy assessment. CPRS-R: parent-rated behavioral indexes. Abbreviated test of everyday attention for children: attention assessment. Computerized go/no-go task: inhibition assessment.	No between-group or within-group difference was found in the changes of the various measures of symptoms throughout the study period. In a subgroup of 17 children with learning difficulties an increased erythrocyte DHA was more strongly associated with improved word reading ($r = 0.683$), improved spelling ($r = 0.556$), an improved ability to divide attention ($r = 0.676$), and lower parent ratings of oppositional behavior ($r = 0.777$), hyperactivity ($r = 0.702$), restlessness ($r = 0.705$), and overall ADHD symptoms ($r = 0.665$).
Milte et al., 2015 [49]	87 ADHD or parent-rated symptoms higher than the 90th percentile on the CPRS-R (67 males), including parent-reported learning difficulties. Age range: 6–13 years (8.91 ± 1.73 years).	12 months Three-way, crossover clinical trial Group 1: EPA→DHA→LA Group 2: DHA→LA→EPA Group 3: LA→EPA→DHA	EPA-rich oil: EPA 1109 mg+ DHA 108 mg/day. DHA-rich oil: DHA 1032 mg + EPA 264 mg/day. LA oil: 1467 mg/day. Each capsule also contained low concentration of vitamin E.	WIAT-III word reading and spelling subtests: literacy assessment. WISC-III vocabulary subtest: literacy assessment. CPRS-R: parent-rated behavioral indexes. Abbreviated Test of Everyday Attention for Children: attention assessment. Computerized go/no-go task: inhibition assessment.	No between-group or within-group difference was found in the changes of the various measures of symptoms throughout the study period. An increased proportion of erythrocyte EPA + DHA was associated with improved spelling ($r = 0.365$) and attention ($r = -0.540$) and reduced oppositional behavior ($r = -0.301$), hyperactivity ($r = -0.310$), cognitive problems ($r = -0.326$), DSM-IV hyperactivity ($r = -0.270$) and DSM-IV inattention ($r = -0.343$).

Table 1. *Cont.*

Mohammadzadeh et al., 2019 [50]	60 ADHD (49 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (PUFA group: 8.20 ± 1.72 years; Placebo Group: 7.7 ± 1.65 years).	Eight weeks DBRCT 31 subjects taking MPH + PUFA. 29 subjects taking MPH + Placebo.	Omega 3: EPA 180 mg + DHA 120 mg/day (from second week 2 times a day). Placebo: similar to Omega 3. MPH: 10 mg/day (in 2 doses); 20–30 mg/kg/day (in 2 doses) from second week.	ADHD-RS-IV parent rated	No significant effect was found.
Perera et al., 2012 [51]	94 ADHD (69 males), including ODD, CD, SLD and tics comorbidities. Age range: 6–12 years (Omega 3 group: 9.4 ± 1.5 years; Placebo group: 9.2 ± 1.5 years).	Six months DBRPCT 48 subjects * taking Omega 3/6. 46 subjects* taking Placebo. *subjects took MPH before trial.	Omega capsules: Omega 3 296.37 mg+ Omega 6 180.75 mg (ratio 1.6:1). Placebo: similar to Omega 3/6.	Parent-rated checklist assessing the following domains: aggressiveness, restlessness, inattention, distractibility, easy anger, impulsiveness, fighting, cooperation, completing work, wait for turn, academic performance. Total score range: 11–33.	Significant reduction in severity score in treatment group compared to placebo in the following measures: aggressiveness, restlessness, completing work, and academic performance, inattention, impulsiveness, and cooperation with parents and teachers.
Rodríguez et al., 2020 [52]	66 ADHD (47 males), including SLD, Anxiety, Tourette's syndrome, psychomotor/behavioral problems comorbidities. Age range: 6–18 years (11.7 ± 3.1 years).	Six months DBRPCT 32 subjects * taking PUFA 34 subjects * taking Placebo * psychostimulant medication was allowed	PUFA sachet: DHA 1000 mg+ EPA 90 mg+ DPA 150 mg + vitamin E 4.5 mg+ carbohydrates 0.94 g (1 sachet/day in subjects ≤32 kg; 2 sachets/day in subjects >32 kg). Placebo: similar to PUFA sachet.	CPRS: parent-rated behavioral indexes. EDAH scale: parent-rated behavioral indexes. AULA Nesplora virtual test: test of attentional processes, impulsivity and motor activity. D2-test: paper and pencil test for selective and sustained attention.	CPRS: Significant within-group time effect: supplementation group showed improvement in behavioral variables; placebo group showed a behavioral symptomatology worsening. EDAH scale: Significant time x treatment interaction effect: supplementation group in post – treatment condition showed better behavioral indexes compared to placebo group. AULA Nesplora virtual test: Non-significant trend of higher amelioration in supplementation group. d-2 test: significant within-group time effect: both study groups showed improvements in cognitive variables.

Table 1. *Cont.*

Widenhorn-Müller et al., 2014 [53]	95 ADHD (74 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (Omega 3 group: 8.90 ± 1.48 years; Placebo group: 8.92 ± 1.24 years).	Four months DBRPCT 46 subjects taking Omega 3. 49 subjects taking Placebo.	Omega 3: EPA 600 mg + DHA 120 mg/day. Active capsules also contained 15 mg Vitamin E. Placebo: similar to Omega 3.	HAWIK-IV: General cognitive ability, working memory, speed of information processing. DIS-YPS-II: parent-and teacher-rated questionnaires corresponding to the ICD-10 and DSM-IV diagnostic criteria for ADHD. CBCL: parent-rated questionnaire addressing behavioral and emotional problems. TRF: teacher-rated questionnaire addressing behavioral and emotional problems and academic performance. KITAP and TAP: computerized test batteries as measures for attentional performance.	HAWIK-IV: significant time x treatment interaction: supplementation group showed an improvement in working memory function compared to placebo–taking group. Improved working memory correlated with increased erythrocyte EPA and DHA and decreased AA.

(b)

Authors, Year	Sample and Age	Methodology and Durations	Daily Doses	Outcome Measures	Main Results
Abbasi et al., 2011 [15]	40 ADHD (28 males), no other neuropsychiatric comorbidities. Age range: 7–13 years (ALC group: 8.84 ± 2.03 years; Placebo group: 8.36 ± 1.53 years).	Six weeks DBRPCT 19 subjects taking MPH + Acetyl-L-carnitine (ALC). 19 subjects taking MPH + Placebo.	MPH week 1: 10 mg/day. MPH week 2: 20 mg/day. MPH week 3: 30 mg/day. ALC: 500–1500 mg/kg/day. Placebo + MPH: 20–30 mg/day/Kg.	Teacher and Parent rated ADHD-RS-IV.	Teacher and Parent rated ADHD-RS-IV: no significant between-groups outcome results. However, those in the ALC group experienced fewer adverse events than the placebo group regarding headaches and irritability.
Ghajar et al., 2018 [17]	50 ADHD (40 males), not excluding ODD. Age range: 6–17 years (l-carnosine group: 9.12 ± 2.18 years; Placebo group: 8.28 ± 1.59 years).	Eight weeks DBRPCT 25 subjects taking MPH + l-carnosine. 25 subjects taking MPH + Placebo.	MPH: 0.5–1.5 mg/kg/day. Week 1:10 mg/day. Week 2-end: 20 mg/day. Subjects >30 kg: 30 mg/day. l-carnosine: 800 mg/day. Placebo: 800 mg/day.	Primary outcome: Parent rated ADHD-RS-IV. Secondary outcome: Teacher rated ADHD-RS-IV. Both rated at baseline and at weeks four and eight.	Primary outcome: Parent rated ADHD-RS-IV. Significant time x treatment interaction effect both at weeks 4 and 8: MPH + supplementation group showed greater improvements compared to MPH + placebo group. Secondary outcome: Teacher rated ADHD-RS-IV. No significant time x treatment interaction effect.

Table 1. *Cont.*

Hirayama et al., 2013 [21]	36 ADHD (34 males), no other neuropsychiatric comorbidities. Age range: 4–14 years (Phosphatidylserine group: 9.1 ± 1.7 years; Placebo: 8.7 ± 3.0 years).	Eight weeks DBRPCT 19 subjects taking Phosphatidylserine (PS). 17 subjects taking Placebo.	PS: 100 mg/day. Placebo: 100 mg/day.	ADHD diagnostic criteria of DSM-IV-TR. WISC-III (Digit Span Test). go/no-go experiment.	Significant treatment effect: supplementation group showed post-treatment improvements compared to pre-treatment condition in ADHD, AD and HD symptoms (DSM-IV-TR), short-term auditory memory (WISC-III) and total number of errors in the reverse differentiation test (inattention–impulsivity), as well as total inattention errors and total errors over time (Go/No-Go). No significant differences were observed in other measurements and in the placebo group.

(c)

Authors, Year	Sample and Age	Methodology and Durations	Daily Doses	Outcome Measures	Main Results
Arnold et al., 2011 [54]	52 ADHD (43 males), ODD, CD comorbidities. Age range: 6–14 years (Zinc group 1: 9.61 ± 3.36 years; Zinc group 2: 8.89 ± 2.31 years; Placebo group: 10.24 ± 2.69 years).	13 weeks (8 + 5) DBRPCT + 8 weeks OL Phase 1 28 subjects taking Zinc glycinate (group 1 and 2). 24 subjects taking Placebo. Phase 2/3 28 subjects taking Zinc glycinate + d-amphetamine. 24 subjects taking Placebo + d-amphetamine.	Zinc glycinate group 1: 15 mg/day (20 subjects). Zinc glycinate group 2: 15 mg/2 times day (8 subjects). AMPH: 25 kg: 5 mg/day; 25–45 kg: 10 mg/day; >45 kg: 15 mg/day. Placebo: similar to Zinc glycinate.	Parent and Teacher rated SNAP IV: checklist of DSM-IV ADHD symptoms. CPRS-R: parent-rated behavioral indexes. Short-term recognition memory task. Continuous performance task 11. Seat activity using a "wiggle" seat. CGI-S and CGI-I: assessment of severity and improvement as reported by clinician. Parent and child children's depression inventory.	Phase 1: Parent and teacher rating showed no consistent tendency of superiority of zinc over placebo. Neuropsychological cognitive motor results are inconsistent, although a bit more favorable to zinc. *Phase 2/3:* Optimal mg/kg AMPH dose with in zinc group 2 was 37% lower than with placebo.

Table 1. *Cont.*

Noorazar et al., 2020 [55]	60 ADHD (48 males), no other neuropsychiatric comorbidities. Age range: 7–12 years (Control group: 9.30 ± 1.38 years; Zinc group: 8.87 ± 1.97 years).	Six weeks DBRPCT 30 subjects taking MPH+ Zinc sulfate syrup. 30 subjects taking MPH + Placebo.	MPH: 0.5–1 mg/kg/day. Zinc sulfate syrup: 10 mg/day Placebo: 10 mg/day.	CPRS-R: parent-rated behavioral indexes.	CPRS-R. Significant time x treatment interaction effect: MPH + supplementation group showed greater improvements compared to MPH + placebo group in inattention score.
Salehi et al., 2016 [56]	150 ADHD (111 males), no other neuropsychiatric comorbidities. Age range: 6–15 years (Control group: 9.12 ± 2.2 years; Omega 3 group: 8.6 ± 1.7 years; Zinc group: 9.5 ± 2.5 years).	Eight weeks DBRCT 50 subjects taking MPH+ Placebo. 50 subjects taking MPH+ Omega 3. 50 subjects taking MPH+ Zinc sulfate.	MPH: 0 mg/day for subjects <20 kg; 10 mg/2 times a day >20 kg. Omega 3: 100 mg EPA for subjects <25 kg; 200 mg for subjects 26–35 kg;400 mg for subjects >35 kg/day. Zinc sulfate: 22 mg/day.	CPRS-R (parent-rated behavioral indexes) and CTRS-R (teacher-rated behavioral indexes) every 2 weeks.	CPRS-R and CTRS-R: Significant time x treatment interaction effects in children with attention deficit disorder subtype: - zinc group showed greater improvements compared to placebo group; - Omega 3 group showed greater improvements compared to the zinc group.
Dehbokri et al., 2019 [57]	96 ADHD (80 males), no other neuropsychiatric comorbidities. Age range: 2–18 years (Vitamin D group: 9.76 ± 2.38 years; Placebo group: 8.58 ± 2.02 years).	Six weeks DBRCT 51 subjects taking MPH + Vitamin D. 45 subjects taking MPH + Placebo.	MPH: unspecified. Vitamin D3: 50,000 IU/week. Placebo: similar to Vitamin D3.	CPRS-R: parent-rated behavioral indexes.	CPRS-R: Significant time x treatment interaction effect: supplementation group showed a significant decrease in hyperactivity, impulsivity and attention problems compared to placebo group. These results improved considerably in patients with insufficient levels of Vitamin D at baseline.
Elshorbagy et al., 2018 [58]	35 ADHD with vitamin D deficiency, including ODD, SLD comorbidities (number of males unspecified). Age range: 7–14 years (9.3 ± 2.6 years).	12 weeks Case-Control Prospective Interventional Study 16 subjects taking MPH + Vitamin D. 19 subjects taking MPH + Placebo.	MPH: 0.3–1 mg/kg/3 times a day. Vitamin D3: 3000 IU/day. Placebo: similar to Vitamin D3.	CPRS-R: parent-rated behavioral indexes. Weekly Parent Ratings Behaviour.	CPRS-R: Significant time x treatment interaction effect: ADHD who received vitamin D showed a significant improvement in conceptual level, inattention, opposition, hyperactivity and impulsivity compared with placebo group.

Table 1. *Cont.*

Mohammadpour et al., 2018 [25]	62 ADHD (46 males), no other neuropsychiatric comorbidities. Age range: 5–12 years (Vitamin D group: 7.70 ± 1.77 years; Placebo group: 8.03 ± 1.44 years).	Eight weeks DBRPCT 25 subjects taking MPH + Vitamin D. 29 subjects taking MPH + Placebo.	MPH: 0.3–1 mg/kg/3 times a day. Vitamin D tablets: 2000 IU/day. Placebo: similar to Vitamin D.	WPREMB: parent-rated morning and evening behavioural indexes. Parent rated ADHD-RS-IV. CPRS-R: parent-rated behavioral indexes.	WPREMB: Significant time x treatment interaction effect: ADHD who received vitamin D showed a significant improvement in total score and evening symptoms compared to placebo group. ADHD-RS: Significant within-group time effect: ADHD who received vitamin D showed an improvement in total score.

(d)

Authors, year	Sample and age	Methodology and durations	Daily doses	Outcome measures	Main results
Borlase et al., 2019 [59]	27 ADHD drug naïve (27 males), excluding only ASD and epilepsy comorbidities. Age range: 7–12 (Micronutrients group: 10.75 ± 1.50 years; Placebo group: 10.17 ± 1.36 years).	10 weeks DBRPCT 13 subjects taking Micronutrients (DEN Formula). 14 subjects taking Placebo.	Micronutrients (comprising 13 vitamins, 17 minerals, 4 amino acids): titration over a week up to 12 capsules/day (in 3 doses). If there was no clinical response after four weeks, subjects could choose to take 15 pills/day. Placebo: similar to micronutrients.	CGI-I: assessment of improvement as reported by clinician. Clinician-rated ADHD-RS-IV. CPRS-R: parent-rated behavioral indexes. CTRS-R: teacher-rated behavioral indexes. Magnetic Resonance Imaging (MRI)	Questionnaires: Significant advantage of supplementation group over placebo for general functioning, emotional dysregulation, aggression and inattention. MRI: No significant between-groups differences. In the treatment group there was a non-significant trend for: - decreased choline in the striatum; - decreased glutamate in the prefrontal cortex; - increased grey matter in the anterior thalamus; - increased white matter in the fornix; - improved network integrity of the default mode network, dorsal attention network and frontal executive network.

Table 1. *Cont.*

Hemamy et al., 2020 [60]	66 ADHD (46 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (Vitamin D group: 9.06 ± 1.76 years; Placebos group: 9.15 ± 1.46 years).	Eight weeks DBRCT 33 subjects taking MPH + Vitamin D + Magnesium. 33 subjects taking MPH + Placebos.	MPH: unspecified. Vitamin D: 50,000 IU/week. Mg: 6 mg/kg/day. Placebo: similar to Vitamin D or Mg.	CPRS-R: parent-rated behavioral indexes.	CPRS-R: Significant time x treatment interaction effect: ADHD who received supplementation showed a significant improvement in conduct problem score, social problem and anxiety score compared to placebo group.
Rucklidge et al., 2018 [61]	93 ADHD (69 males), excluding only ASD and epilepsy comorbidities. Age range: 7–12 years (Micronutrients group: 10.06 ± 1.56 years; Placebo group: 9.43 ± 1.53 years).	10 weeks FBRPCT 47 subjects taking Micronutrients. 46 subjects taking Placebo.	Micronutrients: 3–12/15 capsule/day divided into 3 doses (it contains 13 vitamins, 17 minerals, 4 amino acids). Placebo: similar to micronutrients.	CGI-I and C-GAS: assessment of severity and improvement as reported by clinician. Clinician-rated ADHD-RS-IV. CPRS-R: parent-rated behavioral indexes. CTRS-R: teacher-rated behavioral indexes. SDQ: parent- and teacher-rated emotional and behavioral indexes. BRIEF: teacher-rated behavioural measures of executive skills in everyday environment.	CGI-I: the number of responders in supplementation group was 20 (51%) versus 11 (27%) on placebo. Clinician-rated ADHD-RS-IV. Improvement in inattention and hyperactivity symptoms, aggression, emotional dysregulation, conduct problem and problem behaviour in ADHD who received supplementation compared with placebo group.
Darling et al., 2019 [62]	84 ADHD no drug naïve (62 males). See Rucklidge 2018. 43 subjects from Micronutrients group; 41 subjects from Placebo group.	Naturalistic Follow-up Study after 12 month post-baseline 19 subjects stayed on trial micronutrients. 21 subjects switched to medications. 35 subjects stopped all treatments. Nine subjects mixed micronutrients and medications. 27/84 subjects added psychological/ other intervention.	Micronutrients: 8–15 capsule/day (it contains 13 vitamins, 17 minerals, 4 amino acids).	CPRS-R: parent-rated behavioral indexes. SDQ: parent-rated emotional and behavioral indexes. Parent-rated CMRS for a measure of emotion dysregulation. Parent-rated SCARED-R for a measure of anxiety symptoms. Eating Behaviour Questionnaire. Acceptability of Treatment questionnaire.	More of those who stayed on supplementation (84%) were identified as "Much" or "Very Much" improved overall relative to baseline functioning, compared to 50% of those who switched to psychiatric medications and 21% of those who discontinued treatment. 79% of those still taking micronutrients, 42% of those using medications, and 23% of those who discontinued treatment were considered remitters based on parent-reported ADHD.

Table 1. *Cont.*

Rucklidge et al., 2019 [63]	71 ADHD (55 males). See Rucklidge 2018. Age range: 7–12 (9.7 ± 1.5 years).	Data from Rucklidge (2018) +10 weeks OL 40 subjects from RCT phase (taking micronutrients). 31 subjects from OL phase (taking micronutrients).	Micronutrients: 3–12/15 capsule/day divided into 3 doses (it contains 13 vitamins, 17 minerals, 4 amino acids). No Placebo.	Clinician-rated ADHD-RS-IV. CGI-I and C-GAS: assessment of severity and improvement as reported by clinician. CPRS-R: parent-rated behavioral indexes. Parent-rated CMRS for a measure of emotion dysregulation. SDQ: parent-rated emotional and behavioral indexes.	Varying predictors were found across outcomes: lower pre-treatment folate and B12 levels, being female, greater severity of symptoms and co-occurring disorders in pre-treatment condition, more pregnancy complications and fewer birth problems were identified as possible predictors of greater improvement for outcome measures.

(e)

Authors, year	Sample and age	Methodology and durations	Daily doses	Outcome measures	Main results
Katz et al., 2010 [64]	92 ADHD (92 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (CHP group:9.82 ± 1.56 years; Placebo group: 9.36 ± 1.97 years).	Four months DBRPCT 73 subjects taking Compound Herbal Preparation (CHP). 19 subjects taking Placebo.	CHP: 3 mL three times daily, before meals, diluted in 50 to 60 mL of water. Placebo: similar to CHP.	TOVA task to measure attention Daily side effect questionnaire	TOVA task: Significant within-group time effect: supplementation group showed significant improvement in the 4 subscales and overall scores, compared with no improvement in the control group. No serious side effects were reported.
Ko et al., 2014 [65]	70 ADHD/ADHD NOS (44 males), no other neuropsychiatric comorbidities. Age range: 6–15 (KRG group = 10.94 ± 2.26 years; Placebo group = 10.86 ± 2.41 years).	Eight weeks DBRPCT 33 subjects taking Korean Red Ginseng (KRG). 37 subjects taking Placebo.	KRG: 1g (extract/pouch) twice a day. Placebo dose: one pouch twice a day.	Primary outcome: DSM-IV criteria for inattention and hyperactivity scale scores. Secondary outcomes: QEEG TBR: EEG theta/beta ratio. Salivary cortisol. DHEA levels.	Primary outcome: Active treatment significantly improved the inattention scores and hyperactivity scores. Secondary outcomes: -Supplementation group showed a significantly decrease in QEEG TBR. -No significant effect of supplementation on cortisol and DHEA levels. -No serious adverse reactions to KRG.

Table 1. *Cont.*

Li et al., 2011 [66]	72 ADHD (47 males), no other neuropsychiatric comorbidities. Age range: 6–13 years (NDG group: 9.3 ± 1.8 years; MPH group: 9.2 ± 2.2 years).	Eight weeks DBRCT 36 subjects taking MPH. 36 subjects taking Ningdong granule (NDG).	MPH: 1 mg/kg/day. NDG: 5 mg/kg/day.	Teacher and Parent ADHD-RS to measure behavior. Blood levels of dopamine (DA) and homovanillic acid (HVA) Side effect questionnaire	Teacher and parent ADHD-RS: Scores were reduced from baseline to week 8 in both groups, but there were no significant differences between NDG and MPH groups. MPH group had more side effects than NDG group (significant effect only in hypersomnia). DA levels showed no significant change during the study. HVA in supplementation group was higher at the end of the research, but there was no significant difference between two groups. HVA increasing was associated with improved scores of Teacher and Parent ADHD-RS.
Salehi et al., 2010 [68]	50 ADHD (39 males), no other neuropsychiatric comorbidities. Age range: 6–14 years (G. biloba group: 9.12 ± 1.61 years; MPH group: 9.61 ± 2.26 years).	Six weeks DBRCT 25 subjects taking Ginkgo biloba. 25 subjects taking MPH.	G. biloba: 80–120 mg/day/kg (80 mg/day for <30 kg and 120 mg/day for >30 kg). MPH: 20–30 mg/day/kg (20 mg/day for <30 kg and 30 mg/day for >30 kg).	Primary outcomes: Parent and Teacher ADHD-RS to measure behavior. Secondary outcomes: Side effect checklist. Physiological parameters.	Parent and Teacher ADHD-RS: Supplementation was less effective than MPH. The difference between supplementation and MPH groups in the frequency of side effects was not significant, except for more frequent decreased appetite, headache and insomnia in the MPH group.
Shakibaei et al., 2015 [69]	60 ADHD (39 males), no other neuropsychiatric comorbidities. Age range: 6–12 years (G. biloba group: 7.83 ± 1.21; Placebo group: 8.41 ± 1.40 years).	Six weeks DBRPCT 31 subjects taking MPH* + Ginkgo biloba. 29 subjects taking MPH* + Placebo. *subjects took MPH before the trial.	MPH: 20 mg/day (10 mg/b.i.d) for subjects <30 kg; 30 mg/day (10 mg/t d s) for subjects >30 kg. G. biloba: 80 mg/day (40 mg/b.i.d) for subjects <30 kg; 120 mg/day (40 mg/t d s) for subjects >30 kg. Placebo: similar to G. biloba tablet.	Primary outcomes: Parent and Teacher ADHD-RS to measure behavior. Secondary outcomes: C-GAS: assessment of symptoms severity as reported by clinician. Physiological parameters. Side effect checklist.	Parent and Teacher ADHD-RS: -A significant improvement was found in inattention score and parent total rating score in supplementation group. -Response rate was higher in supplementation group compared to placebo based only on parent rating. C-GAS: No significant between-group difference after treatment. No between-group significant difference in side effects.

Table 1. *Cont.*

Tan et al., 2016 [70]	146 ADHD (124 males), excluding syndromes, inborn errors of metabolism, brain lesions, chronic liver disease, anticoagulant/antiplatelet drugs. Age range: 6–12 years (TRF [a] group: 9.4 ± 1.9; Placebo group: 9.4 ± 1.7).	One month run in with placebo + 6 months RPCT 73 subjects taking TRF [a] (43 subjects taking medication). 73 subjects taking Placebo (35 subjects taking medication).	TRF [a] capsules: 200 mg/day. Placebo: similar to TRF [a].	VAPRS: parent-rated ADHD symptoms. VATRS: teacher-rated ADHD symptoms. Side effects questionnaire. Tocotrienol levels (blood exams).	VAPRS: significant improvement in both groups. VATRS: improvement in TRF [a] group but not statistically significant. Side effects: non-significant differences between groups. Tocotrienol levels: higher levels in TRF [a] group and significant correlation with the change in VAPRS.

(f)

Authors, year	Sample and age	Methodology and durations	Daily doses	Outcome measures	Main results
Pärtty et al., 2015 [71]	75 TD children (40 males). Age range at RCT: 0–6 months after birth. Age range at follow-up: 13 years. Diagnoses at 13 years: 3 ADHD; 1 AS; 2 ADHD + AS.	Six months after birth DBPCRT+ Follow-up at 13 years 40 subjects taking *Lactobacillus rhamnosus* GG. 35 subjects taking Placebo.	*Lactobacillus rhamnosus* GG: 1×10^{10} colony-forming units\day for 4 weeks before delivery + for 6 months after delivery.	ICD-10 diagnostic criteria for diagnoses of ADHD or Asperger syndrome (AS) filled in at follow-up. Gut microbiota: in situ hybridization (FISH) and qPCR and blood group secretor type.	ADHD or AS was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group ($p = 0.008$). The mean numbers of *Bifidobacterium* species bacteria in feces during the first 6 months of life was lower in children with ADHD or AS log cells/g than in healthy children.

Note: AA: arachidonic acid; AD: attention deficit; ADHD: attention deficit hyperactivity disorder; ADHD NOS: attention deficit hyperactivity disorder not otherwise specified; ADHD-RS: attention deficit hyperactivity disorder rating scale; AL: alpha-linolenic acid; ALC: Acetyl-L-carnitine; AMPH: d-amphetamine; AS: Asperger syndrome; ASD: autism spectrum disorder; ASQ-P: Conners' abbreviated questionnaires; ATX: atomoxetine; BRIEF: behavior rating inventory of executive function; CBCL: child behavior checklist; CD: conduct disorder; CGI-S/I: clinical global impression—severity scale/improvement scale; C-GAS: children's global assessment scale; CGQ: child health questionnaire–parent form; CHQ: child health questionnaire; CHP: compound herbal preparation; CLA: conjugated linoleic acid; CPRS-R: revised Conners' parent rating scale; CPT: continuous performance task; CTRS-R: revised Conners' teacher rating scale; DA: dopamine; DHA: docosahexaenoic acid; DHEA: dehydroepiandrosterone; DBRCT: double blind randomized controlled/clinical trial; DBRPCT: double blind randomized placebo-controlled/clinical Trial; DEN: daily essential nutrients; DIS-YPS-II Diagnostik psychischer Störungen im Kindes-und Jugendalter; DPA: docosapentaenoic acid; DSM-IV: diagnostic and statistical manual of mental disorders (4th ed.); EPA: eicosapentaenoic acid; FBRPCT: fully blinded randomized placebo-controlled trial; GLA: gamma linoleic acid; HAWIK-IV: Hamburg Wechsler Intelligence Scales for Children–IV; HD: hyperactivity disorder; HVA: homovanillic acid; IU: international unit; KITAP Test-batterie zur Aufmerksamkeitsprüfung für Kinder; KRG: Korean red ginseng; LA: linoleic acid; M: males; MOAS: modified overt aggression scale; MPH: methylphenidate; MSVA: Magallanes scale of visual attention; (f)-MRI: (functional) magnetic resonance imaging; NDG: ningdong granule; ODD: oppositional defiant disorder; OL: open label; (LC)-PUFAs: (long-chain) polyunsaturated fatty acids; PS: phosphatidylserine; QEEG TBR: quantitative electroencephalography theta/beta ratio; RPCT: randomized placebo-controlled trial; RPCCT: randomized placebo-controlled crossover trial; RPT: randomized pilot trial; RT: randomized trial; SCARED: screen for child anxiety related emotional disorders; SDQ: strengths and difficulties questionnaire; SLD: specific learning disorder; SNAP: Swanson, Nolan, and Pelham rating scale; TAP Testbatterie zur Aufmerksamkeitsprüfung; TD: typically developing; TOVA: test of variable of attention; TRF: teacher's report form; TRF [a]: tocotrienol-rich fractions; VAPRS: Vanderbilt ADHD parent rating scale (NICHQ); VATRS: Vanderbilt ADHD teacher rating scale (NICHQ); WIAT-III: Wechsler individual achievement test; WISC: Wechsler intelligence scale for children; WPREMB: weekly parent ratings of evening and morning behavior.

These studies supplemented with various omega-3 fatty acids. In total, 18 studies provided docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [34–42,44–50,52,53], one study provided alpha linolenic acid (ALA) [43], and one study did not specify which omega-3 was used. Three studies supplemented omega-6: one used gamma-linolenic acid (GLA) [36], while two did not specify which omega-6 was used [35,51]. One study provided, together with EPA and DHA, conjugated linoleic acid (CLA), a precursor of a distinct family of PUFAs (both omega-3 and omega-6) [47]. In two linked studies, authors prescribed linoleic acid (LA) omega-6 as a control condition compared to two omega-3 groups [48,49]. Seven studies added vitamins to EPA and DHA [40,44,47–49,52,53]; each of the seven provided vitamin E, whereas in Cornu et al. added vitamins A and D [40]. Six studies allowed pharmacotherapy concomitant with PUFA supplementation [34–37,50,52], while two added to EPA and DHA supplementation with PS [46] or docosapentaenoic acid [52]. Although PUFAs represent now the most used supplementation in this field, there is too much heterogeneity around the specific PUFAs used. It remains unclear if the efficacy of results depend on individual type of omega-3/6 or the whole of macronutrients.

Randomization between treatment and placebo groups is equal, except for one study [46], but there is still too much heterogeneity around the number of treatment groups.

Concerning outcomes, several studies used both multiple questionnaires/ratings [36,37,41,44,46] and cognitive tasks [38–40,42,43,48,49,52,53] and only one includes fMRI assessment [38]. However, other many studies kept in consideration only one questionnaire [34,35,45,47,50,51], as a result future researches could integrate better outcome measures.

3.1.2. Results

Regarding results, 13 studies highlighted various improvements related to PUFAs supplementation [35,36,38,39,41,44–46,48,49,51–53]. Six of those used EPA and DHA combinations [38, 39,41,45,48,49], three used unspecified omega3 + omega6 combinations [35,36,51], three added vitamin E to the omega3 formula [44,52,53], and one study prescribed PS together with omega3 [46]. In these studies, ameliorations were not related to specific cognitive or behavioral domains. The remaining seven studies [34,40,42,43,47,49,50] did not find positive results linked to PUFAs supplementation. Future investigations with homogeneous methodologies are needed to clarify the reason of non-significant results or could better specify the role of PUFAs supplementation on ADHD symptoms.

3.2. Peptides and Amino Acids Derivatives

3.2.1. Methodologies

We identified three studies [15,17,21] using Acetyl-L-carnitine (ALC), l-carnosine, and PS (Table 1b). It is not possible to depict a systematic comparison of those studies, given the heterogeneous supplementation approaches. Specifically, two works [15,17] compared subjects who tok a placebo to a group that took supplementation as an add-on to MPH. On the contrary, one study [21] used PS alone in the active treatment group and placebo in control group. All studies comprised uniform samples, except Ghajar et al. [17], who also included children with ODD and applied equal randomization in treatment and placebo groups. Two studies [15,17] considered similar outcome measures, including parent and teacher questionnaires regarding children's behavioral and cognitive symptoms. Hirayama et al. [21] used a go/no-go task and ADHD diagnostic criteria. Although these studies focused on different supplementations, they applied similar methodologies, especially regarding sample, randomization, and outcomes. The use of neuropsychological and physiological parameters could be improved and integrated to better understand response to treatment mechanisms. Moreover, future researches could address PS efficacy as an add-on to MPH.

3.2.2. Results

Regarding these studies results, ALC alone did not improve ADHD symptoms [15], but it reduced adverse effects when taken in addition to MPH. Moreover, l-carnosine seemed to improve behavioral problems according to parents [17]. PS had effects on ADHD symptoms, short-term auditory memory, and cognitive tasks [21]. In conclusion, l-carnosine and PS seem to have some effects on ADHD symptoms or cognitive domains but it remains unclear their specific role and mechanisms of action.

3.3. Single Micronutrient (Zinc or Vitamin D)

3.3.1. Methodologies

Some studies tested zinc [54–56] or vitamin D [25,57,58] (Table 1c). Zinc was used as sulfate [55,56] or glycinate [54] and vitamin D as generic [25] or D3 [57,58]. All studies provided micronutrients in addition to MPH [25,55–58] or dextroamphetamine [54]. Moreover, only Arnold et al. [54] compared the effects of micronutrients (and no pharmacological treatment) with placebo. All studies except two [54,58] included patients without comorbidity. Each study applied equal randomization between groups, even if the number of subjects was low [e.g., 58]. These works used similar methodologies, but several studies [25,55,57,58] used only parent-ratings as outcome measure.

3.3.2. Results

A link between zinc consumption and attention improvement was found in two studies [55,56]: zinc treatment improved inattention scores on parent questionnaires [55] and had effects on attention deficit disorder subtype of ADHD [56]. One study [54] did not find significant differences between zinc supplementation and placebo in the outcome measures; however, children taking zinc supplementation in addition to dextroamphetamine showed better drug dose optimization. All studies regarding vitamin D supplementation highlighted positive outcomes on parent-rated behavioral indexes or ADHD symptoms [25,57,58].

3.4. Micronutrients Mix

3.4.1. Methodologies

Several studies focused on broad combinations of vitamins and minerals [59–63] (Table 1d). One used a mixture of vitamin D and magnesium [60], two provided "daily essential nutrient formula", which contained 13 vitamins, 17 minerals, and 4 amino acids [59,61]. The remaining studies represent further analyses [63] and follow-up research [62] of the Rucklidge et al. paper [61]. All studies were comprised of children with several comorbidities and applied equal randomization between groups. All studies used multiple ratings, except for Hemamy et al. [60], and one work using magnetic resonance imaging (MRI) data as an outcome (however, this last did not find any significant effect) [59].

3.4.2. Results

These studies highlighted improvements in several behavioral, emotional, and cognitive ADHD symptoms. Furthermore, the follow-up study [62] offers additional evidences regarding possible efficacy of micronutrients mix. However, these studies are characterized by low numerosity and high heterogeneity of samples and treatments.

3.5. Plant Extracts or Herbal Supplementations

3.5.1. Methodologies

Seven studies focused on plant or herbal extracts containing a mix of micronutrients, vitamins, and macronutrients (Table 1e). It is not possible to depict a systematic comparison of those studies, given the heterogeneous supplementation approaches. Specifically, one work used Ginkgo biloba

plant extract as an add-on to MPH [69]. Others examined the efficacy of an herbal compound [64], Korean red ginseng (KRG) [65] or tocotrienol-rich fractions [70], as a single treatment compared to placebo, ningdong granule [66], sweet almond syrup [67], or Ginkgo biloba [68], compared to MPH. These studies focused on patients with ADHD symptoms without comorbidities and they applied an equal randomization, except for one work [64]. Each study used multiple ratings as outcomes, one of which [65] considered neurophysiological assessment and another cognitive tasks measures [64].

3.5.2. Results

All but two studies [68,70] found beneficial effects related to supplementation, in terms of improved symptomatology and/or less adverse effects as compared to MPH. Improvement in attention indexes was found in studies using a blend of herbs [64], Korean red ginseng [65], and Ginkgo biloba as an add-on to MPH [69]. Parent-, teacher-, or clinician-rated behavioral improvement was reported with KRG [65], ningdong granule [66], sweet almond syrup [67], and Ginkgo biloba as an add-on to MPH [69]. No adverse effects of supplementations were highlighted except for one study that reported increased appetite with sweet almond syrup [67], whereas half of the studies reported adverse effects of MPH [66–68]. One study [65] showed that KRG reduced the electroencephalography theta/beta ratio, a marker of cognitive processing capacity, significantly more than placebo. These results are heterogeneous and preliminary, and thus future homogeneous investigations that consider physiological parameters could offer more systematic evidences regarding herbal or extract supplementations. Furthermore, conflicting results [e.g., 68–69] between identical supplementation may be due to the different objectives: in one case authors aimed at comparing effects of supplementation with MPH [68], in the other case effects of MPH and non-pharmacological treatment together were compared to placebo [69].

3.6. Probiotics: Methodologies and Results

Only one paper focused on probiotics supplementation, through a different study design compared to the other reviewed studies [71] (Table 1f). A six-months-lasting probiotic supplementation was administered soon after childbirth and a follow-up assessment was conducted after 13 years. The quantity of Bifidobacterium species bacteria in the feces of children later diagnosed with ADHD or Asperger syndrome was found to be lower as compared to healthy children. ADHD or Asperger syndrome was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group ($p = 0.008$). This last study offers preliminary suggestions regarding probiotics supplementation as a preventive treatment, however further randomized clinical trials are needed to offer more systematic evidence regarding this treatment efficacy.

Figure 2 summarizes the main findings reported by the included works regarding nutritional supplementations on ADHD behavioral or cognitive symptoms; the vertical axis indicates the number of studies.

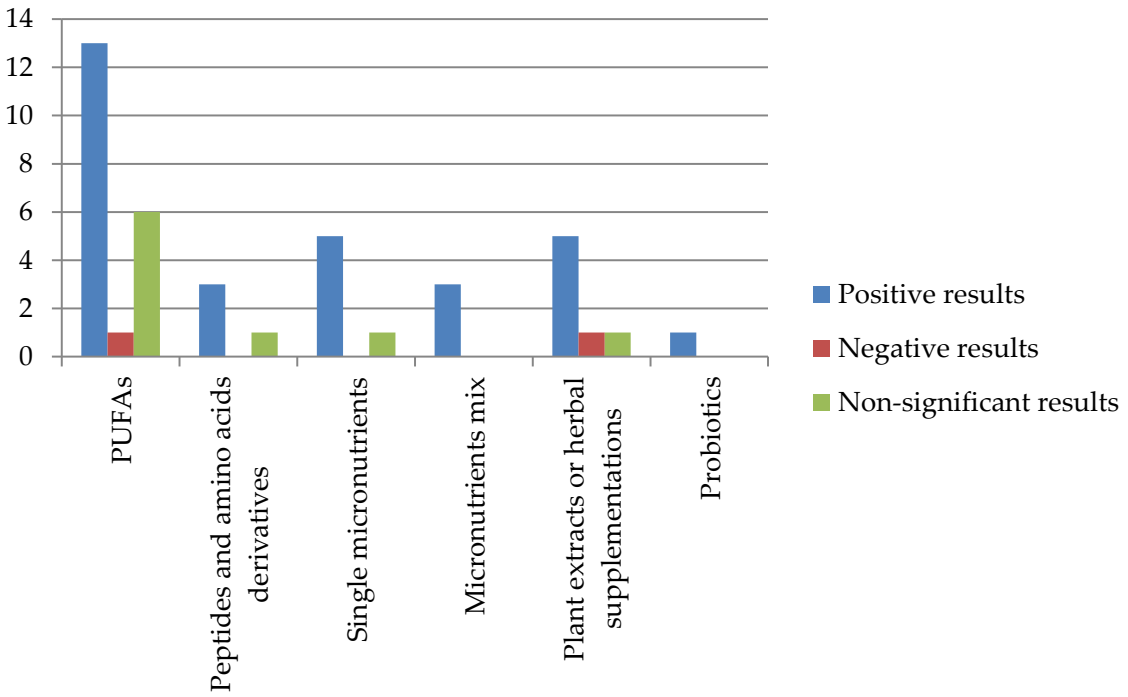

Figure 2. Effect of supplementations in ADHD symptoms.

4. Discussion

We investigated the recent literature about the efficacy of non-pharmacological treatments for ADHD in children and adolescents, alone or in combination with pharmacological treatment.

4.1. Discussion of Methodologies

It is relevant that nearly half of the reviewed studies used supplementation with PUFA (mostly EPA and DHA as omega3 PUFAs and, for some, omega6; see Table 1a). This supplementation approach could be linked to previous evidence suggesting the involvement of lower blood levels of DHA in children and adolescents with ADHD [12].

The other reviewed studies addressed the efficacy of peptides and amino acids derivatives (Table 1b), micronutrients (alone or in combination; see Table 1c,d), and plant or herbal extracts (Table 1e); one study investigated the association between early-life probiotics supplementation and ADHD or Asperger syndrome diagnoses at puberty (Table 1f). These supplementation approaches are less frequently reported in the scientific literature as compared to PUFA supplementation.

Each reviewed study used different combinations and doses of drugs and/or non-pharmacological supplementations. Therefore, it is not possible to draw systematic conclusions on optimal type or dose of compound that could be useful in the treatment of ADHD symptomatology.

Regarding outcome measures, Table 2 depicts a summary of sources of information that were considered in the reviewed studies. Table 2 highlights the need to consider homogeneous outcome variables in future research to obtain more systematic evidence related to the same outcomes. Moreover, objective neurophysiological outcomes should be more consistently evaluated together with clinical evidence.

Table 2. Summary of sources of information that were considered in the reviewed studies.

	Self Rating Scales	Parent Rating Scales	Teacher Rating Scales	Clinician Rated Scales	Psychometric Tests	Computerized Tasks	Neurophysiological Measures
PUFAs	[39,40]	[34–46,48–53]	[37,39,43,44, 46,47,53]	[36,41]	[40,42,48,49, 52,53]	[38,39,42,43, 48,49,52,53]	[38]
Peptides and amino acids derivatives		[15,17]	[15,17]	[21]	[21]	[21]	
Single micronutrient		[25,54–58]	[54,56]	[54]	[54]	[54]	
Micronutrients mix		[59–63]	[59,61]	[59,61,63]			[59]
Plant / herbal extracts	[64,66–70]	[64,66–70]	[66–70]	[64,65]		[64]	[65]
Probiotics				[71]			

4.2. Discussion of Results

The majority of reviewed papers reported improvements but no specific effect of different supplements was found, thus suggesting a non-specific beneficial influence of micro- and macro-nutrients on a broad spectrum of functions and symptoms. A possible explanation of this result could be ascribed to general environmental and dietary influences that have been previously associated to the severity of ADHD symptoms in children and adolescents, such as low socioeconomic status, parents' education, and unhealthy diet [72,73]. In this framework, it is still unclear whether ADHD onset and persistence over time represent the cause or the effect of unhealthy dietary patterns that could lead to nutritional deficits [72,73]. In any case, this review suggests that non-pharmacological supplementation, prescribed on the basis of individual nutritional deficiencies, could constitute a valid clinical path. It is not clear whether supplementation has a role for patients with no dietary imbalance. Moreover, the substances that are contained in various supplementations could benefit brain functioning but may also influence overall physiological functioning in children and adolescents, given a non-specific effect of these compounds. Clinicians should support alternative or additional treatment options only after appropriate blood tests and medical examinations.

In any case, the supplementation approach seems to be valid in combination with pharmacological treatment, as highlighted by positive results of MPH combination with PUFAs [35–37,52,56], peptides or amino acid derivatives [15,17], zinc [55,56], vitamin D [25,57,58], vitamin D and magnesium [60], and sweet almond syrup [67]. In these studies, ameliorations were found in behavioral symptoms as reported by parents and clinicians, together with less adverse events compared to pharmacotherapy alone. Hence, drugs and ad hoc nutritional supplementation could represent a valid therapeutic approach.

Other studies focused on children and adolescents who were not under pharmacological treatment for reasons including low compliance, adverse effects or non-response. This second group of studies found mixed results, in terms of finding beneficial effects of supplementation alone and of finding no effect at all. However, the majority of these studies reported a beneficial effect of supplements over placebo.

Specifically, 8 out of 14 studies regarding PUFA supplementation alone found symptoms amelioration over placebo in attention, psychosocial functioning, emotional problems, behavior as reported by parents and teachers, and working memory [38,39,41,44–46,51,53]. The only study addressing phosphatidylserine supplementation found positive effects of treatment over placebo in behavioral and cognitive symptomatology as reported by clinicians and through a go/no-go computerized task [21]. However, one study prescribed zinc supplementation against placebo and found no improvement in behavior, memory, or attention [54]. Five studies used plant or herbal extracts versus placebo. Two found significant beneficial effects of a patented blend of herbs (compound herbal preparation) and Korean red ginseng on attention and symptomatology as reported by clinicians [64,65].

Two studies found similar effects of ningdong granule or sweet almond syrup as compared to MPH treatment in behavioral measures reported by parents and teachers, with fewer side effects related to herbal supplementation than MPH [66,67]. Lastly, one study reported greater parent- and teacher-rated behavioral amelioration effects of MPH as compared to Ginkgo biloba supplementation alone [68] and another [70] did not find efficacy using tocotrienol-rich fractions compared to placebo. The only study concerning early-life probiotic supplementation revealed positive effects compared to placebo preventing ADHD onset later in life [71]. Studies regarding micronutrients mix supplementation found beneficial effects over placebo in general functioning, emotional dysregulation, aggression, and attention [59,61,62]. Importantly, a follow-up work by Rucklidge et al. identified various factors related to response to treatment with micronutrients mix, such as lower pre-treatment folate and B12 levels, being female, greater severity of symptoms and co-occurring disorders in pre-treatment condition, more pregnancy complications, and fewer birth problems [63]. This work highlighted the role of biological and environmental variables related to response to non-pharmacological treatment. This last area of research needs further research, given the high heterogeneity of results due to confounding biological and environmental variables.

5. Limitations

There were limitations within the articles described in this review. Results should be interpreted in the light of high heterogeneity related to various methodological factors. Indeed, the included works considered heterogeneous treatments, trial durations, methodologies (e.g., supplementation used as unique or combined treatment), and outcomes, even within the same category of supplements. Hence, it was not possible to carry out a meta-analysis of research results, which instead would be auspicable to provide clinicians with more systematic evidence. Moreover, samples were not uniformly involving only children with ADHD diagnoses; other comorbidities or typically developing children were included in some samples. Studies in this research field are also susceptible of cultural influences such as local dietary habits, thus making results difficult to generalize.

Although the majority of studies used similar parent and/or teacher assessment measures as primary outcomes, in many cases clinicians' evaluation or neurophysiological / neuropsychological assessments were lacking. Only three studies [38,59,65] used neurophysiological data, like magnetic resonance imaging or electroencephalography. These kinds of assessments should be included in future research.

Lastly, the majority of studies found beneficial effects, but this may be due to the fact that only studies that found effects were published. However, a formal evaluation of bias was not conducted due to the non-systematic nature of this review.

6. Conclusions

This review suggest that supplementation approaches may be effective in add-on to pharmacotherapy in improving some behavioral and neuropsychological indicators in children and adolescents with ADHD. The heterogeneity of results suggests that supplementation should be personalized based on each patient's dietary issues. Several supplementation components that are still poorly investigated and may be effective. Moreover, some nutritional supplementations could represent an alternative treatment or rehabilitation in situations of non-response or poor compliance or lack of tolerability of drug treatments, a field that must still be investigated further.

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https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-game-based-digital-therapeutic-improve-attention-function-children-adhd

FDA News Release

FDA Permits Marketing of First Game-Based Digital Therapeutic to Improve Attention Function in Children with ADHD

June 15, 2020

Today, the U.S. Food and Drug Administration (FDA) permitted marketing of the first game-based digital therapeutic device to improve attention function in children with attention deficit hyperactivity disorder (ADHD). The prescription-only game-based device, called EndeavorRx, is indicated for pediatric patients ages 8 to12 years old with primarily inattentive or combined-type ADHD who have demonstrated an attention issue. EndeavorRx is indicated to improve attention function as measured by computer-based testing and is the first digital therapeutic intended to improve symptoms associated with ADHD, as well as the first game-based therapeutic granted marketing authorization by the FDA for any type of condition. The device is intended for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

“The EndeavorRx device offers a non-drug option for improving symptoms associated with ADHD in children and is an important example of the growing field of digital therapy and digital therapeutics,” said Jeffrey Shuren, M.D., J.D., director of the FDA’s Center for Devices and Radiological Health. “The FDA is committed to providing regulatory pathways that enable patients timely access to safe and effective innovative digital therapeutics.”

ADHD is a common disorder that begins in childhood, affecting approximately 4 million children ages 6-11. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and very high levels of activity. According to the Centers for Disease Control and Prevention, diagnosis of ADHD should be conducted by a trained health care professional and follow an evaluation of symptoms or pattern of symptoms, such as inattention, hyperactivity, and impulsivity that interfere with functioning or development.

The FDA reviewed data from multiple studies in more than 600 children, including studies that evaluated, among other things, whether participants demonstrated improvements in attention function, as measured by the Test of Variables of Attention (TOVA), academic performance measures, and other assessment tools. There were no serious adverse events reported. The most common adverse events observed with EndeavorRx are: frustration, headache, dizziness, emotional reaction, and aggression.

The FDA reviewed the EndeavorRx through the De Novo premarket review pathway, a regulatory pathway for low- to moderate-risk devices of a new type. This action creates a new regulatory classification, which means that subsequent devices of the same type with the same intended use may go through the FDA's 510(k) premarket notification process, whereby devices can obtain marketing authorization by demonstrating substantial equivalence to a predicate device.

The FDA granted marketing authorization for the EndeavorRx to Akili Interactive.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Il bambino troppo intelligente: gioie o dolori?

GIUSEPPE ABBRACCIAVENTO
SC di Neuropsichiatria Infantile, IRCCS Materno-Infantile "Burlo Garofolo", Trieste

Li conoscono in pochi, pur avendoli a volte in famiglia. Difficile sentire parlare di "plusdotati", sebbene le statistiche indichino che il 2-3% dei bambini e adolescenti vivano questa condizione. È un mondo poco conosciuto, il loro: fatto a volte di perdita di autostima, abbandono scolastico e isolamento sociale. Chi li segue punta a curarli, ma soprattutto a riconoscerli per farli uscire dalla loro invisibilità (in famiglia come a scuola). L'articolo ci aiuta, con grande competenza, in questa possibile e necessaria presa in carico.

Giovanna, 14 anni, giunge un pomeriggio al Pronto Soccorso accompagnata dal padre per un attacco di panico. Durante il colloquio Giovanna non ne parla se non su mia richiesta. Racconta della sua vita e riesce a fare sintesi degli eventi che hanno avuto maggiore peso nella sua infanzia, nello specifico si sofferma sulla grave psicopatologia che ha colpito la madre, per cui ha dovuto trascorrere un breve periodo in affido per poi tornare a vivere solo con il padre. Nel giro di poche battute mi dice: «Io so perché sto male, ho paura che mi venga la stessa patologia di mamma, il mio problema non sono gli attacchi di panico ma questo». La ragazza racconta piangendo questa sua paura.Continua poi raccontando che spesso si ritrova a farsi domande di carattere astratto: «mi capita di chiedermi il senso della vita, siamo così insignificanti nell'universo e mi fa paura pensare all'universo infinito». Le domande che si pone mi portano a intuire la sua ricchezza intellettiva. La ragazza esplicita di non aver mai pensato o effettuato atti anticonservativi e mi sembra sollevata dopo la mia proposta di effettuare dei colloqui per capire come aiutarla.

Nel corso dei colloqui successivi raccolgo altri indizi sulla sua eccezionalità non così evidente. Frequenta un istituto professionale dove ha ottimi voti. Non è la più brava della classe, ma mi riferisce di studiare non più di un'ora al giorno e di non dover ripetere le materie di studio in quanto le basta la lezione ascoltata o una singola lettura. Trascorre la quasi totalità del suo tempo fuori casa, in comitiva, senza fare particolari attività. Mi racconta che quando è con altre persone riesce a non pensare. Emerge inoltre che Giovanna, negli anni passati aveva già effettuato un percorso di supporto psicologico per via della situazione familiare.

Dopo un confronto con la collega che seguiva la ragazza ho la conferma relativa alla sua plusdotazione, già registrata e valutata precedentemente con un quoziente intellettivo (QI) di 144.

Con colloqui a cadenza settimanale, nel giro di circa 3 mesi la sintomatologia di attacchi di panico si risolve, l'umore appare orientato in senso eutimico e gli aspetti di ansia sono limitati a sporadici e isolati episodi.

L'alto potenziale intellettivo, oltre a essere celato e non visibile agli adulti di riferimento, rappresenta per Giovanna una vulnerabilità, considerando uno sviluppo disarmonico dove ragionamenti complessi non sono accompagnati da uno sviluppo emotivo o esperienziale che le permetta di ottimizzare le sue risorse. Accompagnamo pertanto Giovanna a riprendere il percorso di sostegno psicologico associato a un programma di adeguamento degli impegni scolastici ed extrascolastici al suo livello cognitivo.

THE GIFTED CHILD: JOY OR UNHAPPINESS?
(Medico e Bambino 2020;39:377-383)

Key words
Intelligent; Gifted child, Autism spectrum, Psychological symptoms

Summary
The giftedness is a non-pathological condition for which there is no clear definition. Although the giftedness cannot be indicated by a single value obtained from the tests, consistently with the statistic values obtained from the WISC-IV test, it is estimated that this condition could characterize about 2% of the population in childhood and adolescence. In addition to this value obtained from psychometric tests, to characterize intellectual surplus, other factors must be considered: specific cognitive skills and abilities, personal commitment, motivation, context of life and characterial characteristics. The main clinical pictures that can be associated to giftedness are: learning disabilities attention deficit hyperactivity disorder, autism spectrum and psychological symptoms (internalizing and externalizing behavioural problems). To improve the understanding and treatment of these disorders and symptoms, it is appropriate to research the condition of giftedness. However, the obstinate research for a high cognitive potential could trigger relationship problems, mainly in the family environment, such as exposing the gifted child to conditions of greater vulnerability and psycological risk.

INTRODUZIONE

La definizione di plusdotazione richiama inevitabilmente il concetto di intelligenza, di come questa venga misurata e tutto ciò che concerne il significato di norma.

Il tema della plusdotazione cognitiva va introdotto precisando che la definizione di una norma di intelligenza viene valutata considerando un insieme di fattori misurabili e non misurabili, questi ultimi di carattere sociale, etico e culturale. Il concetto di intelligenza è infatti strettamente correlabile alla cultura nella quale è utilizzato: e questo è vero anche per altri concetti di carattere generale e socialmente mediati, come quello di bello, buono, simpatico, e altri ancora. Il concetto di intelligenza è quindi influenzato da *input* evoluzionistici che riguardano gli individui e la società nella quale si trovano, mentre il passaggio da "intelligenza potenziale" a "intelligenza in uso" dipenderà da fattori (facilitanti o inibenti) caratteriali e ambientali. Di questi ultimi vanno menzionati le diseguaglianze in salute, la povertà, gli eventi avversi in età evolutiva, l'accesso ai diritti fondamentali dell'infanzia, al gioco, allo studio e a stimoli evolutivi adeguati all'età cronologica e mentale dell'individuo. È necessario quindi comprendere la complessità del tema mantenendo un approccio critico e non dogmatico, per meglio facilitare i compiti evolutivi dei piccoli e quasi grandi (adolescenti) che incontriamo nella nostra pratica clinica e che chiedono il nostro sostegno.

INTELLIGENZA E PLUSDOTAZIONE: DI COSA STIAMO PARLANDO

È solo attraverso una concettualizzazione e rappresentazione dell'intelligenza che possiamo definire una condizione nella quale questa risulta in eccesso. In questo senso, è utile confrontare le differenti condizioni che si collocano fuori norma per intelligenza, sia per difetto che per eccesso. Prima di approfondire cosa si deve intendere per plusdotazione, e per capirsi meglio, conviene quindi richiamare come viene definita la disabilità intellettiva. Secondo il *Manuale Diagnostico e Statistico dei Disturbi Mentali* quinta edizione (DSM-5), per definire questa condizione non basta il valore numerico del QI ma è necessaria la presenza di tre criteri:

1. deficit delle funzioni intellettive,
2. deficit del funzionamento adattivo e
3. esordio dei deficit in periodo di sviluppo.

Inoltre, la valutazione di severità della disabilità intellettiva, distinta in lieve, moderata, grave ed estrema, non considererà (o non considererà soltanto) il punteggio dei test di intelligenza, bensì terrà conto della compromissione del funzionamento adattivo (valutato in tre ambiti: concettuale, sociale e pratico), compromissione che determinerà quindi il livello di assistenza necessario per quel soggetto *(Tabella I)*.

CRITERI DIAGNOSTICI DELLA DISABILITÀ INTELLETTIVA (DSM-5)

Deficit delle funzioni intellettive	Difficoltà di ragionamento, *problem solving*, pianificazione, pensiero astratto, capacità di giudizio, apprendimento scolastico e apprendimento dall'esperienza, confermati sia da una valutazione clinica sia da test di intelligenza individualizzati, standardizzati.
Deficit del funzionamento adattivo	Mancato raggiungimento degli standard di sviluppo e socioculturali di autonomia e di responsabilità sociale. Senza un supporto costante, i deficit adattivi limitano il funzionamento in una o più attività della vita quotidiana, come la comunicazione, la partecipazione sociale e la vita autonoma, attraverso molteplici ambienti quali casa, scuola, ambiente lavorativo e comunità.
Esordio dei deficit in periodo di sviluppo	

Tabella I

DEFINIZIONI DI PLUSDOTAZIONE INTELLETTIVA

Definizione	Fonte
Individui che mostrano, o hanno il potenziale per mostrare, un livello eccezionale di performance, se confrontati con i loro pari, in una o più delle seguenti aree: abilità intellettiva generale, attitudine scolastica, pensiero creativo, *leadership*, arti visive e dello spettacolo	National Association for Gifted Children[2]
Nel *giftedness* (plusdotazione) sono presenti: alto potenziale cognitivo, motivazione e creatività	Renzulli 1978 The three-ring conception of giftedness[3]
Giftedness (plusdotazione) è un'etichetta per indicare il concetto biologico di sviluppo superiore di varie funzioni cerebrali [...] dipende dall'interazione tra eredità biologica e opportunità ambientali	Clark 1979[4]
La definizione di bambino intellettualmente precoce circoscrive la precocità alla dimensione intellettuale e al suo sviluppo.	Louis 2002[5]

Tabella II

Dall'altro lato della campana gaussiana, che per dati statistici dovrebbe riguardare circa il 3% della popolazione generale, non troviamo né definizioni così chiare né delle linee di indirizzo altrettanto precise sull'interpretazione e sull'utilizzo degli strumenti valutativi.

Nella letteratura italiana il termine di plusdotazione intellettiva, usato in prevalenza dagli esperti del settore (nella letteratura internazionale è ampiamente diffusa la definizione *gifted children*, che tradotto significa **bambini plusdotati**), trova una vasta gamma di termini che indicano una condizione di "eccezionalità": alto e altissimo potenziale intellettivo, plusdotazione cognitiva/intellettiva, plusdotazione, dotato/a, superdotato/a, prodigio, intellettualmente precoce, precoce, creativo/a, eccezionale.

Nella plusdotazione cognitiva, al fianco del livello cognitivo, invece di trovare le abilità adattive come fattore caratterizzante, necessario per la definizione di disabilità intellettiva, possiamo trovare altri elementi: livello eccezionale di *performance*, motivazione, creatività, non comuni capacità percettive, non comuni capacità di sensibilità, opportunità ambientale.

Nella *Tabella II* sono riportate alcune delle definizioni di plusdotazione (*giftedness* degli Autori anglosassoni) presenti in letteratura e che comprendono gli elementi soprariportati[2-5].

Sebbene l'intelligenza possa essere considerata un concetto complesso che si costituisce di elementi misurabili e non misurabili, nella pratica clinica, il più delle volte e in modo del tutto erroneo, è il singolo valore numerico ottenuto dalla somministrazione di un test intellettivo a indicare se un soggetto presenta una condizione di plusodotazione cognitiva (con scala multifattoriale WPPSI-IV - *Wechsler Preschool e Primary Scale of Intelligence* -, WISC-IV - *Wechsler Intelligence Scale for Children* - o WAIS - *Wechsler Adult Intelligence Scale* - si fa riferimento a valore di QI > 120-130).

TEORIE RELATIVE ALLA MISURAZIONE DELL'INTELLIGENZA

Teoria	Sintesi
Teoria unitaria dell'intelligenza o teoria del fattore g[6]	Il fattore g rappresenta da solo l'unico elemento che indica il livello di intelligenza di un individuo
Teoria delle tre forme di intelligenza[7]	L'intelligenza viene valutata nelle sue tre forme: logica, pratica e creativa
Teoria delle forme multiple di intelligenza[8]	Intelligenza linguistica, intelligenza musicale, intelligenza logico-matematica, spaziale, corporeo-cinestatica, intrapersonale, interpersonale
Teoria gerarchica dell'intelligenza[9]	Sono presenti varie forme di intelligenza con diverso grado di specificità che concorrono a indicare un valore unitario complessivo di intelligenza

Tabella III

SCHEMATIZZAZIONE DELLA MISURA DELL'INTELLIGENZA SECONDO LA TEORIA GERARCHICA

ABILITÀ/INTELLIGENZA SPECIFICHE		ABILITÀ/INTELLIGENZA GENERALI	
Abilità specifiche (valutate dal test)	**Abilità generali di 1° grado**	**Abilità generali di 2° grado**	**Valore finale unitario**
Ragionamento	Intelligenza non verbale	Abilità generale	QI
Categorizzazione visiva			
Visualizzazione			
Conoscenza delle parole	Intelligenza verbale		
Categorizzazione verbale			
Conoscenza del mondo			
Memoria di lavoro	Memoria di lavoro	Abilità di processo	
Memoria a breve termine			
Velocità con forme	Velocità mentale		
Velocità con simboli			

Tabella IV

MISURAZIONE DEL LIVELLO INTELLETTIVO E TEORIA GERARCHICA DELL'INTELLIGENZA

La misurazione del livello intellettivo rimanda a una data concezione dell'intelligenza e della sua misurazione *(Tabella III)*[6-9]. La teoria alla quale ci riferiamo e che al momento trova maggiore consenso è relativa alla **teoria gerarchica dell'intelligenza**.

Nella formulazione di un valore unitario di intelligenza attraverso il modello gerarchico proposto anche da Cornoldi[9], si accetta la presenza di più forme di intelligenza o di abilità, delle quali alcune sono più rilevanti di altre e che si compongono per indicare un valore complessivo del QI.

Una schematizzazione semplificata sulla teoria gerarchica è riportata nella *Tabella IV*.

Questa definizione di intelligenza, e quindi il relativo modello valutativo (che corrisponde ai test oggi in uso), permetterà di tracciare per ogni individuo un QI e il relativo profilo di intelligenza.

Per uno stesso valore di QI potremo avere infiniti profili intellettivi diversi. Ad esempio, potremmo trovare due individui con un QI totale identico ma, dei due, uno potrebbe eccellere nel "ragionamento" senza però discostarsi dalla media nelle altre abilità, mentre l'altro potrebbe avere valori fuori dalla norma in eccesso nella sola competenza di "velocità con simboli".

Il profilo cognitivo potrebbe informare sul potenziale intellettivo, individuando chi è solo talentuoso (alto valore in una specifica abilità), chi è plusdotato (chi ha un alto valore in una o più abilità generali) e chi è un genio. In quest'ultimo caso oltre al talento/plusdotazione potrebbero essere presenti altri fattori come la creatività, la motivazione, l'impegno[10].

LA PRECOCITÀ DI SVILUPPO

La complessa impalcatura che regola l'intelligenza e che può essere costituita da profili cognitivi differenti a loro volta associati, come abbiamo visto, a differenti fattori che influenzano l'intelligenza in uso, rende difficile individuare caratteristiche tipiche della plusodtazione cognitiva. È utile tuttavia sottolineare che la precocità nelle acquisizione delle tappe di sviluppo è un fattore che più di altri suggerisce la presenza di un elevato potenziale intellettivo, ne dà conferma il fatto che alcuni Autori indicano la plusdotazione attraverso il concetto di "precocità"[11].

Una buona anamnesi di sviluppo permetterà di valutare tale precocità che andrà esplorata nelle sue diverse aree di sviluppo (gioco, linguaggio, abilità motorie, accesso a concetti astratti e complessi, competenze di

problem solving, acquisizione dei prerequisiti scolastici, abilità scolastiche, pensiero creativo, competenze comunicative e relazionali, autonomie e abilità adattive).

CHI HA BISOGNO DI AIUTO? LA PRATICA CLINICA

Una descrizione delle tipologie di plusdotazione cognitiva permette di distinguere più chiaramente gli individui con plusdotazione cognitiva che necessitano di un sostegno[12]:

- **Tipo di successo**: individuo apprezzato da compagni e adulti, non presenta problemi nella gestione dei riconoscimenti.
- **Tipo autonomo**: sin da piccolo mostra le sue capacità, sono individui precoci, che tendono a ottenere apprezzamento e riconoscimento a scuola. Spesso assume un ruolo di *leadership*.
- **Tipo drop-out**: individuo che manifesta rabbia verso gli altri, ostilità nei confronti della scuola, umore deflesso e talvolta comportamenti problematici (scarso rispetto delle regole, dell'autorità, comportamenti pericolosi per sé o per gli altri), con difficoltà a integrarsi nel gruppo dei pari, atteggiamenti di evitamento o isolamento con sintomi di ansia o umore depresso.
- **Tipo con doppia eccezionalità**: il termine eccezionalità si riferisce a ciò che non rientra nella "norma", si parla quindi di eccezionalità nei termini di plusdotazione cognitiva ma anche di eccezionalità nel fare peggio dei compagni in alcune abilità o discipline (disturbi specifici dell'apprendimento, ADHD).
- **Tipo sotterraneo**: le competenze cognitive non sono evidenti nell'ambito scolastico o nelle *performance* del soggetto. Talvolta ci sono sentimenti di vergogna e si cerca di nascondere le proprie abilità non volendo apparire superiore.

Le tipologie di bambini e adolescenti alle quali dovremo prestare attenzione, riconoscendo la condizione di plusdotazione cognitiva e fornendo quindi adeguati strumenti di supporto, sono la categoria *drop out* e *con doppia eccezionalità*.

Meritano attenzione anche soggetti tipo *sotterraneo*. Se l'alto potenziale intellettivo non viene riconosciuto da sé o da altri, questo può influire su una possibile disarmonia evolutiva (aspetti emotivi meno sviluppati e non in linea con le competenze cognitive più avanzate), causando così disagio e varie forme di sofferenza. Come è avvenuto nel caso di Giovanna.

Nella pratica clinica del neuropsichiatra (e probabilmente anche del pediatra), le due tipologie che prevalgono per frequenza sono quelle *con doppia eccezionalità* e *sotterraneo*.

Il primo tipo spesso è associato a disturbi degli apprendimenti scolastici o a difficoltà nell'area dell'attenzione. Nel caso in cui venga riscontrata una doppia eccezionalità, queste andranno lette necessariamente in continuità, prevedendo interventi di potenziamento alle competenze deficitarie e di valorizzazione delle abilità eccellenti.

Nel caso del *tipo sotterraneo*. Non possiamo fare stime su quanti bambini con questo profilo giungano all'attenzione di un clinico che scova la loro bravura, e quanti invece percorrono in sordina e ostinato dis-equilibrio il loro percorso evolutivo sino all'età adulta. In questo caso il mancato accesso a stimoli adeguati potrebbe non valorizzare risorse e talenti che con il tempo potrebbero non essere mai riconosciute e quindi sviluppate: povertà, discriminazione, limitato accesso a scelte di indirizzo di studi diversificati, scarso supporto affettivo e cognitivo.

Se ci capita di rintracciare questa tipologia di individui, non saranno le abilità scolastiche o il livello di *performance* generale a fornire particolari indizi o *input* per ricercare la plusdotazione cognitiva. In questa tipologia di soggetti potremmo imbatterci in vari sintomi di carattere emotivo-comportamentale. Talvolta prevalgono sentimenti autosvalutanti, ansia o sentimenti di vergogna; sentimenti che indicano una difficoltà a comprendere una condizione di eccezionalità che risulterà distanziante rispetto al resto dei compagni. In altri casi questi soggetti possono avere difficoltà a integrare le competenze intellettive elevate con aspetti esperienziali ed emotivi ancora immaturi e non in grado di supportare l'intensità e la profondità dei pensieri e dei ragionamenti prodotti.

Come nel caso di Giovanna, che in passato ha incontrato adulti che hanno sempre tentato di rispondere alle domande, evitando che le domande rimanessero aperte (infatti nell'età dell'infanzia, il contrario potrebbe generare ansia e confusione).

Quindi quando Giovanna ha iniziato a porsi domande complesse di carattere astratto "che senso ha la realtà se quello che viviamo non sappiamo se è reale", come in altre situazioni vissute, ricercava una risposta puntuale, e con difficoltà tollerava l'incertezza della risposta, la possibilità di non riuscire ad avere una sola risposta o di ricevere una non risposta.

In questi casi il supporto psicologico e, lì dove necessario, una terapia sintomatica, potrebbero rendere più armonico lo sviluppo cognitivo-psicologico e quindi facilitare il non lungo periodo di transito verso l'adultità.

SINDROME DI EX-ASPERGER

Marco, di 9 anni, giunge in ambulatorio per difficoltà del linguaggio. Marco è esposto a bilinguismo italiano-polacco in quanto la madre saltuariamente gli parla nella sua lingua di origine.
Dalla raccolta anamnestica emerge un ritardo del linguaggio, con prime parole a 3 anni; all'epoca presentava gesto comunicativo e uso del corpo dell'altro a scopo comunicativo (utilizzava la mano della madre per comunicare). Emerge inoltre marcata goffaggine motoria e difficoltà di coordinazione che vengono confermate dalla visita neurologica e dalla valutazione complessiva.
A 3 anni su iniziativa dei genitori viene portato in Logopedia; tuttavia la logopedista interrompe il trattamento per difficoltà di adattamento del bambino rispetto al contesto riabilitativo: "il bambino non riesce a seguire i compiti e a entrare in relazione con l'adulto".
Con il tempo, sebbene le problematiche di linguaggio si attenuino, presenta un pronunciato accento polacco, che si manifesta con prosodia e intonazione peculiari. Inoltre il bambino produce

parole stereotipate, come l'intercalare "già". Nel corso della visita si evidenzia scarso contatto di sguardo e non rispetto dei turni nella conversazione.
Marco continua il suo percorso scolastico. Questo si caratterizza per le costanti difficoltà relazionali e di integrazione, che con il tempo peggiorano fino a portare la famiglia a ritirare il bambino da scuola all'età di 8 anni. Si intraprende un percorso di homeschooling riducendo ulteriormente gli spazi e le occasioni sociali.
"Le insegnanti e i compagni di classe non mi capivano, mi trattavano male […] i bambini mi tormentavano, mi mandavano via dal gioco, non mi facevano giocare con loro, le maestre non mi capivano".
Sin da piccolo Marco presenta degli interessi ristretti, in particolar modo rivolti verso gli aerei. Nel dialogare con l'altro inserisce argomenti correlati agli aerei. Il bambino durante la visita mostra di conoscere tutti gli orari di partenza e di arrivo degli aerei relativamente agli aeroporti di Venezia, Trieste e Treviso (informazioni verificate su internet).
Viene somministrata la scala ADOS (Autism Diagnostic Observation Schedule) da cui si evidenziano le difficoltà di Marco a riconoscere le emozioni nell'altro. Durante il test il bambino dice "cosa noi facciamo" continuando poi a descrivere le azioni compiute.
Le difficoltà sociali e di interazione emergono anche dal colloquio:
"Hai degli amici? - Faccio il conto che i miei giochini sono i miei amici"
"Hai una fidanzata? - Che cos'è una fidanzata?".
"Piccola bambina con occhiale ha rubato il mio secchietto delle matite, ho perso la ragione e le ho tirato il maglione".
Infine alla valutazione del livello cognitivo con la WISC-IV si evidenzia un profilo cognitivo nella norma con QI totale di 94 (punti di forza in competenze visuopercettive, punteggio di 120; punti di debolezza in memoria di lavoro e velocità di elaborazione, ottenendo un punteggio in entrambe le aree pari a 82).
Il quadro complessivo, per presenza di criteri diagnostici, per grado di compromissione della vita quotidiana, rientra in una condizione di spettro autistico con sintomi moderati senza compromissione del livello cognitivo e senza compromissione delle competenze di linguaggio (ma non in un quadro di plusdotazione cognitiva).

È utile chiarire alcuni aspetti della sindrome - descritta nella prima metà del '900 dal pediatra Hans Asperger - per poter comprendere se, e come, utilizzare questa etichetta diagnostica.

Sebbene con l'ultima revisione del DSM-5 la sindrome di Asperger non sia presente nosograficamente, venendo inglobata nella categoria dei "disturbi dello spettro autistico", persiste l'utilizzo del termine con riferimento ai criteri diagnostici comparsi per la prima volta nella versione precedente del DSM (DSM-IV). Nel DSM IV la sindrome di Asperger, inserita all'interno del capitolo dedicato ai "disturbi pervasivi dello sviluppo", descriveva una condizione caratterizzata da compromissione clinicamente significativa dell'area sociale, lavorativa o di altre aree importanti del funzionamento, associata ad atipie comportamentali (es. difficoltà a mantenere il contatto di sguardo, talvolta discorsi inappropriati al contesto) in assenza di compromissione del linguaggio e del livello cognitivo.

La plusdotazione cognitiva non è quindi né un criterio diagnostico né una prerogativa del disturbo, tuttavia gli interessi ristretti e l'attenzione selettiva verso specifiche aree rendono il soggetto eccellente ed esperto in una certa area di competenza.

Oggi, secondo il DSM-5, la nuova definizione, che non utilizza più l'eponimo, è quella di "disturbo dello spettro autistico, senza compromissione intellettiva associata e senza compromissione del linguaggio associato". Sebbene la gravità del disturbo dello spettro autistico si basi sul grado di compromissione sociale e sui *pattern* comportamentali ristretti e ripetitivi, nel caso di questa specifica condizione, vista l'assenza di compromissione cognitiva e di linguaggio, si presume un livello basso di gravità.

Per quanto detto sarebbe quindi corretto utilizzare la terminologia proposta dal DSM-5 al fine di evitare confusione nella comprensione del disturbo e di non intenderlo, in una accezione semplicistica ed errata ma senz'altro molto divulgata, di soggetto con problemi di socializzazione ma settorialmente iperdotato. Nella pratica clinica, infatti, non è raro l'utilizzo inappropriato del termine "Asperger", per indicare condizioni che non rientrano nello spettro autistico o per definire condizioni di rilevanza non clinica (persona intelligente, bizzarra e goffa).

Va invece tenuto presente che il bambino e l'adolescente con disturbo dello spettro autistico con le caratteristiche di quella che veniva chiamata sindrome di Asperger presentano, in particolare per le difficoltà di relazione, una marcata e grave sofferenza psichica. Infatti, l'aumento significativo del rischio suicidario negli adolescenti e giovani adulti con tali caratteristiche cliniche sottolinea la necessità di una precoce diagnosi e di un tempestivo e adeguato intervento terapeutico e di supporto[13,14].

CONSIDERAZIONI CONCLUSIVE E INDICAZIONI PER IL PEDIATRA

A oggi non sono presenti linee di indirizzo sull'approccio alla plusdotazione, tantomeno è presente una visione univoca sul tema a livello nazionale e internazionale[15].

Facendo alcuni esempi, in Canada la plusdotazione è considerata una anomalia potenziale che un bambino può manifestare. In Israele esiste un programma di formazione per individui con plusdotazione intellettiva per i futuri *leader* di molti settori scientifici, mentre in Francia vi sono adattamenti scolastici per l'apprendimento diversificato.

In Italia, dopo alcune isolate esperienze negli anni passati di scuole private dedicate a bambini con plusdotazione cognitiva, nell'ultimo anno, con una Nota ministeriale, si riconosce l'inserimento di individui plusdotati (quoziente intellettivo pari o superiore a 130) all'interno del sistema degli alunni con Bisogni Educativi Speciali (BES). Viene prevista anche la possibilità di redazione di un Piano Didattico Personalizzato, in una logica di personalizzazione degli apprendimenti[16].

Per i pediatri di famiglia, che più di altri seguono le traiettorie di sviluppo dei bambini, è importante avere in mente che una piccola percentuale dei

IL BAMBINO TROPPO INTELLIGENTE: COSA DEVE SAPERE UN PEDIATRA (UN GENITORE E LA SCUOLA)

Come riconoscere	Come approcciare
Ha imparato a leggere precocemente (4-5 anni)	Non trasmettere il senso di eccezionalità o anormalità
Ha cominciato sin da piccolo a mostrare un certo interesse intenso e continuativo per un certo argomento	Non fare confronti con gli altri bambini
Mostra capacità straordinaria per capire argomenti e idee complesse	Non enfatizzare la diversità, ma accoglierla
Mostra di possedere ampie conoscenze su diversi argomenti e di possedere una grande memoria	Non nutrire elevate aspettative ed essere troppo richiestivi
Mostra eccezionali iniziativa e indipendenza in giochi e *hobby*, o nel fare le cose per sé stesso	Non scoraggiare la curiosità dei figli, ma aiutarli a scoprire il mondo
Dice che la sua attività scolastica è noiosa perché troppo facile	Porre al bambino poche e chiare regole contemporaneamente
Prende spesso voti molto alti a scuola	Non avere paura, come genitori, di non essere adeguati nei confronti del figlio e di non essere abbastanza intelligenti
Passa molte ore a leggere	Creare momenti liberi per riflettere, divagare e anche annoiarsi.
Ha speciali *hobby* o interessi	Fare attenzione agli aspetti positivi
Mostra particolari capacità immaginative e idee originali nel suo tempo libero	

Tabella V

MESSAGGI CHIAVE

- ❏ La plusdotazione cognitiva è una condizione non patologica per la quale non esiste una definizione univoca.
- ❏ Sebbene non possa essere indicata da un unico valore ricavato dai test, coerentemente con i valori statici ricavati dalla somministrazione del test WISC-IV, si stima che tale condizione potrebbe caratterizzare circa il 2% della popolazione nell'età dell'infanzia e dell'adolescenza.
- ❏ Oltre ai valori ottenuti dai test psicometrici, per caratterizzare la plusdotazione intellettiva è necessario considerare altri fattori: specifiche competenze e abilità cognitive, impegno, motivazione, contesto di vita, caratteristiche caratteriali.
- ❏ I principali quadri clinici che si possono associare alla plusdotazione intellettiva e per i quali è necessario ricercare tale condizione sono: disturbo dell'apprendimento, disturbo da deficit di attenzione, disturbo dello spettro autistico e sintomi psicologici (esternalizzanti e internalizzanti).
- ❏ In queste circostanze è quindi opportuno ricercare la condizione di plusdotazione cognitiva al fine di migliorare la comprensione del disturbo/sintomi di base e quindi migliorare anche le proposte terapeutiche individualizzate.
- ❏ D'altra parte, la ricerca ostinata di un alto potenziale cognitivo potrebbe innescare dinamiche relazionali, prevalentemente nell'ambito familiarie tali da esporre il bambino/adolescente con plusdotazione intellettiva, a una condizione di maggiore vulnerabilità e rischio psicologico.

bambini e adolescenti con una difficoltà scolastica o con una problematica di carattere emotivo o comportamentale potrebbe essere sottesa da una plusodotazione cognitiva che, se riconosciuta, permetterebbe di ottimizzare gli interventi di potenziamento e di supporto attraverso le caratteristiche positive del bambino.

Dall'altro lato, come abbiamo detto, non tutti i bambini/adolescenti con plusdotazione cognitiva meritano una presa in carico o un'attenzione "clinica". Quando un bambino è sereno e la sua infanzia è preservata, il compito degli adulti sarà quello di fornire gli strumenti utili per affrontare le varie sfide evolutive, senza necessità di etichette o di indici che rischiano poi di incastrare i percorsi in aspettative o previsioni.

Anche la scuola in quest'ottica potrebbe mettere a disposizione di ogni singolo alunno degli strumenti necessari a valorizzare i punti di forza e a potenziare invece le abilità meno solide. A questo proposito merita di essere ricordato quanto affermato da Morin: "L'intelligenza non è solo quello che i testi misurano ma è anche quello che sfugge loro"[17]. Sarebbe infatti rischioso individuare l'intelligenza nei soli dati relativi agli strumenti valutativi o a quelle competenze più evidenti. Nel considerare questa categoria di "diversi" che attira l'attenzione della società sin dai tempi della mitologia greca con eroi dalle doti e dai talenti eccezionali, è utile contestualizzare la plusdotazione all'interno del nostro sistema culturale. Ammaniti descrive come la società di oggi esponga bambini e adolescenti a un investimento narcisistico che è mosso dalla famiglia e dalla società stessa. Oggi i bambini sono sempre più spesso chiamati a confrontarsi con aspettative e richieste da parte degli adulti e sempre più precocemente sono portati a competere con i coetanei che nel confronto costante esplicitano la differenza (quando non integrata nel gruppo), diventando fonte di giudizio e vergogna[18].

È infatti necessario considerare che, in questo clima, il riconoscimento dell'eccezionalità (e una certa modalità di riconoscimento sociale) non necessariamente potrebbe essere conciliabile con la serenità dell'individuo. Provocatoriamente Cornoldi[10] a conclusione del suo testo pone un interrogativo ai genitori: "date priorità alla serenità o alla manifestazione dell'eccezionalità di vostro figlio?". È noto che, nel caso di bambini con alto potenziale intellettivo, gli adulti possano mettere in atto processi di negazione, di dequalifica o non riconoscimento, per paura della diversità, per senso di inadeguatezza o per disagio socioeconomico della famiglia. Dall'altra parte, direi in modo più frequente, sono presenti invece comportamenti di iperinvestimento nel bambino, meccanismi di aspettative e previsioni, proiezioni dell'adulto che invadono i processi evolutivi nell'adolescenza.

Inoltre, nel caso siano presenti delle doti, queste potrebbero venire strumentalizzate dall'adulto di riferimento con richieste di iperaddestramento che può poi portare nel bambino/adolescente, a intenso malessere, perdita di interesse nell'attività svolta e rifiuto a proseguire nelle attività in cui eccelle.

Bisogna necessariamente riconoscere quindi come questi atteggiamenti degli adulti, che spesso sono presenti anche in assenza di una condizione di plusdotazione del bambino, possano rappresentare un potenziale rischio per la serenità, il tempo e la qualità dell'infanzia. Ed è proprio questa consapevolezza che guiderà il pediatra a scegliere le parole da dire e le azioni da intraprendere a garanzia e a difesa della salute e dello sviluppo del bambino.

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