NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD DICEMBRE 2021

Acad Pediatr. 2021;21:1253-61.

A QUALITY IMPROVEMENT INITIATIVE TO IMPROVE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FOLLOW-UP RATES USING SCHOOL-BASED TELEMEDICINE.

Milne Wenderlich A, Li R, Baldwin CD, et al.

Objective: Patients with a new diagnosis of attention-deficit/hyperactivity disorder (ADHD) who are prescribed stimulant medication need regular follow-up. Guidelines recommend follow-up within 30 days of stimulant initiation or change but this goal is seldom achieved. This quality improvement (QI) study in an urban academic outpatient practice aimed to: 1) assess whether use of school-based telemedicine increases rates of follow-up within 30 days and decreases the number of days to follow-up for ADHD, and 2) compare rates of 30-day follow-up via in-person vs telemedicine visits.

Methods: We performed three Plan-Do-Study-Act cycles over a 12-month period: QI interventions included clinic wide education, paper prompts for clinicians, and creation of a database to track ADHD patients. We measured days from the index visit to the follow-up visit, and the mode of both visits (in-person or telemedicine). Data were collected for 6 months pre-intervention and 12 months post-intervention.

Results: Follow-up within 30 days increased from 19% (of 191 visits) to 33% (of 661 visits) (P < .001). The time to follow-up decreased from 67 to 34 days (P < .001). Follow up visits by telemedicine were more also more likely to be within 30 days (62% vs. 32%, P < .001).

Discussion: A QI intervention for ADHD care increased rates of follow-up within 30 days, particularly when telemedicine was used, and decreased the number of days to follow-up. This intervention could serve as a model to improve follow-up for ADHD in other settings

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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.

Advances in Experimental Medicine and Biology. 2021;1344:113-27.

THE ROLE OF THE CIRCADIAN SYSTEM IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Bondopadhyay U, Diaz-Orueta U, Coogan AN.

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition characterised by the core symptoms of inattention, impulsivity and hyperactivity. Similar to many other neuropsychiatric conditions, ADHD is associated with very high levels of sleep disturbance. However, it is not clear whether such sleep disturbances are precursors to, or symptoms of, ADHD. Neither is it clear through which mechanisms sleep and ADHD are linked. One possible link is via modulation of circadian rhythms. In this chapter we overview the evidence that ADHD is associated with alterations in circadian processes, manifesting as later chronotype and delayed sleep phase in ADHD, and examine some mechanisms that may lead to such changes. We also interrogate how the circadian clock may be a substrate for therapeutic intervention in ADHD (chronotherapy) and highlight important new questions to be addressed to move the field forward

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Am J Med Genet B Neuropsychiatr Genet. 2021 Oct;186:401-11.

A POLYGENIC RISK SCORE ANALYSIS OF ASD AND ADHD ACROSS EMOTION RECOGNITION SUBTYPES.

Waddington F, Franke B, Hartman C, et al.

This study investigated the genetic components of ADHD and ASD by examining the cross-disorder trait of emotion recognition problems. The genetic burden for ADHD and ASD on previously identified emotion recognition factors (speed and accuracy of visual and auditory emotion recognition) and classes (Class 1: Average visual, impulsive auditory; Class 2: Average-strong visual & auditory; Class 3: Impulsive & imprecise visual, average auditory; Class 4: Weak visual & auditory) was assessed using ASD and ADHD polygenic risk scores (PRS). Our sample contained 552 participants: 74 with ADHD, 85 with ASD, 60 with ASD + ADHD, 177 unaffected siblings of ADHD or ASD probands, and 156 controls. ADHD- and ASD-PRS, calculated from the latest ADHD and ASD GWAS meta-analyses, were analyzed across these emotion recognition factors and classes using linear mixed models. Unexpectedly, the analysis of emotion recognition factors showed higher ASD-PRS to be associated with faster visual emotion recognition. The categorical analysis of emotion recognition classes showed ASD-PRS to be reduced in Class 3 compared to the other classes (p value threshold [pT] = 1, p = .021). A dimensional analysis identified a high ADHD-PRS reduced the probability of being assigned to the Class 1 or Class 3 (pT = .05, p = .028 and p = .044, respectively). Though these nominally significant results did not pass FDR correction, they potentially indicate different indirect causative chains from genetics via emotion recognition to ADHD and ASD, which need to be verified in future research

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Annu Int Conf IEEE Eng Med Biol Soc. 2021 Nov;2021:4358-61.

INVESTIGATING ADHD SUBTYPES IN CHILDREN USING TEMPORAL DYNAMICS OF THE ELECTROENCEPHALOGRAM (EEG) MICROSTATES.

Luo N, Luo X, Yao D, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children, usually categorized as three predominant subtypes, persistent inattention (ADHD-I), hyperactivity-impulsivity (ADHD-HI) and a combination of both (ADHD-C). Identifying reliable features to distinguish different subtypes is significant for clinical individualized treatment. In this work, we conducted a two-stage electroencephalogram (EEG) microstate analysis on 54 healthy controls and 107 ADHD children, including 54 ADHD-Is and 53 ADHD-Cs, aiming to examine the dynamic temporal alterations in ADHDs compared to healthy controls (HCs), as well as different EEG signatures between ADHD subtypes. Results demonstrated that the dynamics of resting-state EEG microstates, particularly centering on salience (state C) and frontal-parietal network (state D), were significantly aberrant in ADHDs. Specifically, the occurrence and coverage of state C were decreased in ADHDs (p=0.002; p=0.0015), while the duration and contribution of state D were observably increased (p=0.0016; p=0.0001) compared to HCs. Moreover, the transition probability between state A and C was significantly decreased (p=9.85e-7; p=2.33e-7) in ADHDs, but otherwise increased between state B and D (p=1.02e-7; p=1.07e-6). By contrast, remarkable subtype differences were

found primarily on the visual network (state B) between ADHD-Is and ADHD-Cs. Specifically, ADHD-Cs have higher occurrence and coverage of state B than ADHD-Is (p=9.35e-5; p=1.51e-8), suggesting these patients more impulsively aimed to open their eyes when asked to keep eyes closed during the data collection. In summary, this work carefully leveraged EEG temporal dynamics to investigate the aberrant microstate features in ADHDs and provided a new window to look into the subtle differences between ADHD subtypes, which may help to assist precision diagnosis in future. Clinical Relevance- This work established the use of EEG microstate features to investigate ADHD dysfunction and its subtypes, providing a new window for better diagnosis of ADHD

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Arch Pediatr. 2021;28:668-76.

SLEEP QUALITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER.

Yildiz Miniksar D, Ozdemir M.

Sleep disturbances are associated with an increased risk of attention-deficit and hyperactivity disorder (ADHD), which can also lead to sleep problems. In this study we aimed to determine the variables that affect the relationship between ADHD and sleep quality. Moreover, we aimed to compare these variables in children and adolescents with ADHD and healthy controls. This cross-sectional study was conducted using a random sample of 122 ADHD patients and 100 healthy children in Turkey. A self-administered questionnaire was distributed to assess sleep quality using the Pittsburgh Sleep Quality Index (PSQI). The risk of impairment in sleep quality was associated with the presence of ADHD (OR: 13.3; 95% CI: 6.1ΓÇô29.1), the presence of somatic disease (OR: 4.9; 95% CI: 1.9ΓÇô12.2), and a family history of the psychiatric disorder (OR: 4.2; 95% CI: 1.3ΓÇô13.1). The PSQI total score was higher in children with parental separation compared to those without parental separation (p=0.006). As the economic level of the participants decreased, the PSQI total score increased significantly (p=0.006). It was determined that combined-type ADHD was associated with impairment in sleep quality more than the other subtypes (p<0.001 and p=0.031, respectively). Our findings show that children with ADHD have significantly more sleep problems than healthy controls and that sociodemographic variables and familial characteristics affect sleep quality in healthy children and children with ADHD

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Arch Dis Child Educ Pract Ed. 2021;106:322-25.

FIFTEEN-MINUTE CONSULTATION: TO PRESCRIBE OR NOT TO PRESCRIBE IN ADHD, THAT IS THE QUESTION.

Swanepoel A.

Attention-deficit hyperactivity disorder (ADHD) is fraught with controversy. Some clinicians believe it is a biological neurodevelopmental disorder which should be treated with medication. Others are adamant that ADHD is a social construct in which children, who have suffered developmental trauma, are medicalised. Evolutionary science may help us find a solution to this dichotomy by seeing ADHD as an example of an evolutionary mismatch in which children with ADHD are caught in a school environment that does not suit their natures. By considering how to improve the 'goodness of fit' between the child and their environment, clinicians can be more flexible in finding solutions that are ethically sound

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Autism. 2021.

SHORTER AVERAGE LOOK DURATIONS TO DYNAMIC SOCIAL STIMULI ARE ASSOCIATED WITH HIGHER LEVELS OF AUTISM SYMPTOMS IN YOUNG AUTISTIC CHILDREN.

Major S, Isaev D, Grapel J, et al.

Prior eye-tracking studies involving autistic individuals have focused on total looking time or proportion of looking time to key regions of interest. These studies have not examined another important feature, the ability to sustain attention to stimuli. In particular, the ability to sustain attention to a dynamic social stimulus might reflect more advanced self-regulatory skills that may enhance engagement with and comprehension of social information. In a sample of 155 autistic children (2-8 years of age), we examined children's average look duration while they viewed a complex, dynamic stimulus containing both social and nonsocial elements. After accounting for children's age and intelligence quotient, we found that shorter average look duration was

associated with increased autism spectrum disorder severity across multiple clinical measures. To calculate average look duration, we divided the length of total looking time in seconds by the total number of uninterrupted looks to the video media. Thus, the ability to sustain attention while viewing complex dynamic information could be important for comprehending dynamic social information. Lay Abstract: Many studies of autism look at the differences in how autistic research participants look at certain types of images. These studies often focus on where research participants are looking within the image, but that does not tell us everything about how much they are paying attention. It could be useful to know more about how well autistic research participants can focus on an image with people in it, because those who can look at images of people for longer duration without stopping may be able to easily learn other skills that help them to interact with people. We measured how long autistic research participants watched the video without breaking their attention. The video sometimes had a person speaking, and at other times had toys moving and making sounds. We measured the typical amount of time autistic research participants could look at the video before they looked away. We found that research participants with more severe autism tended to look at the video for shorter amounts of time. The ability to focus without stopping may be related to social skills in autistic people

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Behav Change. 2021.

COMPARING THE TRANSFER EFFECTS OF THREE NEUROCOGNITIVE TRAINING PROTOCOLS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SINGLE-CASE EXPERIMENTAL DESIGN.

Zhang DW, Johnstone SJ, Li H, et al.

The current study used behavioural and electroencephalograph measures to compare the transferability of three home-based interventions - cognitive training (CT), neurofeedback training (NFT), and CT combined with NFT - for reducing symptoms in children with attention-deficit/hyperactivity disorder (AD/HD). Following a multiple-baseline single-case experimental design, twelve children were randomised to a training condition. Each child completed a baseline phase, followed by an intervention phase. The intervention phase consisted of 20 sessions of at-home training. Tau-U analysis and standardised visual analysis were adopted to detect effects. Results showed that CT improved inhibitory function and NFT improved alpha EEG activity and working memory. The combined condition, which was a reduced 'dose' of CT and NFT, did not show any improvements. The three conditions did not alleviate AD/HD symptoms. While CT and NFT may have transfer effects on executive functions, considering the lack of improvement in symptoms, this study does not support CT and NFT on their own as a treatment for children with AD/HD

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BMC Pediatr. 2021;21.

LONG-TERM EFFECTIVENESS OF BEHAVIOURAL INTERVENTION IN PRESCHOOL CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SOUTHEAST CHINA A RANDOMIZED CONTROLLED TRIAL.

Huang XX, Ou P, Qian QF, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is the most common behavioral disorder. Behavioural intervention in preschool children with ADHD is considered effective. This study discussed the long-term effectiveness of behavioural intervention in the context of nondrug therapy.

Methods: The study was a prospective, randomised controlled trial in which 201 preschoolers diagnosed with ADHD who were not receiving any treatment were assigned to two groups from January 2018 to May 2019, 101 were assigned to the conventional group and 100 to the behavioural intervention group. The behavioural intervention group included parental training, behavioural therapy, attention training, relief therapy and game therapy, in addition to the conventional group offerings. Children were evaluated at a baseline, at the end of the 12-month intervention and six months after the intervention. The primary and secondary outcome variables included attention time, the impulse-hyperactivity and hyperactivity index from Conners parent symptom questionnaire (PSQ), full-scale attention quotient (FAQ) and full-scale response control quotient (FRCQ) from integrated visual and auditory comprehensive continuous performance tests. The attention time was observed and recorded by parents, and others were performe(PSQ)d by physicians in the clinic. All statistical analyses were conducted using SPSS V26.0 (IBM), including the descriptive statistics and mixed-effects models and so on.

Results: The participants mean age was (66.17-¦9.00) months in the behavioural group and (67.54-¦6.22) months in the conventional group. A total of 190 participants completed a follow-up six months after the intervention. The attention time, Conners parent symptom questionnaire (PSQ), full-scale attention quotient (FAQ) and full-scale response control quotient (FRCQ) increased significantly over time, and the behavioural group improvements were higher than those of conventional group. There was a significant main effect of time (pretest/posttest/follow-up) and group on all outcome measures (t=-12.549-4.069, p<0.05), and a significant interaction of time and group on attention time, impulsivity/hyperactivity, FAQ and FRCQ (t =-3.600-3.313, p<0.05).
Conclusion: Behavioural intervention can effectively improve behaviour management and relieve symptoms in children with ADHD. These effects lasted at least six months. This study provides a promising approach for improving clinical efficacy with preschool children with ADHD

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BMJ Case Rep. 2021 Dec;14.

AUTISM SPECTRUM DISORDER IN A CHILD WITH MEGALENCEPHALY-CAPILLARY MALFORMATION-POLYMICROGYRIA SYNDROME (MCAP).

St John LJ, Rao N.

Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is a rare disorder that arises as a result of a somatic mosaic mutation in the PIK3CA gene. It characteristically presents with postnatal or congenital megalencephaly, cutaneous capillary malformations, postaxial polydactyly and often segmental or focal body overgrowth. We report a 7-year-old boy with known MCAP who was diagnosed at around 10 months old with a mosaic change in the PIK3CA gene. He was found to have hall-mark clinical signs; macrocephaly and four-limb postaxial polydactyly. Since diagnosis, he has had multiple clinical features, most of which typically present in children with MCAP. He has now been diagnosed with autism spectrum disorder (ASD), demand avoidance and is under assessment for attention deficit hyperactivity disorder. Although some cases have been raised to the M-CM Network, to our knowledge this is the first case of ASD in MCAP to be reported in the literature

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Brain Dev. 2021.

BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PERFORM WIDER AND FEWER FINGER TAPPING THAN TYPICALLY DEVELOPING BOYS PEER COMPARISONS AND THE EFFECTS OF METHYLPHENIDATE FROM AN EXPLORATORY PERSPECTIVE.

Enokizono T, Ohto T, Tanaka M, et al.

Aim: This study aimed to investigate the differences in fine motor and coordination skills between boys with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) boys and the effect of methylphenidate (MPH) in boys with ADHD.
Methods: Fourteen boys aged 7-12 years who were diagnosed with ADHD and previously treated with MPH were instructed to tap their thumbs and index fingers together repetitively for 10 s after attaching magnetic sensors. The participants executed in-phase and anti-phase tapping. A two-way analysis of variance for comparing boys with ADHD and TD boys and the paired t-test to investigate the effect of MPH between sessions with and without MPH were performed.
Results: Boys with ADHD showed a significantly lower number of taps and a significantly higher average of local maximum distance than TD boys. Energy balance was significantly lower in ADHD boys than in TD boys. MPH caused a significant difference in the standard deviation (SD) of phase difference in anti-phase tapping.
Conclusion: Our studies indicated that finger-tapping movements in boys with ADHD tended to be significantly wider and fewer than those in TD boys, and MPH may improve the phase difference of bimanual fine motor coordination skills in boys with ADHD who are above 1.0 SD. The results should be interpreted with caution because we conducted statistical tests for many outcomes and groups without considering the multiplicity factor from an exploratory perspective

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Brain Sciences. 2021;11.

DIFFERENCES IN PERFORMANCE OF ASD AND ADHD SUBJECTS FACING COGNITIVE LOADS IN AN INNOVATIVE REASONING EXPERIMENT.

Papaioannou A, Kalantzi E, Papageorgiou CC, et al.

We aim to investigate whether EEG dynamics differ in adults with ASD (Autism Spectrum Disorders) and ADHD (attention-deficit/hyperactivity disorder) compared with healthy subjects during the performance of an innovative cognitive task, Aristotle's valid and invalid syllogisms, and how these differences correlate with brain regions and behavioral data for each subject. We recorded EEGs from 14 scalp electrodes (channels) in 21 adults with ADHD, 21 with ASD, and 21 healthy, normal subjects. The subjects were exposed in a set of innovative cognitive tasks (inducing varying cognitive loads), AristotleΓÇÖs two types of syllogism mentioned above. A set of 39 questions were given to participants related to validΓÇôinvalid syllogisms as well as a separate set of questionnaires, in order to collect a number of demographic and behavioral data, with the aim of detecting shared information with values of a feature extracted from EEG, the multiscale entropy (MSE), in the 14 channels (brain regions). MSE, a nonlinear information-theoretic measure of complexity, was computed to extract a feature that quantifies the complexity of the EEG. Behavior-Partial Least Squares Correlation, PLSC, is the method to detect the correlation between two sets of data, brain, and behavioral measures. -PLSC, a variant of PLSC, was applied to build a functional connectivity of the brain regions involved in the reasoning tasks. Graph-theoretic measures were used to quantify the complexity of the functional networks. Based on the results of the analysis described in this work, a mixed 14 2 3 ANOVA showed significant main effects of group factor and brain region* syllogism factor, as well as a significant brain region* group interaction. There are significant differences between the means of MSE (complexity) values at the 14 channels of the members of the pathological groups of participants, i.e., between ASD and ADHD, while the difference in means of MSE between both ASD and ADHD and that of the control group is not significant. In conclusion, the valid-invalid type of syllogism generates significantly different complexity values, MSE, between ASD and ADHD. The complexity of activated brain regions of ASD participants increased significantly when switching from a valid to an invalid syllogism, indicating the need for more resources to face the task escalating difficulty in ASD subjects. This increase is not so evident in both ADHD and control. Statistically significant differences were found also in the behavioral response of ASD and ADHD, compared with those of control subjects, based on the principal brain and behavior saliences extracted by PLSC. Specifically, two behavioral measures, the emotional state and the degree of confidence of participants in answering questions in Aristotle's valid-invalid syllogisms, and one demographic variable, age, statistically and significantly discriminate the three groups ASD. The seed-PLC generated functional connectivity networks for ASD, ADHD, and control, were projected on the regions of the Default Mode Network (DMN), the reference connectivity, of which the structural changes were found significant in distinguishing the three groups. The contribution of this work lies in the examination of the relationship between brain activity and behavioral responses of healthy and pathological participants in the case of cognitive reasoning of the type of Aristotle's valid and invalid syllogisms, using PLSC, a machine learning approach combined with MSE, a nonlinear method of extracting a feature based on EEGs that captures a broad spectrum of EEGs linear and nonlinear characteristics. The results seem promising in adopting this type of reasoning, in the future, after further enhancements and experimental tests, as a supplementary instrument towards examining the differences in brain activity and behavioral responses of ASD and ADHD patients. The application of the combination of these two methods, after further elaboration and testing as new and complementary to the existing ones, may be considered as a tool of analysis in helping detecting more effectively such types of disorders

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Brain Sciences. 2021;11.

ATTACHMENT REPRESENTATIONS IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Dekkers TJ, Hornstra R, van den Hoofdakker BJ, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) in children is associated with several adverse family characteristics, such as higher parenting stress, more conflicted parentΓÇôchild relation-ships, lower parental competence, and higher levels of parental psychopathology. Hence, children with ADHD more often grow up under suboptimal circumstances, which may impact the development of their attachment

representations. Here, we investigated whether children with ADHD have more insecure and disorganized attachment representations than their typically developing peers, and which factors could explain this association. We included 104 children between 4 and 11 years old, 74 with ADHD (without Conduct Disorder) and 30 typically developing control children. Children completed a state-of-the-art story stem task to assess their attachment representation, and we measured parentsΓÇÖ expressed emotion (as an index of parentΓÇôchild relationship quality), parentsΓÇÖ perceived sense of competence, parental education levels, and parent-rated ODD symptoms of the child. We found that, after controlling for multiple comparisons, children with ADHD had less secure and more ambivalent and disorganized attachment representations relative to their typically developing peers. These group differences were independent of comorbid ODD and parental education levels. There were no group differences on avoidant attachment representations. Explorative analyses within the ADHD group showed that attachment representations were not related to parent child relationship quality, perceived parenting competence, parental education levels, and comorbid ODD symptoms. We conclude that children with ADHD disproportionately often have attachment problems. Although this conclusion is important, treatment implications of this co-occurrence are yet unclear as research on ADHD and attachment is still in its infancy

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Can J Sch Psychol. 2021 Dec;36:318-34.

ASSESSMENT OF SOCIAL SELF-PERCEPTIONS OF ACCEPTANCE AND ENMITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

García-Castellar R, Sánchez-Chiva D, Jara-Jiménez P, et al.

This study analyzes the self-perceptions of social competence in children with attention-deficit/hyperactivity disorder (ADHD). It compares two groups of participants, children with ADHD (N = 20) and children without ADHD (N = 20) ages between 8 and 12 years old. Sociometric questionnaires were completed by two groups of participants and 707 peers, as well as a questionnaire that evaluates children's behavior from parents' and teachers' perspectives. Results indicate that children with ADHD correctly perceive enmity, but incorrectly perceive friendship. Children with ADHD have low rates of positive reciprocity and qualities that indicate friendship differs considerably from the children without ADHD. The children with ADHD have a different profile of social self-perception than children without ADHD, especially regarding recognizing friendship. The results contribute to the understanding of perceptions of elements of peer relationship and friendships with strong ecological validity. This small scale study provides a proof of concept for improving ecological validity in the methods of evaluating social skills and social emotion learning programming for children with ADHD

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Child Dev. 2021 Nov;92:e1186-e1197.

ATYPICAL DEVELOPMENTAL TRAJECTORIES OF EARLY PERCEPTION AMONG SCHOOL-AGE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER DURING A VISUAL SEARCH TASK.

Luo X, Guo J, Li D, et al.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by cognitive deficits associated with attention. Prior studies have revealed the potential impact of ADHD on basic perception and cognitive ability in patients with ADHD. In this study, bilateral posterior P1 and N1 were measured in 122 Chinese children aged 7–12 years (64 with ADHD) to investigate the developmental characteristics of early perception during visual processing in school-age children with ADHD. For children with ADHD, a larger P1 activity with an atypical developmental pattern was evoked and observed for the visual search performance. These findings offer new insights into the mechanisms of cognitive developmental deficits and intervention techniques in children with ADHD

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CNS Drugs. 2022;36:71-81.

PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF SHP465 MIXED AMPHETAMINE SALTS AFTER ADMINISTRATION OF MULTIPLE DAILY DOSES IN CHILDREN AGED 4ΓÇô5 YEARS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ilic K, Kugler AR, Yan B, et al.

Background: Given the limited treatment options for younger children with attention-deficit/hyperactivity disorder (ADHD), a clinical study for SHP465 treatment was warranted.

Objectives: We aimed to evaluate the pharmacokinetics, safety, and tolerability of SHP465 mixed amphetamine salts (MAS) 6.25 mg after multiple once-daily doses in children aged 4-5 years with ADHD.

Methods: In this open-label multicenter study, SHP465 MAS 6.25 mg once daily was administered for 28 days to children aged 4-5 years with ADHD; baseline ADHD Rating Scale-5 total score 28 (boys) or 24 (girls) and Clinical Global Impression-Severity scale score 4. Blood samples were collected in the pharmacokinetic-rich group predose on day 1 week 1 and day 7 week 4 (predose, postdose at 2, 5, 8, 12, 16, 24, and 48 hours); and in the pharmacokinetic-sparse group predose on day 1 weeks 1, 2, and 3 and 24 hours postdose on day 7 week 4. Key pharmacokinetic parameters included maximum plasma drug concentration (Cmax), plasma trough drug concentration, time to Cmax during a dosing interval (tmax), area under the concentration-time curve from time 0 to time of last collected sample, area under the concentration-time curve over the dosing interval (24 h) at steady state (AUCtau,ss), first-order rate constant associated with the terminal phase of elimination, terminal half-life (t1/2), total clearance of drug from plasma after oral administration, and apparent volume of distribution at steady state. Safety endpoints included treatment-emergent adverse events and vital signs.

Results: Mean -¦ standard deviation age and body mass index of 24 participants (66.7% male) were 4.8 -¦ 0.41 years and 17.2 -¦ 3.18 kg/m2, respectively. The most common ADHD was the combined presentation (91.7%); ratings were 50% markedly ill and 45.8% moderately ill on the Clinical Global Impression-Severity scale. Plasma d-amphetamine and l-amphetamine steady state was attained by predose on treatment day 8, consistent with the half-life. Peak steady-state plasma concentration (median tmax) for both d-amphetamine and l-amphetamine occurred at 7.92 h postdose on day 7 week 4 and thereafter declined monoexponentially, with a geometric mean t1/2 of 10.4 and 12.3 h for d-amphetamine and l-amphetamine, respectively. For both d-amphetamine and l-amphetamine, Cmax and AUCtau, ss were comparable between children aged 4 years (n = 3) and children aged 5 years (n = 8) regardless of sex. In total, 14 treatment-emergent adverse events were reported by 45.8% (11/24) of participants. Five treatment-emergent adverse events, reported for four (16.7%) participants, were considered treatment related; affect lability occurred in two (8.3%) participants, and insomnia, accidental overdose, and increased blood pressure each occurred in one (4.2%) participant.

Conclusions: In children aged 4-5 years with ADHD, following multiple once-daily administrations of SHP465 MAS 6.25 mg, the pharmacokinetic profile of plasma d-amphetamine and l-amphetamine was generally consistent among participants. Between-individual variability of plasma d-amphetamine and l-amphetamine steady-state exposure was low to moderate. SHP465 MAS was generally well tolerated in this study.

Trial Registration: ClinicalTrials.gov, NCT03327402 (31 October, 2017)

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CNS Spectr. 2021.

DISRUPTIVE MOOD DYSREGULATION DISORDER: DOES VARIANCE IN TREATMENT RESPONSES ALSO ADD TO THE CONUNDRUM? THE WIDENING GAP IN THE EVIDENCE IS A SIGNAL NEEDING ATTENTION.

Gupta M, Gupta N.

The new diagnosis of disruptive mood dysregulation disorder (DMDD) was introduced in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), to address the overdiagnosis of bipolar disorder in children and adolescents. However, there are ongoing debates about its nosology given chronic persistent irritability in children and adolescents has contextual valence. Those meeting the criteria for DMDD may in fact have an oppositional defiant disorder, attention deficit hyperactivity disorder, or other behavioral disorders. Similarly, in the last few years, there are many different types of treatment studies that have also

yielded mixed results. These counterintuitive findings need a meticulous review for a wider debate given its clinical utility for patients, families, and practicing clinicians

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Dev Cognitive Neurosci. 2021;50.

BRAIN STRUCTURE ASSOCIATIONS WITH PHONEMIC AND SEMANTIC FLUENCY IN TYPICALLY-DEVELOPING CHILDREN.

Gonzalez MR, Baar WFC, Hagler DJ, et al.

Verbal fluency is the ability to retrieve lexical knowledge quickly and efficiently and develops during childhood and adolescence. Few studies have investigated associations between verbal fluency performance and brain structural variation in children. Here we examined associations of verbal fluency performance with structural measures of frontal and temporal language-related brain regions and their connections in 73 typically-developing children aged 7-13 years. Tract-based spatial statistics was used to extract fractional anisotropy (FA) from the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF), and the white matter underlying frontal and temporal language-related regions. FreeSurfer was used to extract cortical thickness and surface area. Better semantic and phonemic fluency performance was associated with higher right SLF/AF FA, and phonemic fluency was also modestly associated with lower left SLF/AF FA. Explorative voxelwise analyses for semantic fluency suggested associations with FA in other fiber tracts, including corpus callosum and right inferior fronto-occipital fasciculus. Overall, our results suggest that verbal fluency performance in children may rely on right hemisphere structures, possibly involving both language and executive function networks, and less on solely left hemisphere structures as often is observed in adults. Longitudinal studies are needed to clarify whether these associations are mediated by maturational processes, stable characteristics and/or experience

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Early Child Dev Care. 2021 Nov;191:2037-44.

COMMUNICATION SKILLS AMONG PERSIAN CHILDREN WITH AUTISM SPECTRUM DISORDERS, ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND LEARNING DISABILITY.

Dadgar H, Bakhtiyari J, Khatoonabadi AR.

This study investigated the communication skills of children with autism spectrum disorders (H. M. Geurts & M. Embrechts), Attention Deficit/Hyperactivity Disorder (Hilde M Geurts & Mariëtte Embrechts), and learning disability (H. M. Geurts & M. Embrechts) using the Children Communication Checklist to identify any commonalities in communication profile among these conditions. Participants were 60 children with age ranges of 6.0–9.11 years (Mean = 8.2, SD = 1.21) that assigned equally into three groups: ASD, ADHD, and LD. All children were diagnosed by psychiatric according to DSM-V criteria. The differences among groups were significant on the Syntax, Coherence, Context, Rapport, Social and Interests. There were no significant differences between ADHD and LD groups on general communication measures and pragmatic composite. These findings revealed a very different picture and suggested more differences than similarities among children with ADHD, ASD, and LD

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Emot Behav Difficulties. 2021;26:341-58.

ROLE OF EDUCATION SETTINGS IN TRANSITION FROM CHILD TO ADULT HEALTH SERVICES FOR YOUNG PEOPLE WITH ADHD.

Benham-Clarke S, Ford T, Mitchell SB, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition. As such most schools, Further Education colleges, vocational training and Higher Education settings will need to support affected children and young people. When young people who require ongoing treatment for ADHD are around 18-áyears of age, they must transition from child to adult mental health services. However, only a small proportion successfully transition. As significant educational transitions are often happening at the same time, there is a need to consider how education and health service transitions may impact on one another. This paper presents findings from a large UK qualitative study involving 144 semi-structured interviews with young people who had ADHD, parents and health professionals. Two themes were identified which support the notion that education transition can impact health transition. Firstly, transition to adult

health services typically requires continued prescription of ADHD medication, yet many young people stop taking their medication due to a belief that it is only needed for education-based learning. Secondly, if a young person is continuing education post-18, a lack of joined-up planning between education and health (outside of special schools) or consistent support in Higher/Further Education can leave young people with ADHD in limbo between health services and struggling within education. Given these findings, we recommend regarding multi-agency service statutory health care transition, educational staff training and ongoing oversight of child to adult health service and adult to adult health service transition effectiveness

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Emot Behav Difficulties. 2021.

FRIENDSHIP QUALITY, EMOTION UNDERSTANDING, AND EMOTION REGULATION OF CHILDREN WITH AND WITHOUT ATTENTION DEFICIT/HYPERACTIVITY DISORDER OR SPECIFIC LEARNING DISORDER.

Kouvava S, Antonopoulou K, Kokkinos CM, et al.

Understanding and regulating emotions influence children's friendships. Children with Attention Deficit/Hyperactivity Disorder (ADHD) and Specific Learning Disorder (SLD) have difficulties in understanding emotions and in controlling themselves. he present study examines how children's friendships and their quality may be affected by emotion understanding and regulation skills. Participants were 64 children with ADHD, 64 children with SLD, and 64 typically developing (TD) children (Mage=9.77 years, SD=1.22) who answered questionnaires about their friendships, and their emotion understanding and regulation. Results showed that ADHD children had less friends, lower friendship qualities, worse understanding of emotions and control of their impulsivity, and used less cognitive reappraisals to regulate emotions, followed by SLD children and finally by TD children. Children with SLD reported using more expressive suppressions for regulating emotions. For all children, emotion understanding and regulation predicted higher friendship quality. The results support the significance of understanding and regulating emotions upon the quality of children's best friendships

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Environ Int. 2022;159.

THE ASSOCIATION BETWEEN PRENATAL PERFLUOROALKYL SUBSTANCE EXPOSURE AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN 8-YEAR-OLD CHILDREN AND THE MEDIATING ROLE OF THYROID HORMONES IN THE HOKKAIDO STUDY.

Itoh S, Yamazaki K, Suyama S, et al.

Background: Disruption of thyroid hormone (TH) levels during pregnancy contributes to attention deficit hyperactivity disorder (ADHD). Exposure to perfluoroalkyl substances (PFAS) during gestation may affect levels of maternal and neonatal TH; however, little is known about the effect of PFAS on ADHD mediated by TH. Objectives: We investigated the impact of maternal PFAS exposure on children's ADHD symptoms with the mediating effect of TH.

Methods: In a prospective birth cohort (the Hokkaido study), we included 770 motherΓÇôchild pairs recruited between 2002 and 2005 for whom both prenatal maternal and cord blood samples were available. Eleven PFAS were measured in maternal serum obtained at 28-32 weeks of gestation using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry. TH and thyroid antibody, including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in maternal blood during early pregnancy (median 11 gestational weeks) and in cord blood at birth. ADHD symptoms in the children at 8 years of age were rated by their parents using the ADHD-Rating Scale (ADHD-RS). The cut-off value was set at the 80th percentile for each sex.

Results: Significant inverse associations were found between some PFAS in maternal serum and ADHD symptoms among first-born children. Assuming causality, we found only one significant association: maternal FT4 mediated 17.6% of the estimated effect of perfluoroundecanoic acid exposure on hyperactivity-impulsivity among first-born children.

Discussion: Higher PFAS levels in maternal serum during pregnancy were associated with lower risks of ADHD symptoms at 8 years of age. The association was stronger among first-born children in relation to hyperactivity-impulsivity than with regard to inattention. There was little mediating role of TH during

pregnancy in the association between maternal exposure to PFAS and reduced ADHD symptoms at 8 years of age

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Eth Human Psychol Psychiatry. 2021;23:100-26.

EVIDENCE THAT THE DIAGNOSIS OF ADHD DOES NOT REFLECT A CHRONIC BIO-MEDICAL DISEASE.

Ophir Y.

Is attention deficit hyperactivity disorder (ADHD) the diabetes of psychiatry? According to the dominant bio-medical model, ADHD is a chronic neuro-genetic condition with numerous negative outcomes. Without clear biological markers, however, this model receives support from the notions that the diagnosis (a) is stable overtime and across populations and (b) requires a constant treatment with chemical substances (e.g., Ritalin). Through three consecutive studies, this research investigates the validity of these two notions in Israel. Studies 1 (N = 502) and 2 (N = 853) addressed young adults while Study 3 (N = 195) focused on mothers to children with ADHD during the COVID lockdown. The findings indicated that the ADHD diagnosis is unreliable. Its prevalence exceeded 20%, a substantially higher figure than the consensual 5% estimate, and was not consistent between different communities (i.e., the less conservative the person is, the more likely that she/he will be diagnosed). The diagnosis also did not reflect a chronic and harmful condition that requires constant pharmacological management. Indeed, rates of prescribed medications were extremely high, thus implying the dominancy of the bio-medical model. However, in practice, medications were used very selectively, mainly during school/college times (i.e., not when schools were closed), to improve school-related performances. These findings, alongside a critical review of the current status of the physiological literature on ADHD (offered in the general discussion), undermine the bio-medical perception of ADHD. The clinical label of ADHD does not seem to reflect an objective chronic brain disease, but a modern social phenomenon in which children's normative traits are being medicalized, mainly in response to external school-related demands

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Eur J Integr Med. 2021;48.

WHAT ARE FAMILIES USING TO HELP MANAGE ADHD IN THE UK?

Fibert P, Relton C.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is associated with long-term negative outcomes which mainstream treatments are not improving. Families try a variety of non-mainstream treatments. This is the first survey conducted in the UK describing what they use. The aim was to conduct a preliminary survey of treatments being used to help manage ADHD in the UK.

Methods: A survey was piloted within the Sheffield Treatments for ADHD Research (STAR) project. Participants recruited to an observational cohort via a broad variety of non-NHS, non-treatment seeking settings throughout the UK were asked questions about medication, behaviour-change programmes, service use, and what else they use. This question was open ended with a view to using answers to inform a larger survey.

Results: 175 families of children aged 5-18 with carer reported ADHD, ADHD symptom scores 55+, and any additional diagnoses were recruited. 123 took ADHD medication, 49 took sleep medications. 113 families participated in parenting classes. 83 consulted psychologists. 32 participated in conventional therapies such as psychotherapy, counselling, or CBT. 13 used aids such as reward charts or fiddle toys. 8 participated in physical activities. 54 used non-mainstream therapies, such as nutritional interventions (n=21), homeopathy (n=32), massage (n=5), cranial osteopathy (n=4), aromatherapy (n=2), reiki (n=2), meditation (n=2) and hypnotherapy (n=2).

Conclusions: Despite using mainstream treatments, 31% of families surveyed also use non-mainstream treatments to help with ADHD management. There is increasing interest in natural treatments amongst doctors, particularly for children. This survey provides useful information for them and other stakeholders about what is being used. Having demonstrated the feasibility of recruiting a representative sample and collecting information, and a preliminary understanding of the types of interventions being used, collection of similar information from a larger sample, and effectiveness testing of the treatments they use is the next step.

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Eur J Integr Med. 2021;48.

MULTI-NUTRIENT SUPPLEMENTS AS INTEGRATIVE MEDICINE FOR CHILDREN WITH ADHD.

Leung B, Arnold LE, Hatsu IE, et al.

Introduction: Integrating multi-nutrients into treatment has shown improvement in children with ADHD and comorbid irritability, aggression and anger. The aim of this presentation is to discuss 1) the emerging trends that broad-spectrum formulas (vitamins + minerals + antioxidants) demonstrated more robust effects compared to formulas with single or narrow number of ingredients in the treatment of psychiatric disorders; 2) results of a randomized controlled trial of multi-nutrients intervention in children with ADHD (the MADDY Study).

Methods: A multi-site double blinded placebo controlled clinical trial of a 36-ingredient multi-nutrient supplement to treat ADHD symptoms in children age six to twelve. Children were randomized to the active or placebo group for eight weeks of treatment. Behavioural symptoms and emotional dysregulation were measured with the Strength and Difficulties Questionnaire (SDQ), Parent Targeted Problems (PTP), and the Pediatric Adverse Events Rating Scale (PAERS).

Results: Of 135 enrolled in the trial, complete data was available for 126 children. The SDQ showed no difference by group for total difficulties (p=0.63); both improved from baseline to end of RCT (p<0.01), but a trend for greater improvement for all subscales of the SDQ in the micronutrient group compared to the placebo group. The first-nominated PTPs was significantly (p=.02) better for micronutrients (3.73) than for placebo (4.23). The average of all PTPs (1 & 2) was also significantly (p=.05) better for micronutrients (3.85) than for placebo (4.25). Grouping of symptoms from the PAERS showed anxiety (+¦=-0.315, p=0.029) and ADHD (+¦=-0.361, p=0.044) was better for micronutrients compared to placebo. The physiological response indicate the micronutrient group grew six millimeters more than the placebo group (p=0.002).

Conclusion: Results of the study supports emerging evidence of integrating multi-nutrients intervention to treat ADHD symptoms. Supplementing with multi-nutrients may be a meaningful and promising approach to treating behavioural disorders in children. Keywords: Children, ADHD, Emotional dysregulation, Multi-nutrients, Clinicalxs trial

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

UNDERSTANDING ADHD IN BLACK ADOLESCENTS IN URBAN SCHOOLS: A QUALITATIVE EXAMINATION OF FACTORS THAT INFLUENCE ADHD PRESENTATION, COPING STRATEGIES, AND ACCESS TO CARE.

Shippen N, Horn SR, Triece P, et al.

The high school years are a challenging developmental period for adolescents with attention-deficit/hyperactivity disorder (ADHD), their families, and those who work with them in the school system. Moreover, racially minoritized families and schools in low-resource, urban settings often experience additional adverse experiences that can make access to evidence-based mental health care particularly difficult. This qualitative investigation into the experiences of Black high school students with ADHD, their caregivers, teachers, and school mental health providers (SMHPs) aimed to understand this community s experiences with ADHD across development and to explore the barriers/facilitators to adequate services. Through focus group interviews with stakeholders (i.e., 6 adolescents with a diagnosis of ADHD, 5 caregivers of adolescents with ADHD, 6 teachers, 5 school mental health providers), themes emerged related to (1) developmental changes observed in ADHD presentation in high school students and (2) contextual factors (including barriers/facilitators to optimal school and home functioning). These themes led to the development of an ecological model that show various contextual factors influencing the experiences of Black adolescents with ADHD in under-resourced urban public high schools (e.g., adolescents coping strategies, caregiver involvement, teacher burden or lack of ADHD-knowledge, socio-economic status, access to care). This qualitative study represents the first step of a treatment development project assessing the implementation of a depression prevention intervention for Black adolescents with ADHD in urban public-school settings. Clinical implications (e.g., coordination of care between home and schools, increasing attention to social determinants of health, ensuring culturally competent discussion of ADHD and its treatment) are discussed

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Frontiers in Neuroscience. 2021;15.

AUTISTIC TRAITS AND EMPATHY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, AUTISM SPECTRUM DISORDER AND CO-OCCURRING ATTENTION DEFICIT HYPERACTIVITY DISORDER/AUTISM SPECTRUM DISORDER.

Aiello S, Vagni D, Cerasa A, et al.

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) are two of the most represented neurodevelopmental conditions in childhood. The diagnostic shift introduced by the DSM-5, allowing a combined diagnosis of ADHD and ASD, poses different clinical challenges related to diagnostic overshadowing, accuracy of clinical judgment and potential delay in an ASD diagnosis in children presenting with ADHD. Here we tried to disentangle the clinical phenotype and specificity of the two co-occurring conditions in relation to autism traits and empathy, by comparing children with ASD with and without comorbid ADHD with children presenting ADHD only and children with typical development. The child versions of the Autism Quotient (C-AQ) and Empathy Quotient (C-EQ) were administered to a total sample of 198 male children between 6 and 14 years old with age appropriate language skills and normal intelligence. Univariate analysis demonstrated no significant differences in the C-AQ total and subscale scores as well as the C-EQ between children with ASD and children with ASD + ADHD, while children with ADHD alone presented an intermediate phenotype between ASD and TD. Furthermore, a receiver operating characteristic (ROC) analysis was applied to discriminate among the different phenotypes. We found that the C-AQ and C-EQ were accurate at distinguishing with satisfactory reliability between: (a) ASD vs. non- ASD (N-ASD) groups comprising both ADHD and TD children (Area Under the Curve AUC 88% for C-AQ and 81% for C-EQ); (b) ASD and TD (AUC 92% for C-AQ and 95% for C-EQ); (c) ASD and ADHD (AUC 80% for C-AQ and 68% for C-EQ). Our data confirm the reliability of the C-AQ and C-EQ as behavioral markers to differentiate ASD (regardless of comorbid ADHD) from an ADHD condition and TD. Interestingly, in our sample an ADHD condition does not increase the severity of the clinical phenotype in terms of autism traits distribution and empathy, suggesting that the psychological measures detected by the two quantitative instruments are independent of ADHD traits. This evidence will contribute to the translational efforts in developing better tailored treatments and preventive strategies

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Front Psychiatry. 2021;12.

DOES EXPOSURE TO GENERAL ANESTHESIA INCREASE RISK OF ADHD FOR CHILDREN BEFORE AGE OF THREE?

Song J, Li H, Wang Y, et al.

Objective: The objective of the study was to evaluate the relationship between frequency of exposure to general anesthesia before the age of 3 and subsequent risk of diagnosis for attention-deficit hyperactivity disorder (ADHD).

Method: We searched PubMed, Embase, Web of Science, and Cochrane Library database for eligible inclusion in the meta-analysis. The indicated outcomes were extracted from the included studies, and the combined effects were calculated using the RevMan software 5.3.

Results: Compared with no exposure to general anesthesia, single exposure to general anesthesia did not increase the risk of ADHD for children before the age of 3 [hazard ratio (HR): 1.14, 95%; confidence intervals (CI): 0.97-1.35; p = 0.11; I2 = 0%], while multiple exposures to general anesthesia did increase the risk of ADHD (HR: 1.83; 95% CIs: 1.00-3.32; p = 0.05; I2 = 81%).

Conclusion: Multiple, but not single, exposures to general anesthesia in children before age of 3 increased the risk of ADHD

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Front Psychiatry. 2021;12.

UNRAVELING THE OPTIMUM LATENT STRUCTURE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EVIDENCE SUPPORTING ICD AND HITOP FRAMEWORKS.

Gomez R, Liu L, Krueger R, et al.

Attention Deficit/hyperactivity disorder (ADHD) is conceptualized differently in the Diagnostic and Statistical Manual (DSM-5), the International Classification of Diseases-10 (ICD-10), and the Hierarchical Taxonomy of Psychopathology (HiTOP) frameworks. This study applied independent cluster confirmatory factor analysis

(ICM-CFA), exploratory structure equation model with target rotation (ESEM), and the S-1 bi-factor CFA approaches to evaluate seven ADHD models yielded by different combinations of these taxonomic frameworks. Parents and teachers of a community sample of children (between 6 and 12 years of age) completed the Disruptive Behavior Rating Scale (for ADHD symptoms) and the Strengths and Difficulties Questionnaire (for validation). Our findings for both parent and teacher ratings provided the most support for the S-1 bi-factor CFA model comprised of (i) a g-factor based on ICD-10 impulsivity symptoms as the reference indicators and (ii) inattention and hyperactivity as specific factors. However, the hyperactivity-specific factor lacked clarity and reliability. Thus, our findings indicate that ADHD is best viewed as a disorder primarily reflecting impulsivity, though with a separable inattention (but no hyperactivity) component, i.e., ADID (attention deficit/impulsivity disorder). This model aligns with the HiTOP proposals

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IBRO Neuroscience Reports. 2022;12:55-64.

THE EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) COMBINED WITH COGNITIVE TRAINING ON EEG SPECTRAL POWER IN ADOLESCENT BOYS WITH ADHD: A DOUBLE-BLIND, RANDOMIZED, SHAM-CONTROLLED TRIAL.

Westwood SJ, Bozhilova N, Criaud M, et al.

Transcranial direct current stimulation (tDCS) is a possible alternative to psychostimulants in Attention-Deficit/Hyperactivity Disorder (ADHD), but its mechanisms of action in children and adolescents with ADHD are poorly understood. We conducted the first 15-session, sham-controlled study of anodal tDCS over right inferior frontal cortex (rIFC) combined with cognitive training (CT) in 50 children/adolescents with ADHD. We investigated the mechanisms of action on resting and Go/No-Go Task-based QEEG measures in a subgroup of 23 participants with ADHD (n, sham = 10; anodal tDCS = 13). We failed to find a significant sham versus anodal tDCS group differences in QEEG spectral power during rest and Go/No-Go Task performance, a correlation between QEEG and Go/No-Go Task performance, and changes in clinical and cognitive measures. These findings extend the non-significant clinical and cognitive effects in our sample of 50 children/adolescents with ADHD. Given that the subgroup of 23 participants would have been underpowered, the interpretation of our findings is limited and should be used as a foundation for future investigations. Larger, adequately powered randomized controlled trials should explore different protocols titrated to the individual and using comprehensive measures to assess cognitive, clinical, and neural effects of tDCS and its underlying mechanisms of action in ADHD

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Int J Environ Res Public Health. 2021 Dec;18.

PARENTS' EXPERIENCES OF WEIGHTED BLANKETS' IMPACT ON CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND SLEEP PROBLEMS-A QUALITATIVE STUDY.

Larsson I, Aili K, Nygren JM, et al.

Sleep disturbances are common among children with attention-deficit/hyperactivity disorder (ADHD). While pharmacological treatment has increased dramatically, parents often prefer non-pharmacological interventions. Research on experiences of weighted blankets and their effect in sleep improvement is scarce. The aim of this study was to explore parents' experiences of weighted blankets for children with ADHD and sleep problems, and the impact on their children's sleep. The explorative design was based on qualitative content analysis. Interviews were conducted with a purposeful sample of 24 parents of children with ADHD and sleep problems, after completing a sleep intervention with weighted blankets for 16 weeks. Parents reported that children sleeping with weighted blankets: (1) achieved satisfactory sleep, including improved sleep onset latency, sleep continuity, and sleep routines; (2) achieved overall well-being, including improved relaxation and reduced anxiety; and (3) mastered everyday life, including improved balance in life, family function, and participation in school and leisure activities. This study brings forward novel aspects of the effects of improved sleep among children with ADHD. The findings contribute to the understanding of potential positive effects of an intervention with weighted blankets critical for clinical practice to improve sleep, well-being, and everyday life of children with ADHD and their families

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Int J Environ Res Public Health. 2021;18.

MORPHING TASK: THE EMOTION RECOGNITION PROCESS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Greco C, Romani M, Berardi A, et al.

Recognizing a person's identity is a fundamental social ability; facial expressions, in particular, are extremely important in social cognition. Individuals affected by autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) display impairment in the recognition of emotions and, consequently, in recognizing expressions related to emotions, and even their identity. The aim of our study was to compare the performance of participants with ADHD, ASD, and typical development (TD) with regard to both accuracy and speed in the morphing task and to determine whether the use of pictures of digitized cartoon faces could significantly facilitate the process of emotion recognition in ASD patients (particularly for disgust). This study investigated the emotion recognition process through the use of dynamic pictures (human faces vs. cartoon faces) created with the morphing technique in three pediatric populations (7-12 years old): ADHD patients, ASD patients, and an age-matched control sample (TD). The Chi-square test was used to compare response latency and accuracy between the three groups in order to determine if there were statistically significant differences ($p < 0.05$) in the recognition of basic emotions. The results demonstrated a faster response time in neurotypical children compared to ASD and ADHD children, with ADHD participants performing better than ASD participants on the same task. The overall accuracy parameter between the ADHD and ASD groups did not significantly differ

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Int J Environ Res Public Health. 2021;18.

THE EFFECTS OF PHYSICAL EXERCISE ON MENTAL HEALTH: FROM COGNITIVE IMPROVEMENTS TO RISK OF ADDICTION.

Caponnetto P, Casu M, Amato M, et al.

Background: we aimed to investigate the effects of physical activity on cognitive functions and deficits of healthy population and other needy groups. Secondly, we investigated the relation between healthy habits and psychopathological risks. Finally, we investigated the impact of COVID-19 pandemic on exercise addiction and possible associated disorders.

Methods: From April 2021 to October 2021, we conducted a review aimed at identifying the effects of physical exercise on mental health, from cognitive improvements to risk of addiction; we searched for relevant studies on PubMed, Web of Science, EMBASE, PsycINFO and CINHAL.

Results: For the first purpose, results indicated multiple effects such as better precision and response speed in information processing tasks on healthy populations; improvement of executive functions, cognitive flexibility and school performance in children; improvement of attention and executive functions and less hyperactivity and impulsiveness on children with attention deficit hyperactivity disorder (ADHD); improvement of executive and global functions on adults; improvement of overall cognitive functioning on patients with schizophrenic spectrum disorder or bipolar disorder. Data also demonstrated that exercise addiction seems to be related to low levels of education, low self-esteem, eating disorders and body dysmorphisms. Eventually, it was found that people with lower traits and intolerance of uncertainty show a strong association between COVID-19 anxiety and compulsive exercise and eating disorder.

Conclusions: these findings underline on one side the beneficial effects of physical activity on cognitive function in healthy individuals in a preventive and curative key, while on the other side the importance of an adequate evaluation of psychological distress and personality characteristics associated with exercise addiction

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Int J Environ Res Public Health. 2022;19.

POOR SCHOOL-RELATED WELL-BEING AMONG ADOLESCENTS WITH DISABILITIES OR ADHD.

Tiikkaja S, Tindberg Y.

Poor school-related well-being may influence adolescents school performance and lifestyle. Adolescents having disabilities or ADHD are in a vulnerable situation for having poor school-related well-being, compared to adolescents not having disabilities. We used cross-sectional data from a school-based survey among 15-18 year-olds (N = 4071) in Sàrmland, Sweden, to analyse the association between poor school-related well-

being and disabilities or ADHD. The analyses were carried out by logistic regression models, adjusting for background factors, school-related factors, and health-compromising behaviours. Adolescents having disabilities (n=827) or ADHD (n=146) reported that their disability had a negative influence on school. Compared to peers without disability, those having disabilities had an increased chance (OR = 1.40 95% CI: 1.17-1.68) of poor school-related well-being. The corresponding OR was doubled for adolescents reporting ADHD (2.23 95% CI: 1.56-3.18). For the ADHD group, the adjOR for poor school-related well-being remained significant (1.67 95% CI: 1.13-2.50) after adjustments for school-related factors and health-compromising behaviours, but not for the disability group. In conclusion, adolescents having ADHD are a particularly vulnerable group at school, having a greater risk of poor school-related well-being. Schools should actively work to achieve school satisfaction for adolescents having disabilities, to ensure that all students have similar opportunities for favourable development, health and achievement of their academic goals

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Int J Epidemiol. 2021;50:1540-53.

LONG-TERM RISK OF EPILEPSY, CEREBRAL PALSY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AFFECTED BY A THREATENED ABORTION IN UTERO.

Dudukina E, Horv+íth-Puh+¦ E, S+©rensen HT, et al.

Background: The birth of a child affected by a threatened abortion (TAB) in utero is associated with autism spectrum disorder; association with other neurological disorders is unknown.

Methods: This nationwide registry-based cohort study included singletons live-born in Denmark (1979-2010), followed through 2016. The outcomes were epilepsy, cerebral palsy (CP) and attention-deficit/hyperactivity disorder (ADHD). We used Cox regression to compute hazard ratios (HRs), adjusted for birth year, birth order, parental age, morbidity, medication use and maternal socio-economic factors. To remove time-invariant family-shared confounding, we applied sibling analyses.

Results: The study population included 1 864 221 singletons live-born in 1979-2010. Among the TAB-affected children (N = 59 134) vs TAB-unaffected children, at the end of follow-up, the cumulative incidence was 2.2% vs 1.6% for epilepsy, 0.4% vs 0.2% for CP and 5.5% vs 4.2% for ADHD (for children born in 1995-2010). The adjusted HRs were 1.25 [95% confidence interval (CI) 1.16-1.34] for epilepsy, 1.42 (95% CI 1.20-1.68) for CP and 1.21 (95% CI 1.14-1.29) for ADHD. In the sibling design, the adjusted HRs were unity for epilepsy (full siblings: 0.96, 95% CI 0.82-1.12; maternal: 1.04, 95% CI 0.90-1.20; paternal: 1.08, 95% CI 0.93-1.25) and ADHD (full: 1.08, 95% CI 0.92-1.27; maternal: 1.04, 95% CI 0.90-1.20; paternal: 1.08, 95% CI 0.93-1.25). For CP, HRs shifted away from unity among sibling pairs (full: 2.92, 95% CI 1.33-6.39; maternal: 2.03, 95% CI 1.15-3.57; paternal: 3.28, 95% CI 1.36-7.91).

Conclusions: The birth of a child affected by TAB in utero was associated with a greater risk of CP, but not epilepsy or ADHD

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Int J Epidemiol. 2021;50:1615-27.

PARENTAL INCOME AND MENTAL DISORDERS IN CHILDREN AND ADOLESCENTS: PROSPECTIVE REGISTER-BASED STUDY.

Kinge JM, et al.

Background: Children with low-income parents have a higher risk of mental disorders, although it is unclear whether other parental characteristics or genetic confounding explain these associations and whether it is true for all mental disorders.

Methods: In this registry-based study of all children in Norway (n = 1 354 393) aged 5-17 years from 2008 to 2016, we examined whether parental income was associated with childhood diagnoses of mental disorders identified through national registries from primary healthcare, hospitalizations and specialist outpatient services.

Results: There were substantial differences in mental disorders by parental income, except for eating disorders in girls. In the bottom 1% of parental income, 16.9% [95% confidence interval (CI): 15.6, 18.3] of boys had a mental disorder compared with 4.1% (95% CI: 3.3, 4.8) in the top 1%. Among girls, there were 14.2% (95% CI: 12.9, 15.5) in the lowest, compared with 3.2% (95% CI: 2.5, 3.9) in the highest parental-income percentile. Differences were mainly attributable to attention-deficit hyperactivity disorder in boys and

anxiety and depression in girls. There were more mental disorders in children whose parents had mental disorders or low education, or lived in separate households. Still, parental income remained associated with children's mental disorders after accounting for parents' mental disorders and other factors, and associations were also present among adopted children.
Conclusions: Mental disorders were 3- to 4-fold more prevalent in children with parents in the lowest compared with the highest income percentiles. Parents' own mental disorders, other socio-demographic factors and genetic confounding did not fully explain these associations

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Int J Gen Med. 2021;14:2109-15.

IDENTIFICATION OF BRAIN REGIONS WITH ENHANCED FUNCTIONAL CONNECTIVITY WITH THE CEREBELLUM REGION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RESTING-STATE FMRI STUDY.

Ding L, Pang G.

Background: To explore the brain regions with higher functional connectivity with the cerebellum at resting state and the brain functions related to cognitive function in children with attention-deficit hyperactivity disorder (ADHD).
Methods: Thirty children with ADHD and 33 typically developing children (TDC) were examined using resting-state functional magnetic resonance imaging (fMRI) scans. Seedbased functional connectivity (FC) analysis was performed.
Results: Four brain areas with higher FC values were identified in ADHD children. These four areas were the left middle frontal gyrus, right middle frontal gyrus, right superior temporal gyrus and left parahippocampal gyrus (P < 0.05). The results of the CPT show that the number of omission errors was significantly higher in the children with ADHD than in the TD group (5.13-¦5.12 vs 2.18-¦2.36, P = 0.000). The commission number in the ADHD group was also significantly higher than that of the TD group (4.03-¦6.56 vs 2.00-¦2.85, P = 0.002). However, no statistically significant difference was observed in the correct reaction time between the two groups (641.54-¦146.79 ms vs 584.81-¦145.82 ms, P = 0.835).
Conclusion: The dysfunction of cerebellar functional connectivity in specific brain regions may be one of the pathological and physiological causes of cognitive impairment of ADHD

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J Med Internet Res. 2021 Dec;23:e31127.

SHORT FORM OF THE PEDIATRIC SYMPTOM CHECKLIST-YOUTH SELF-REPORT (PSC-17-Y): SPANISH VALIDATION STUDY.

Piqueras JA, Vidal-Arenas V, FalcÃ³ R, et al.

BACKGROUND: The short form, 17-item version of the Pediatric Symptom Checklist-Youth Self-Report (PSC-17-Y) is a validated measure that assesses psychosocial problems overall (OVR) and in 3 major psychopathological domains (internalizing, externalizing, and attention-deficit/hyperactivity disorder), taking 5-10 min to complete. Prior research has established sound psychometric properties of the PSC-17-Y for English speakers.
OBJECTIVE: This study extends psychometric evidence for the acceptability of the PSC-17-Y in a large sample of Spanish adolescents, providing proof of its reliability and structure, convergent and discriminant validity, and longitudinal and gender invariance.
METHODS: Data were collected on 5430 adolescents, aged 12-18 years, who filled out the PSC-17-Y twice during 2018-2019 (7-month interval). We calculated the Cronbach alpha and the McDonald omega coefficients to test reliability, the Pearson correlation for convergent (distress) and criterion validity (well-being, quality of life, and socioemotional skills), confirmatory factor analysis (CFA) for structure validity, and multigroup and longitudinal measurement invariance analysis for longitudinal and gender stability.
RESULTS: Within structural analysis for the PSC-17-Y, CFA supported a correlated 3-factor solution, which was also invariant longitudinally and across gender. All 3 subscales showed evidence of reliability, with coefficients near or above .70. Moreover, scores of PSC-17-Y subscales were positively related with convergent measures and negatively related with criterion measures. Normative data for the PSC-17-Y are presented in the form of percentiles (75th and 90th).

CONCLUSIONS: This work provides the first evidence of the reliability and validity of the Spanish version of the PSC-17-Y administered over the internet to assess mental health problems among adolescents, maintaining the same domains as the long version

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JAMA. 2021 Oct;326:1440.

'A2-ADRENERGIC AGONISTS OR STIMULANTS FOR PRESCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER': CORRECTION.

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

Reports an error in 'a2-adrenergic agonists or stimulants for preschool-age children with attention-deficit/hyperactivity disorder' by Elizabeth Harstad, Justine Shults, William Barbaresi, Ami Bax, Jaclyn Cacia, Alexis Deavenport-Saman, Sandra Friedman, Angela LaRosa, Irene M. Loe, Shruti Mittal, Shelby Tulio, Douglas Vanderbilt and Nathan J. Blum (JAMA: Journal of the American Medical Association, 2021[May][25], Vol 325[20], 2067-2075). The original article included an error in the Results section that indicated an incorrect number of children who received behavioral therapy before medication initiation. This included indicating that 309, rather than 225, children received behavioral therapy prior to initiation of medication in the Results and Table 1. These values have been corrected to indicate that 89 children in the a2-adrenergic agonist group and 136 in the stimulant group received behavioral therapy prior to medication initiation. (All other information in the Results and Table 1 was correct and is unchanged.) This article was corrected online. (The abstract of the original article appeared in record [rid]2021-50987-001[/rid])

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Jornal de Pediatria. 2021.

THE IMPACT OF THE ENVIRONMENT ON NEURODEVELOPMENTAL DISORDERS IN EARLY CHILDHOOD.

Scattolin MADA, Resegue RM, Ros+írio MCD.

Objectives: To review the literature about the environmental impact on children's mental, behavior, and neurodevelopmental disorders.

Sources of data: A nonsystematic review of papers published on MEDLINE-PubMed was carried out using the terms environment and mental health or psychiatric disorders or neurodevelopmental disorders.

Summary of findings: Psychopathology emerges at different developmental times as the outcome of complex interactions between nature and nurture and may impact each person in different ways throughout childhood and determine adult outcomes. Mental health is intertwined with physical health and is strongly influenced by cultural, social and economic factors. The worldwide prevalence of psychiatric disorders in children and adolescents is 13.4%, and the most frequent are anxiety, disruptive behavior disorders, attention deficit hyperactivity disorder and depression. Neurodevelopment begins at the embryonic stage and continues through adulthood with genetic differences, environmental exposure, and developmental timing acting synergistically and contingently. Early life experiences have been linked to a dysregulation of the neuroendocrine-immune circuitry which results in alterations of the brain during sensitive periods. Also, the environment may trigger modifications on the epigenome of the differentiating cell, leading to changes in the structure and function of the organs. Over 200 million children under 5 years are not fulfilling their developmental potential due to the exposure to multiple risk factors, including poverty, malnutrition and unsafe home environments.

Conclusions: Continued support for the promotion of a protective environment that comprises effective parent-child interactions is key in minimizing the effects of neurodevelopmental disorders throughout the lifetime

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Journal for Specialists in Pediatric Nursing. 2021.

CAREGIVERS' PERSPECTIVES ON THE CONTEXTUAL INFLUENCES WITHIN FAMILY MANAGEMENT FOR ETHNICALLY DIVERSE CHILDREN WITH ADHD.

Paidipati CP, Deatrick JA, Eiraldi RB, et al.

Purpose: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting over 9% of children in the United States. Family caregivers are often responsible for the management of their

child's ADHD. Contextual influences, such as healthcare providers, systems, and resources, are factors contributing to the ease or difficulty of family management. The purpose of this article is to qualitatively describe the major contextual influences that impact family management for ethnically diverse children with ADHD.
Design And Methods: This analysis is part of a mixed methods study using a concurrent nested design (QUAL + quant) to understand the phenomenon of family management from a contextual and socioecological perspective. In this analysis, cross-sectional data from caregivers of children with ADHD (N = 50) within a large northeastern city in the United States were collected, analyzed, and interpreted in the qualitative descriptive tradition. Semistructured interviews were conducted with participants to understand the contextual influences within family management. Conventional content analysis resulted in the emergence of barrier and facilitator domains and subdomains.
Results: Caregivers were predominantly female (98%) and between 24 and 61 years with a mean age of 37.54 (SD = 1.18). Caregivers identified their children as Black or African American (56%), White (26%), Multi-Racial (16%), Hispanic or Latinx (8%), and Asian (2%). Contextual influences within family management emerged as barrier or facilitator domains. Barrier domains included: (1) family, (2) healthcare systems, (3) educational systems, (4) stigma, and (5) financial, insurance, and policy issues.
Facilitator domains included: (1) family and community, (2) healthcare providers, and (3) educational providers. Subdomains within each domain are expanded in the article.
Practice Implications: Specialists in pediatric nursing should consider contextual influences within family management for ethnically diverse children with ADHD. As healthcare providers, it is important to recognize system-level barriers or facilitators for caregivers and their children and find creative ways to overcome obstacles and leverage strengths within families, communities, and care systems. Another important area for pediatric specialists to consider is understanding how stigma impacts children with ADHD. Policy-level engagement and advocacy should maximize the political will of nurses, families, and educators to create change within communities

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J Atten Disord. 2021 Dec;25:1955-61.
PARENTAL ADHD KNOWLEDGE IN LATINX FAMILIES: GENDER DIFFERENCES AND TREATMENT EFFECTS.
Gerdes AC, Malkoff A, Kapke TL, et al.
Objective: The current study aimed to extend findings of a study comparing two psychosocial treatments for ADHD in Latinx youth by examining if parental ADHD knowledge improves following treatment and if parental gender differences in ADHD knowledge exist.
Method: Following a comprehensive ADHD assessment, 58 Latinx families of school-aged children (mean age of 8 years) were randomly assigned to either culturally-adapted treatment (CAT) or standard evidence-based treatment (EBT). Parents completed an ADHD Knowledge measure both pre- and post-treatment.
Results/Conclusion: Latinx mothers demonstrated greater knowledge of ADHD symptomatology than fathers at pre-treatment. CAT resulted in improvements in parental knowledge of ADHD for both mothers and fathers, whereas standard EBT resulted in no change in maternal knowledge and reduced paternal knowledge of ADHD symptomatology. Clinical implications will be discussed

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J Atten Disord. 2021 Dec;25:2003-13.
THE LONGITUDINAL RELATIONSHIP BETWEEN SCREEN TIME, SLEEP AND A DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD.
Levelink B, van der Vlegel M, Mommers M, et al.
Objective: To evaluate longitudinal associations between recreational screen time and sleep in early childhood, and attention-deficit/hyperactivity disorder (ADHD) at age 8 to 10 years.
Method: Questionnaires from 2,768 mother-child pairs from the Dutch KOALA Birth Cohort Study were used. General estimating equation logistic regression analyses examined associations between screen time and sleep at age 2, 4, and 6, and ADHD at age 8 to 10. Linear regression analysis examined associations between television time, sleep and CBCL/2-3 scores at age 2.

Results: Longitudinally, neither screen time nor sleep were associated with ADHD. Cross-sectionally, CBCL/2-3 externalizing symptom scores increased by 0.03 with every hour television time (95% CI 0.002–0.05) and increased by 0.02 per hour of less sleep (95% CI -0.03–-0.01).
Conclusion: Despite an association with externalizing symptoms at age 2, screen time and sleep in early childhood were not associated with ADHD. Carefulness is warranted when extrapolating cross-sectional associations at early age to an ADHD diagnosis

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J Atten Disord. 2021 Dec;25:2083-97.

CAN SCHOOL MENTAL HEALTH PROVIDERS DELIVER PSYCHOSOCIAL TREATMENT IMPROVING YOUTH ATTENTION AND BEHAVIOR IN MEXICO? A PILOT RANDOMIZED CONTROLLED TRIAL OF CLS-FUERTE.

Haack LM, Araujo EA, Meza J, et al.

Background: Despite well-established Evidence-Based Treatments (EBTs) for Attention-Deficit/Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD), many low-resource settings lack EBT access.
Methods: We conducted a school-clustered randomized controlled pilot of CLS-FUERTE (a multicomponent behavioral EBT adapted for children in Mexico) with 58 students. We randomly assigned four schools to receive CLS-FUERTE and four to receive school services as usual. We compared groups post-treatment on parent- and teacher-rated ADHD/ODD symptoms and impairment.
Results: CLS-FUERTE fidelity, attendance, engagement, and acceptability was high and students receiving CLS-FUERTE showed greater improvement in teacher-rated ADHD, ODD, and impairment, as well as parent-rated ADHD and impairment, compared to students receiving usual services.
Conclusions: Pilot results suggest that psychosocial EBTs can be successfully implemented by School Mental Health Providers in Mexico

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J Atten Disord. 2021 Dec;25:2028-36.

CHANGES IN PROVIDER TYPE AND PRESCRIPTION REFILLS AMONG PRIVATELY INSURED CHILDREN AND YOUTH WITH ADHD.

Hart LC, Grosse SD, Danielson ML, et al.

Objective: The aim of this paper is to understand associations between age and health care provider type in medication continuation among transition-aged youth with ADHD.
Method: Using an employer-sponsored insurance claims database, we identified patients with likely ADHD and receipt of ADHD medications. Among patients who had an outpatient physician visit at baseline and maintained enrollment at follow-up 3 years later, we evaluated which ones continued to fill prescriptions for ADHD medications.
Results: Patients who were younger at follow-up more frequently continued medication (77% of 11–12 year-olds vs. 52% of 19–20 year-olds). Those who saw a pediatric provider at baseline and follow-up more frequently continued to fill ADHD medication prescriptions than those who saw a pediatric provider at baseline and non-pediatric providers at follow-up (71% vs. 53% among those ages 15–16 years at follow-up).
Conclusion: Adolescents and young adults with ADHD who changed from pediatric to exclusively non-pediatric providers less frequently continued to receive ADHD medications

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J Atten Disord. 2021 Dec;25:2037-47.

EXECUTIVE FUNCTION TRAINING FOR PRESCHOOL CHILDREN WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.

Shuai L, Wang Y, Li W, et al.

Objective: This randomized controlled study explored the efficacy, feasibility, and acceptability of executive function training (EFT) for preschool children with ADHD.
Method: The current study design was an 8 week randomized parallel groups, single-blinded trial, using EFT-P. A total of 96 children with an ADHD diagnosis at age 4 to 5 years old were randomized into the intervention group and waitlist group. In the intervention group, 46 out of 50 participants completed the 8-

week program, compared with 39 out of 46 in the waiting group. The level of ADHD symptoms and the executive function (EF) were evaluated by both neuropsychological tests from NEPSY Second Edition (NEPSY-II) and Behavior Rating Inventory of Executive Function Preschool version (BRIEF-P).
Results: The EFT is feasible to administer and is acceptable for preschool children, with a 93% retention rate. Results showed that following the intervention, the visual-motor precision (p = .024), ADHD diagnostic state (p = .01), and oppositional defiant symptoms (p = .023) improved significantly in preschool children. However, the symptoms of ADHD and other EF evaluations were found to be insignificant.
Conclusion: The EFT is feasible, acceptable, and potentially effective to reduce symptoms and improve EF for preschool children with ADHD. The next step is to extend the program time and provide more frequent practice of activities between the children and the therapist and/or parent, to improve the effectiveness

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J Atten Disord. 2021 Dec;25:1962-76.

WHAT IS THE HEALTH AND WELL-BEING BURDEN FOR PARENTS LIVING WITH A CHILD WITH ADHD IN THE UNITED KINGDOM?

Peasgood T, Bhardwaj A, Brazier JE, et al.

Objective: To explore the burden associated with childhood ADHD in a large observational study.
Methods: We recruited familes with at least one child (6-18 years) with ADHD via 15 NHS trusts in the UK, and collected data from all family members. We made careful adjustments to ensure a like-for-like comparison with two different control groups, and explored the impact of controlling for a positive parental/carer ADHD screen, employment, and relationship status.
Results: We found significant negative impacts of childhood ADHD on parents'/carers' hours and quality of sleep, satisfaction with leisure time, and health-related quality of life (measured by the EuroQol-5D [EQ-5D]). We found a decrement in life satisfaction, mental well-being (as measured by the Short–Warwick Edinburgh Mental Well-Being Scale [S-WEMWBS]), and satisfaction with intimate relationships, but this was not always robust across the different control groups. We did not find any decrement in satisfaction with health, self-reported health status, or satisfaction with income.
Conclusion: The study quantifies the impact on the health and well-being of parents living with a child with ADHD using a survey of families attending ADHD clinics in the United Kingdom

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J Atten Disord. 2021 Dec;25:1977-87.

EFFICACY OF OMEGA-3 AND KOREAN RED GINSENG IN CHILDREN WITH SUBTHRESHOLD ADHD: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL.

Lee J, Lee SI.

Objective: The purpose of the present study was to investigate the efficacy of combined omega-3 and Korean red ginseng supplementation on ADHD symptoms and cognitive function in children with subthreshold ADHD.
Method: 120 children from 6 to 12 years with subthreshold ADHD were enrolled in this 12-week, double-blind, randomized, placebocontrolled study. The primary outcome was measured by Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS). Children Behavior Check List (CBCL), and neuropsychological tests assessing attention, memory, and executive function were included as secondary primary outcome measures.
Results: Significant effects on the scores of ADHDRS, as well as several subscales of CBCL including ADHD and attention problem subscales were revealed.
Conclusion: The combination of omega-3 and Korean red ginseng may have beneficial effects in children with subthreshold ADHD. Increased clinical awareness of ADHD symptoms even at a subthreshold level is needed

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J Atten Disord. 2021 Dec;25:2048-59.

IMPACT OF A NEW PARENT BEHAVIORAL-SCHEMA TRAINING ON CHILDREN WITH ADHD: A PRAGMATIC CONTROL TRIAL.

Solan M, Klomek AB, Ankori G, et al.

Objectives: To examine whether adding schema therapy strategies to the conventional parent behavioral program prevents symptom relapse in children with attention deficit hyperactivity disorder (ADHD).
Method: The intervention was designed as an adaptive pragmatic control trial. The parent behavioral training and schema-enhanced parent behavior therapy (SPBT) protocols were delivered to the control group (40 parents of 23 children) and experimental group (97 parents of 54 children), respectively. Participants were assessed at baseline, mid-treatment, and termination. Parents and teachers indicated the severity of ADHD and comorbid symptoms through their responses to standardized questionnaires designed for this purpose.
Results: A nested growth curve analysis demonstrated that participants in the schema-enhanced intervention group had a lower risk of symptom relapse than the control group.
Conclusion: Participation in the SPBT program significantly reduced relapse rates by the end of the intervention. Future research may determine the long-term effects of the treatment

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Journal of Central Nervous System Disease. 2021;13.

PSEUDO-SEIZURE, AN ATYPICAL PRESENTATION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN A FEMALE: A CASE REPORT.

Yong Qun Leow T, Sadhu R, Mayall M, et al.

Background: This paper describes pseudo-seizure as an atypical presentation of attention-deficit hyperactivity disorder (ADHD) in an adolescent female in the context of psychosocial difficulties. We present the case, which explains the clinical dilemma in such situations, along with selective literature review. Case
Presentation: An adolescent female, who is an academic high achiever, living with parents, presented with unresponsive spells which were initially treated with antiepileptics by the paediatrician without any significant improvement. Later, after further assessments and revision of her diagnosis to conversion disorder, she was referred to the child and youth mental health service team. Further evaluation revealed her symptoms to be a result of multiple psychosocial stressors in the context of her having undiagnosed ADHD. Individual therapy, treatment with stimulant, resulted in significant improvement in her school and home adjustments.
Conclusions: This case demonstrates the diagnostic challenges that high-functioning girls with ADHD coloured by psychosocial stressors can pose and raises the need for reviewing our diagnostic approaches in these situations

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J Child Adolesc Psychopharmacol. 2021 Nov;31:610-22.

EFFICACY AND SAFETY OF A LONG-ACTING MULTILAYER-RELEASE METHYLPHENIDATE FORMULATION (PRC-063) IN THE TREATMENT OF ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL WITH A 6-MONTH OPEN-LABEL EXTENSION.

Weiss MD, Cutler AJ, Kollins SH, et al.

Objectives: To study the safety and efficacy of the long-acting methylphenidate formulation PRC-063 in adolescents with attention-deficit/hyperactivity disorder (ADHD).
Methods: Adolescents 12 to = 17 years who met Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for ADHD and had a baseline ADHD Rating Scale DSM-5 (ADHD-5-RS) score = 24 participated in a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study. Participants were randomized 1:1:1:1:1 to receive placebo or one of four doses of PRC-063 once daily for 4 weeks. The primary endpoint was change from baseline in least-squares mean clinician-rated ADHD-5-RS total score for PRC-063 (all doses combined) versus placebo. Other efficacy assessments included Conners third Edition: Self-Report (C3SR) and Clinical Global Impression-Improvement (CGI-I). A subset of double-blind study participants entered a subsequent open-label, dose-optimized study. Safety outcomes in both studies included treatment-emergent adverse events (TEAEs).
Results: Three hundred fifty-four participants were included in the primary analysis. The least-squares mean change from baseline in ADHD-5-RS total score was -15.17 for PRC-063 versus -10.98 for placebo (least-

squares mean difference -4.2, p = 0.0067). For individual PRC-063 doses, improvements in ADHD-5-RS total score versus placebo were significant for 45 mg (p = 0.0155) and 70 mg (p = 0.0401), but not for 25 or 85 mg. A significant improvement for PRC-063 versus placebo was recorded for C3SR Inattention (p = 0.0168), but not for the other C3SR subscales. About 52.7% of participants randomized to PRC-063 were responders based on CGI-I versus 32.4% of those randomized to placebo (p = 0.0004). Further improvements in ADHD symptoms based on ADHD-5-RS were observed from 1 month through 6 months of open-label treatment (p < 0.0001). There were two serious adverse events (both during the open-label study), one of which (aggressive behavior) was assessed as related to study drug. The only TEAEs that occurred in >10% of participants during double-blind treatment were decreased appetite (20.1%) and headache (15.0%). Most TEAEs were of mild or moderate severity.
Conclusion: PRC-063 significantly improved ADHD symptomatology in adolescents. It was generally well tolerated, with an AE profile consistent with other long-acting stimulants

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J Child Adolesc Psychopharmacol. 2021 Nov;31:578-96.
COST-EFFECTIVENESS AND COST UTILITY OF TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.
Dijk HH, Wessels LM, Constanti M, et al.
Objectives: This systematic review provides an overview of full economic evaluations of attention-deficit/hyperactivity disorder (ADHD) treatments, evaluates their outcomes, and highlights gaps in the literature.
Data Sources: Electronic databases were searched for full economic evaluations of ADHD treatments for children, adolescents, or adults published in English or Dutch.
Results: Twenty-nine studies met the inclusion criteria. Almost all studies that compared medication or psychosocial treatment to no treatment, placebo, or care as usual indicated that medication and psychosocial treatment were cost-effective compared to the control group. Stimulant treatment appeared to be cost-effective for the treatment of ADHD in children and adolescents. Only few studies focus on treatments in adults and psychosocial treatments and the number of studies with long time horizons and without industry funding is limited.
Conclusions: Despite the rising interest in cost-effectiveness, this systematic review shows that more cost-effectiveness research of higher quality is warranted to aid in the optimal use of available treatments and resources for individuals with ADHD. Specifically, more studies should focus on treatments in adults and psychosocial treatments, and more studies with long time horizons and without industry funding are warranted. Nevertheless, we can conclude that treating ADHD is generally cost-effective compared to no treatment

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J Child Adolesc Psychopharmacol. 2021;31:597-609.
A RANDOMIZED, CONTROLLED LABORATORY CLASSROOM STUDY OF SERDEXMETHYLPHENIDATE AND D-METHYLPHENIDATE CAPSULES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Kollins SH, Braeckman R, Guenther S, et al.
Objectives: To evaluate the efficacy and safety of once-daily serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH) capsules (Azstarys) compared with placebo in children with attention-deficit/hyperactivity disorder (ADHD) in a randomized, double-blind, dose-optimized laboratory classroom study.
Methods: Children ages 6-12 with ADHD were enrolled. During a 3-week, open-label, Dose Optimization Phase, subjects initiated treatment with 39.2 mg/7.8 mg/day of SDX/d-MPH and were titrated weekly to an optimal dose (maximum dose of 52.3/10.4 mg). During the double-blind Treatment Phase, subjects were randomized to receive their optimal dose of SDX/d-MPH or placebo for 7 days. On day 7, efficacy was assessed in the laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and Permanent Product Measure of Performance (PERMP). To evaluate safety, adverse events (AEs), vital signs, and electrocardiograms were assessed, and suicide risk was assessed.
Results: A total of 149 subjects completed the study. In the primary efficacy analysis, the mean postdose change from baseline in SKAMP-Combined scores averaged over the laboratory classroom day was

significantly improved with SDX/d-MPH versus placebo (least-squares mean treatment difference [95% confidence interval]: -5.41 [-7.10 to -3.71]; p < 0.001). A significant treatment effect for SDX/d-MPH compared with placebo was observed from 1 to 10 hours postdose. A post hoc analysis more comparable with that conducted in similar studies indicated a 0.5- to 13-hour onset and duration of efficacy. Both average postdose PERMP-Attempted and PERMP-Correct score changes from baseline were significantly improved among those treated with SDX/d-MPH versus placebo (p < 0.001 for both). No serious AEs were reported. During the Dose Optimization Phase, two-thirds of subjects reported AEs; the most common being insomnia and decreased appetite.
Conclusions: SDX/d-MPH showed significant improvement in ADHD symptoms compared with placebo in children 6-12 years of age, with a rapid onset and extended duration of treatment effect. SDX/d-MPH was safe, with AEs comparable with those observed with other stimulant treatments

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J Child Adolesc Psychopharmacol. 2021;31:623-30.
EFFECT OF A MULTILAYER, EXTENDED-RELEASE METHYLPHENIDATE FORMULATION (PRC-063) ON SLEEP IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND, FIXED-DOSE, PLACEBO-CONTROLLED TRIAL FOLLOWED BY A 6-MONTH OPEN-LABEL FOLLOW-UP.
Weiss MD, Surman C, Khullar A, et al.
Objectives: We analyzed patient-reported sleep parameters for an extended-release methylphenidate formulation (PRC-063) in adolescents with attention-deficit/hyperactivity disorder.
Methods: Clinical efficacy and long-term safety/tolerability data from a 4-week, double-blind, placebo-controlled, fixed-dose study (NCT02139111) and a subsequent 6-month, optimized-dose, open-label extension (OLE) study (NCT02168127) were used. In the double-blind study, participants were randomly assigned 1:1:1:1:1 to one of four doses of PRC-063 (25, 45, 70, or 85 mg/day) or placebo. In both the double-blind and OLE studies, sleep outcomes were assessed using the Pittsburgh Sleep Quality Index (PSQI).
Results: During double-blind treatment, no statistically significant least-squares mean difference in change from baseline between PRC-063 (all doses combined; N = 293) and placebo (N = 74) was found for either global PSQI score (-0.3 vs. -0.5; p = 0.6110) or scores for any of the seven PSQI subscales. Compared with the placebo group, a marginally higher proportion of patients in the PRC-063 group (all doses combined) went from being poor to good sleepers (global PSQI score 5; 14.4% vs. 11.3%). In a logistic regression analysis, study treatment was not a predictor of poor sleep (p = 0.5368) at the end of the double-blind study. In the OLE study, there was a trend of improvement in sleep after 1 month of individualized dosing that was maintained through 6 months. Sleep efficiency (time asleep as a proportion of time in bed) showed improvement at the end of the OLE study.
Conclusion: While individual patients may experience changes in sleep as an adverse event, group data evaluating sleep as an outcome found there were no differences between PRC-063 and placebo in self-reported sleep outcomes on the PSQI

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J Child Adolesc Psychopharmacol. 2021;31:639-44.
STIMULANT TREATMENT EFFECT ON ANXIETY DOMAINS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH AND WITHOUT ANXIETY DISORDERS: A 12-WEEK OPEN-LABEL PROSPECTIVE STUDY.
Soul O, Gross R, Basel D, et al.
Objectives: The effect of stimulants on anxiety domains has not been systematically studied. We assessed prospectively the impact of stimulant treatment in children with attention-deficit/hyperactivity disorder (ADHD) on the severity of anxiety domains and on ADHD with comorbid anxiety disorders.
Methods: Children with ADHD (n = 57, aged 6-15 years) started a stimulant or were switched from one stimulant to another. Assessments were conducted at four time points (baseline and weeks 2, 6, and 12) and consisted of parental questionnaires (ADHD rating scale, screen for child anxiety related disorders [SCARED]), and side effect questionnaire completed by a child psychiatrist.
Results: A significant improvement in total SCARED scores was obtained after 12 weeks stimulant treatment in children both with and without anxiety disorders. Significant reductions were detected in generalized

anxiety, separation anxiety, and school avoidance SCARED subscales, but not in panic and social anxiety subscales. ADHD symptoms significantly improved both in children with and without anxiety comorbidities.
Conclusion: We found specific effects of stimulants on anxiety domains. Stimulant treatment, even for ADHD children diagnosed with comorbid anxiety disorders, is relatively safe regarding the risk of anxiety exacerbation. Moreover, the presence of anxiety symptoms or disorders does not interfere with the beneficial effect of the stimulants on the ADHD core symptoms. Clinical trial regestration number: IRB SMC-6893-20

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J Child Adolesc Psychopharmacol. 2021;31:631-38.

THE VALIDITY OF THE WORLD HEALTH ORGANIZATION ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SELF-REPORT SCREENING SCALE FOR DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FIFTH EDITION IN ADOLESCENCE.

Somma A, Adler LA, Gialdi G, et al.

Objectives: Short, self-report screening measures for adolescent and adult attention-deficit/hyperactivity disorder (ADHD) would greatly enhance the likelihood of ADHD subjects to be correctly diagnosed and treated. This study aimed at testing the reliability, factor structure, convergent validity, external validity, and diagnostic accuracy of the official Italian translation of the ADHD Self-Report Screening Scale for DSM-5 (ASRS-5) in a sample of community-dwelling adolescents, extending previous data on adult participants to adolescent participants.
Methods: Five hundred sixty-four community-dwelling male adolescents (mean age Γëà15) were administered the ASRS-5, the Adult ADHD Self-Report Scale 18-item and 6-item versions (ASRS-18 and ASRS-6), the Wender Utah Rating Scale (WURS), and the Structured Clinician Interview for DSM-5-Clinician Version ADHD Module (SCID-5-CV-ADHD). School performance variables were also collected.
Results: The item response theory (IRT) reliability of ASRS-5 was adequate. Dimensionality analyses strongly supported the unidimensional structure of ASRS-5 items; confirmatory factor analysis fit indices supported the adequacy of the one-factor model of ASRS-5. In terms of convergent validity, the ASRS-5 total score was significantly and positively associated with self-report and interview-based ADHD dimensional scores, as well as with school performance variables. Roughly 8.0% of our male adolescents met SCID-5-CV-ADHD criteria for categorical ADHD diagnosis. Ten-fold cross-validated receiver operating curve value was 0.843; precision-recall curve analysis suggests that an ASRS-5 total score >12 may be preferred for screening purposes in adolescence.
Conclusions: Our data showed that the ASRS-5 may represent a psychometrically sound self-report instrument to reliably screen for DSM-5 ADHD, extending the range of application of ASRS-5 from adulthood to adolescence, suggesting that the ASRS-5 could be safely used for screening purposes also in community-dwelling adolescents, at least in its official Italian translation

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J Child Fam Stud. 2021 Dec;30:2966-79.

PARENTING STRESS DURING LATE ADOLESCENCE IN MOTHERS OF INDIVIDUALS WITH ADHD WITH AND WITHOUT ODD.

Gordon CT, Fabiano GA, Schatz NK, et al.

Although children with ADHD continue to experience impairment well into adolescence, research exploring the experiences of their parents during late adolescence is lacking. Thus, we examined changes in parenting stress and family conflict in mothers of adolescents with ADHD during the transition to early adulthood. We also explored predictors of these changes in addition to investigating differences in these trajectories due to comorbid ODD. Forty-nine mothers of adolescents with ADHD only and thirty-seven mothers of adolescents with ADHD/ODD reported on parenting stress and perceptions of family conflict at baseline (mean age = 16.88) and at 3-month, 9-month, and 15-month follow up assessments. Growth curve modeling indicated that both groups of mothers reported relative declines in parenting stress and family conflict across time. However, the mothers of adolescents with ADHD/ODD persistently reported more stress and conflict. Furthermore, decreases in family conflict were more predictive of reduced parenting stress in families of adolescents only diagnosed with ADHD. Our findings suggest that comorbid ODD is associated with

parenting stress during late adolescence. Thus, interventions should focus on further reducing this stress as adolescents with ADHD/ODD transition to adulthood

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J Child Psychol Psychiatry. 2021 Dec;62:1444-52.

EFFECTS OF METHYLPHENIDATE ON EXECUTIVE FUNCTIONING IN CHILDREN AND ADOLESCENTS WITH ADHD AFTER LONG-TERM USE: A RANDOMIZED, PLACEBO-CONTROLLED DISCONTINUATION STUDY.

Rosenau PT, Openneer TJC, Matthijssen AF, et al.

Background: Methylphenidate may improve executive functioning in children with attention-deficit/hyperactivity disorder (ADHD). However, it is unclear if there are still acute effects of methylphenidate on executive functioning after long-term use.

Methods: In a randomized double-blind, placebo-controlled discontinuation study, 94 children and adolescents (ages 8–18 years) who used methylphenidate beyond two years were either assigned to seven weeks of continued treatment with 36 or 54 mg of extended-release methylphenidate or to gradual withdrawal over three weeks to placebo for four weeks. Performance on neuropsychological tasks, measuring working memory, response inhibition, attentional flexibility and psychomotor speed was compared between both groups using mixed models for repeated measures. Additionally, we investigated within the discontinuation group if a deterioration on the investigator-rated Clinical Global Impressions Improvement scale after withdrawing to placebo was related to a worse performance on the neuropsychological tasks. This study was registered in the Netherlands Trial Register (www. Trialregister.nl) with identifier 5252.

Results: After withdrawal of methylphenidate, the discontinuation group made more errors on working memory (ß = -1.62, SD = 0.56, t = -2.88, p = .01, Cohen's f² = .14), independent from reaction time compared to baseline, in contrast to the continuation group. We did not find differences in changes in response inhibition, attentional flexibility and psychomotor speed between the two groups. Also, there were no significant differences in task measures between the participants who deteriorated clinically and those who did not.

Conclusions: Our study shows that methylphenidate has a beneficial effect on working memory after two years of use. Future studies should explore whether cognitive outcomes may aid clinical decision-making on the continued use of methylphenidate, given dissociation between cognitive and behavioural effects of stimulant medication

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Journal of Clinical Medicine. 2022;11.

ACUTE AND LONG-TERM EFFECTS OF AN INTERNET-BASED, SELF-HELP COMPREHENSIVE BEHAVIORAL INTERVENTION FOR CHILDREN AND TEENS WITH TIC DISORDERS WITH COMORBID ATTENTION DEFICIT HYPERACTIVITY DISORDER, OR OBSESSIVE COMPULSIVE DISORDER: A REANALYSIS OF DATA FROM A RANDOMIZED CONTROLLED TRIAL.

Rachamim L, Mualem-Taylor H, Rachamim O, et al.

Attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and tic disorders (TD) commonly co-occur. In addition, specific inattention difficulties and poor impulse control are related to TD in the absence of comorbid ADHD. In this study we reanalyzed data from a recently completed study comparing internet-delivered, self-help comprehensive behavioral intervention for tics (ICBIT) with a waiting-list control group. The current study describes the effects of an (ICBIT) in children and adolescents with TD with and without comorbid diagnoses of ADHD or OCD at post intervention and over three-and six-month follow-up periods. Thirty-eight 7 to 18-year-olds completed the ICBIT. Of these, 16 were diagnosed with comorbid ADHD and 11 were diagnosed with OCD. A significant improvement in tic measures was found in all groups. Both the TD + ADHD and the TD ΓêÆ ADHD groups were similar in the magnitude of tic reduction from baseline to post-treatment, and at the three and six-month follow-up assessments. However, the TD + OCD group benefitted less from intervention than the TD-OCD group. There were meaningful reductions in parental reports of inattention, as well as hyperactive and impulsive symptoms at post intervention and over the 6-month follow-up period. Thus, ICBIT can be effectively delivered in the presence of comorbid ADHD or

OCD symptomatology and may reduce symptoms of inattention and impulsivity. Larger studies of ICBIT in children and teens with TD and comorbid ADHD and OCD are needed to optimize responses to ICBIT

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J Intellect Disabil Res. 2021.

CO-OCCURRING MEDICAL AND BEHAVIOURAL CONDITIONS IN CHILDREN WITH DOWN SYNDROME WITH OR WITHOUT ADHD SYMPTOM PRESENTATION.

Esbensen AJ, Vincent LB, Epstein JN, et al.

Background: Co-occurring attention deficit hyperactivity disorder (ADHD) is a challenge to characterise in the presence of other medical conditions commonly present in children with Down syndrome (DS). The current study examined differences among children with DS with or without ADHD symptomatology in terms of demographics, developmental level, co-occurring medical conditions, and parent and teacher ratings of behaviour and executive functioning.

Methods: Parents and teachers of 108 school-age children with DS provided ratings of ADHD symptoms, behaviour problems and executive functioning skills. Children with DS and ADHD symptom presentation, as identified by a scoring algorithm, were compared with those without ADHD symptom presentation on demographic characteristics, developmental level, co-occurring medical conditions and parent-report and teacher-report measures of behaviours and executive functioning.

Results: Sleep disorders, disruptive behaviour disorder, allergies and seizures were more common in children with DS and ADHD symptom presentation than in children without ADHD symptom presentation. After controlling for ADHD medication use, children with DS and ADHD symptom presentation had poorer performance than those without ADHD symptom presentation on parent behaviour ratings, teacher behaviour ratings and parent but not teacher ratings of executive functioning. No significant group differences in demographic characteristics or developmental level were identified.

Conclusions: Higher rates of co-occurring medical conditions present in children with DS and ADHD symptom presentation support the need for thorough differential diagnoses. The different pattern of group differences between parent-report and teacher-report has implications for diagnostic practices across settings as well as for treatment

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Journal of Medical Internet Research. 2021;23.

ELECTROPHYSIOLOGICAL BRAIN CHANGES ASSOCIATED WITH COGNITIVE IMPROVEMENT IN A PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER DIGITAL ARTIFICIAL INTELLIGENCE-DRIVEN INTERVENTION: RANDOMIZED CONTROLLED TRIAL.

Medina R, Bouhaben J, de Ram+¦n I, et al.

Background: Cognitive stimulation therapy appears to show promising results in the rehabilitation of impaired cognitive processes in attention deficit hyperactivity disorder.

Objective: Encouraged by this evidence and the ever-increasing use of technology and artificial intelligence for therapeutic purposes, we examined whether cognitive stimulation therapy implemented on a mobile device and controlled by an artificial intelligence engine can be effective in the neurocognitive rehabilitation of these patients.

Methods: In this randomized study, 29 child participants (25 males) underwent training with a smart, digital, cognitive stimulation program (KAD_SCL_01) or with 3 commercial video games for 12 weeks, 3 days a week, 15 minutes a day. Participants completed a neuropsychological assessment and a preintervention and postintervention magnetoencephalography study in a resting state with their eyes closed. In addition, information on clinical symptoms was collected from the childs legal guardians.

Results: In line with our main hypothesis, we found evidence that smart, digital, cognitive treatment results in improvements in inhibitory control performance. Improvements were also found in visuospatial working memory performance and in the cognitive flexibility, working memory, and behavior and general executive functioning behavioral clinical indexes in this group of participants. Finally, the improvements found in inhibitory control were related to increases in alpha-band power in all participants in the posterior regions, including 2 default mode network regions of the interest: the bilateral precuneus and the bilateral posterior

cingulate cortex. However, only the participants who underwent cognitive stimulation intervention (KAD_SCL_01) showed a significant increase in this relationship.
Conclusions: The results seem to indicate that smart, digital treatment can be effective in the inhibitory control and visuospatial working memory rehabilitation in patients with attention deficit hyperactivity disorder. Furthermore, the relation of the inhibitory control with alpha-band power changes could mean that these changes are a product of plasticity mechanisms or changes in the neuromodulatory dynamics

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J Nerv Ment Dis. 2021 Dec;209:905-10.

CAN TEMPERAMENT AND CHARACTER TRAITS BE USED IN THE DIAGNOSTIC DIFFERENTIATION OF CHILDREN WITH ADHD?

Ucuz I, Uzun Cicek A, Cansel N, et al.

In this study, it was aimed to determine the contributions of temperament and character traits to the diagnosis of attention deficit hyperactivity disorder (ADHD) in children. Thirty-six patients between the ages of 9 and 14 with a diagnosis of combined type ADHD and 39 healthy children were included in the study. The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version–Turkish Version and the Turgay DSM-IV Disruptive Behavior Disorders Rating Scale parent form were used to assess hyperactivity/impulsivity and inattentiveness, and comorbid disorders. The Junior Temperament and Character Inventory–Revised form was used to evaluate temperament–character traits. The classification-based association rules (CBARs) method was used for finding rules predicting ADHD accurately. Low persistence and self-directedness scores, and higher disorderliness and fatigability subgroup scores were found in the ADHD group. In CBARs, the separation of children with ADHD from healthy controls could be made with 0.83 accuracy, 0.80 sensitivity, and 0.86 specificity. The results of our study support the view that temperament–character traits can help clinical diagnosis of ADHD

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J Nerv Ment Dis. 2021 Nov;209:829-34.

THE RELATIONSHIP OF COMORBID OVERWEIGHT-OBESITY WITH COLD EXECUTIVE FUNCTIONS, VERBAL SHORT-TERM MEMORY, AND LEARNING IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Guler HA, Turkoglu S.

The aim of this study was to investigate the relationship between comorbid obesity/overweight and cold executive functions, verbal short-term memory, and learning in children with attention deficit and hyperactivity disorder (ADHD). Our study was conducted on 100 drug-naive participants, including 70 patients with ADHD and 30 healthy controls. In our study, patients diagnosed with ADHD were divided into two groups according to body mass index as above the 85th percentile and at or below the 85th percentile. Cold executive functions were evaluated by the Stroop Test (ST) and Cancellation Test (CT). Serial Digit Learning Test (SDLT) was administered to measure verbal short-term memory and learning capacity. To evaluate the severity of ADHD objectively, the parents completed the Conners' Parents Rating Scale–Revised Short Version (CPRS-RS). There was no statistically significant difference in ST, SDLT, CT scores, and CPRS-RS subscale scores between the two groups with ADHD. This study show that overweight/obesity comorbid with ADHD may not be associated with cold executive functions, verbal short-term memory, learning, or ADHD symptom severity

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Journal of Pediatric Orthopaedics Part B. 2022;31:E24-E30.

THE INVESTIGATION OF FOOT STRUCTURE WITHIN CHILDREN WHO HAVE ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A CASE-CONTROLLED STUDY.

Mutlu EK, Birinci T, Aytutuldu GK, et al.

The impairments in motor performance could be related to the foot structure in children with attention-deficit/ hyperactivity disorder (ADHD) while considering the close relationship between foot structure and lower extremity alignment. This study aimed to investigate the foot structure and its relationships between disease severity, physical activity and psychiatric traits in children with ADHD. Children with ADHD (n = 50; mean age: 12.02 -¦ 1.83 years) and typically developing peers (n = 30; mean age: 12.86 -¦ 2.56 years) were included. The static footprint analysis was collected by using digital images. The ImageJ program was used

to calculate Clarke's angle, Staheli arch index (SAI) and Chippaux-Smirak index (CSI). The Turgay DSM-IV disruptive behavior disorders rating scale (T-DSM-IV-S), physical activity questionnaire for older children (PQ-C), children's depression inventory and state-trait anxiety inventory for children were all used to assess symptoms of ADHD, physical activity, depression, stress and anxiety, respectively. Approximately 52ΓÇô53% of children with ADHD had mild to severe flatfoot, while only 8-13% of typically developing peers had flatfoot based on SAI and CSI (P = 0.01). Significant correlation was found between Clarke's angle and PQ-C (r = 0.21, P = 0.04). Besides, T-DSM-IV-S was significantly correlated with SAI (r = 0.24, P = 0.01) and CSI (r = 0.25, P = 0.01) in children with ADHD. Children with ADHD had a significantly greater tendency of flatfoot compared to typically developing peers. Besides, the deterioration of the foot structure of children with ADHD was associated with disease severity

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J Psychopathol Behav Assess. 2021 Dec;43:793-807.

FACTORS RELATED TO AGREEMENT BETWEEN PARENT AND TEACHER RATINGS OF CHILDREN'S ADHD SYMPTOMS: AN EXPLORATORY STUDY USING POLYNOMIAL REGRESSION ANALYSES.

Saffer BY, Mikami AY, Qi H, et al.

Inter-rater agreement about children's symptoms of attention-deficit/hyperactivity disorder (ADHD) is crucial for accurately identifying and treating children with this condition. Decades of empirical research demonstrate that parents and teachers rarely agree about children's ADHD symptoms, yet few studies have tested the factors that relate to parent-teacher agreement. This exploratory study examined potential associations between parent-teacher agreement about child ADHD symptoms, and child factors (academic functioning, demographic characteristics, externalizing psychopathology, and social functioning), in a community (n = 752; mean age = 7.28; 51.3% male; 46.5% White) and in a clinical (n = 213; mean age = 8.58; 69.0% male; 70.4% White) sample. Agreement was examined using polynomial regression analyses, which overcome mathematical limitations and constraints imposed by using difference scores. Parent-teacher agreement about ADHD symptoms related to several academic and social functioning variables in the community sample. Most relationships were non-linear (e.g., quadratic, cubic). The 3-dimensional distribution of the results revealed that parent-teacher agreement was strongest for children functioning approximately 1 standard deviation below the mean (but not lower) on grades, academic enablers, academic performance, and social functioning. In the clinical sample, only teacher-rated social functioning related to parent-teacher agreement about ADHD symptoms. These findings provide a more nuanced understanding of parent-teacher agreement, thereby advancing theoretical knowledge. An implication for assessment and treatment is that children with very poor, or conversely, very good, social and academic functioning are at risk for parent-teacher disagreement on ADHD symptom ratings

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Klin Padiatr. 2021.

EFFECT OF PSYCHOSOCIAL FACTORS ON GROWTH.

Gohlke BC, Bettendorf M, Binder G, et al.

Background Genes, hormones and factors such as nutrition and psychosocial environment affect growth. Objective What is the significance of various psychosocial factors on growth?

Methods Evaluation of results of a working meeting of paediatric endocrinologist with current literature research.

Results Psychosocial deprivation in children can be associated with growth hormone deficiency (GHD) and short stature. GHD can be reversed by a change of environment and psychosocial support. War and migration are often associated with underweight, growth disturbances and poor health care. These factors can improve after the end of conflicts, but children often remain too short. Consumption of alcohol or opiates during pregnancy are associated with lower birth weight and increased risk of early and small for gestational age (SGA) childbirth. Children with attention deficit hyperactivity disorder show a slight slowdown in growth after they started stimulant therapy. However, they reach normal adult height.

Conclusions In children with idiopathic short stature, psychosocial causes should be taken into account in the differential diagnosis. Notably there is an increased risk of growth disturbances in children from conflict regions or after prenatal drug exposure

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Mindfulness (N Y). 2021 Dec;12:3011-25.

FAMILY MINDFULNESS TRAINING FOR CHILDHOOD ADHD: SHORT- AND LONG-TERM EFFECTS ON CHILDREN, FATHERS AND MOTHERS.

Bögels SM, Oort FJ, Potharst E, et al.

Objectives: We evaluated the effects of the family mindfulness-based intervention (MBI) 'MYmind' for children with ADHD and their parents, and examined child and parent predictors of child outcome.

Methods: Using a pragmatic quasi-experimental waitlist design, children aged 7–19 years (n = 167), clinically referred with a DSM-IV ADHD diagnosis, and both their parents completed waitlist (average waiting time was 8 weeks), pre-test, post-test, 8-week, and 1-year follow-up measurements. MYmind consisted of eight weekly 1.5-h mindfulness-based group sessions for children and parallel for parents, and a follow-up session. We assessed children's and both parents' ADHD symptoms and other psychopathology, child executive function, parental stress, parental overreactivity, and mindful parenting.

Results: Multilevel analyses revealed medium-to-large effect-sized reduced child ADHD symptoms between pre- and post-test, becoming stronger at follow-ups, while no waitlist effects occurred. Parents above the ADHD threshold improved on adult ADHD symptoms with similar sized effects. Children's and parents' other psychopathology, child executive function, parental overreactivity, and mindful parenting improved, whereas parental stress only improved at 1-year follow-up. Child age, child gender, ADHD medication, parental ADHD, and parent participation did not predict child outcome. Parent gender however interacted with parental ADHD to predict child outcome; children of fathers (but not mothers) above the ADHD threshold improved more than children of fathers below the ADHD threshold at post-test and at 8-week follow-up. Reduced paternal ADHD from pre- to post-test mediated this effect.

Conclusions: Family MBI (MYmind) may reduce childhood ADHD and improve parental functioning. Fathers with ADHD symptoms appear important in helping offspring with ADHD

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Mindfulness (N Y). 2021 Nov;12:2794-809.

A MINDFULNESS-BASED INTERVENTION FOR ADOLESCENTS WITH BEHAVIOR DISORDERS: CONTROLLED TRIAL WITH PARTIAL RANDOMIZATION.

Roux B, Pérez-Peña M, Philippot P.

Objectives: Mindfulness-based interventions (MBIs) are widely used with adults and children to treat anxiety and depressive symptomatology. However, only few studies with a rigorous design have been conducted among adolescents with behavior disorders even though this population suffers from symptoms that can be addressed by MBIs such as inattention and hyperactivity. The present study investigated the effect of a MBI on internalizing and externalizing symptoms in adolescents with behavior disorders.

Methods: A sample of adolescents with behavior disorders (N = 129) living in a residential service for youth were allocated to one of three treatment conditions: a treatment as usual condition, a health psychoeducation condition, and a MBI condition. The three groups were compared over a period of three assessment points plus a 1-year follow-up on self-report questionnaires, questionnaires rated by adolescents' educators, and behavioral tasks. To test the MBI efficacy, multilevel analyses were performed, controlling for gender and medication.

Results: All groups improved on most measures, likely due to the intensive institutional care provided by default. The MBI significantly improved attentional capacities, but had no significant differential impact on depressive symptomatology, mindfulness, impulsivity, hyperactivity, or oppositional behaviors in comparison to the other conditions.

Conclusions: MBIs may help adolescents with behavior disorders at the attentional level. Further research is needed to determine the potential benefits of mindfulness on externalizing and internalizing symptoms in this population

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Minerva Pediatrics. 2021;73:398-404.

SERUM CYTOKINES IN PEDIATRIC NEUROPSYCHIATRIC SYNDROMES: FOCUS ON ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Donfrancesco R, Nativio P, Borrelli E, et al.

BACKGROUND: Inflammation may represent a common underlying mechanism in a wide range of diseases, including neuropsychiatric disorders. Cytokine involvement has been investigated in some studies on patients with childhood neuropsychiatric diseases. The aim of this study was to determine whether cytokines are involved in ADHD to provide a rationale for immune-based therapeutic strategies in this disorder.

METHODS: Sixty children were studied: 34 consecutive drug-naïve children with ADHD (30 males and 4 females; mean age of 10.10 years, SD=2.43 age) and 26 healthy control children (22 males and 4 females; mean age of 10.70 years, SD=1.81). All cytokines but IL-2 (IL4-IL6-IL10- IL17-TNFA and IFNG) were studied by ELISAs; IL-2 was instead studied by means of paired anti-cytokine Abs and cytokine standards obtained from PharMingen.

RESULTS: Data reveal higher IL-6 and IL-10 levels in ADHD patients than in the control group (P=0.03). No differences emerged between the two groups for the other cytokines.

CONCLUSIONS: Our study showed an imbalance between pro- and anti-inflammatory cytokines that may play a pivotal role in the pathogenesis of ADHD

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NeuroImage. 2021;245.

COMMON FUNCTIONAL BRAIN NETWORKS BETWEEN ATTENTION DEFICIT AND DISRUPTIVE BEHAVIORS IN YOUTH.

Wong TY, Zhang H, White T, et al.

Attention deficits (AD) and disruptive behavior (DB) are highly comorbid youth externalizing behaviors. This study aimed to study reliable functional brain networks shared by AD and DB in youth aged from 8 to 21 years from the Philadelphia Neurodevelopmental Cohort (PNC). The PNC study assessed AD and DB behaviors via Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). This study employed sparse canonical correlation analysis (SCCA) to examine the correlation of AD and DB behaviors with resting-state functional connectivity maps of the brain regions identified via activation likelihood estimation (ALE) meta-analyses on attention deficit/hyperactivity disorder (ADHD) and DB disorder (DBD). Our meta-analyses identified that the middle cingulate cortex, pre-supplementary motor area (pre-SMA), and striatum had a great consensus in existing ADHD studies and the amygdala and inferior parietal lobule were consistently found in existing DBD studies. Our SCCA analysis revealed that the AD and DB behavioral items relevant to inattention and delinquency were correlated with the functional connectivity of the pre-SMA with the ventral attentional and frontoparietal networks (FPN), and the striatum with the default mode (DMN) and dorsal attentional networks. The AD and DB behavioral items relevant to inattention and irritability were associated with the functional connectivity between the amygdala and the DMN and FPN. Our findings suggest that the functional organization of the ADHD- and DBD-related brain regions provides insights on the shared neural basis in AD and DB

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NeuroImage. 2021 Dec;244.

EMPIRICAL BAYES ESTIMATION OF PAIRWISE MAXIMUM ENTROPY MODEL FOR NONLINEAR BRAIN STATE DYNAMICS.

Jeong SO, Kang J, Pae C, et al.

The pairwise maximum entropy model (pMEM) has recently gained widespread attention to exploring the nonlinear characteristics of brain state dynamics observed in resting-state functional magnetic resonance imaging (rsfMRI). Despite its unique advantageous features, the practical application of pMEM for individuals is limited as it requires a much larger sample than conventional rsfMRI scans. Thus, this study proposes an empirical Bayes estimation of individual pMEM using the variational expectation-maximization algorithm (VEM-MEM). The performance of the VEM-MEM is evaluated for several simulation setups with various sample sizes and network sizes. Unlike conventional maximum likelihood estimation procedures, the VEM-MEM can reliably estimate the individual model parameters, even with small samples, by effectively incorporating the group information as the prior. As a test case, the individual rsfMRI of children with attention deficit hyperactivity disorder (ADHD) is analyzed compared to that of typically developed children using the

default mode network, executive control network, and salient network, obtained from the Healthy Brain Network database. We found that the nonlinear dynamic properties uniquely established on the pMEM differ for each group. Furthermore, pMEM parameters are more sensitive to group differences and are better associated with the behavior scores of ADHD compared to the Pearson correlation-based functional connectivity. The simulation and experimental results suggest that the proposed method can reliably estimate the individual pMEM and characterize the dynamic properties of individuals by utilizing empirical information of the group brain state dynamics

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Neurol India. 2021 Nov;69:1518-23.

MACHINE LEARNING TECHNIQUES FOR THE DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FROM MAGNETIC RESONANCE IMAGING: A CONCISE REVIEW.

Periyasamy R, Vibashan VS, Varghese GT, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a neuro-developmental disease commonly seen in children and it is diagnosed via extensive interview procedures, behavioral studies, third-party observations, and comprehensive personal history. ADHD causes regional atrophy in brain regions and alters the pattern of functional brain connectivity networks. Automated/computerized methods based on magnetic resonance imaging (MRI) can replace subjective methods for the identification of ADHD.

OBJECTIVES: The aim of this study was to analyze various machine-learning algorithms for ADHD by feeding in vital input features extracted from functional brain connectivity and different existing methods and to review factors crucial for the diagnosis of ADHD.

METHODS: This paper is a concise review of machine learning methods for the diagnosis of ADHD from MRI. Techniques for feature extraction, dimensionality reduction/feature selection, and classification, employed in the computerized techniques for the diagnosis of ADHD from MRI and the accuracy of classification offered by the individual methods, are focussed on the review.

CONCLUSIONS: Machine learning algorithms with features of functional brain connectivity networks as input, with hierarchical sparse feature elimination, exhibits the highest accuracy. Augmentation of the behavioral features does not contribute much to increased accuracy. The level of accuracy offered by the frameworks meant for the computer-aided diagnosis of ADHD, available in the literature, does not justify their feasibility in clinical practice. Computerized methods that exploit highly specific biomarkers of ADHD like brain iron concentration in Globus Pallidus, Putamen, Caudate nucleus, and thalamus as features are not available

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Neurophysiol Clin. 2021.

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) ALTERS THE PATTERN OF INFORMATION PROCESSING IN CHILDREN WITH ADHD: EVIDENCE FROM DRIFT DIFFUSION MODELING.

Nejati V, Rasanan AHH, Rad JA, et al.

Objective: Performance accuracy and reaction time in cognitive tasks are routinely used to evaluate the efficacy of tDCS to affect cognitive task performance. tDCS alters the excitability of targeted brain areas and thereby alters performance of cognitive tasks. The drift diffusion model (DDM) provides some additional measures to explore information processing style, such as (non)decision time, bias for decision, and speed of information processing. DDM parameters are informative for the study of cognitive impairments in children with ADHD. In the present study, we aimed to evaluate the impact of tDCS on cognitive performance via DDM measures.

Methods: This study conducted DDM modeling and reanalysis of two exploratory, single-blinded, within-subject design experiments, which were published earlier. In the first experiment, twenty- four children with ADHD performed a Go/ No- Go task during anodal or sham tDCS over the right dlPFC. In the second experiment, twenty- five children with ADHD performed the 1- back working memory task during anodal or sham tDCS over the left dlPFC. We reanalyzed the data after DDM modeling.

Results: The conventional performance measures revealed no significant effect of tDCS on No- Go accuracy in the first experiment and 1-back accuracy in the second experiment. The 1-back reaction time and speed-accuracy tradeoff were however improved under the real stimulation condition. The DDM measures identified

increased No-Go- bias and decision time with respect to inhibitory control, and an increased threshold and amount of information required for response in the 1- back test.
Conclusion: In children with ADHD, anodal tDCS over the right dlPFC induces more conservative and less impulsive decisions. Furthermore, anodal tDCS over the left dlPFC enhanced efficacy of working memory performance with respect to agility and capacity. The experimental results show that drift diffusion modeling is useful for evaluation of the impact of tDCS on the style of information processing

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Neuropsychopharmacology. 2021;46:9-10.
NEURAL NETWORK MODELING OF TRIGEMINAL NERVE STIMULATION IN ADHD.
Loo S.
Background: External trigeminal nerve stimulation (TNS) is a noninvasive method of brain modulation that recently received FDA device clearance for the treatment of children with ADHD, ages 7-12 years old. In the pivotal trial of TNS, subjects randomized to active TNS exhibited significantly greater improvements in ADHD symptoms ($p < .005$) relative to sham and 52% of participants showed clinically meaningful improvement) compared to 14% in the sham group ($p=.003$). Within the same trial, electroencephalography (EEG) recorded at baseline and after 4-weeks of TNS treatment revealed significant treatment group effects in the right frontal (F4) and frontal midline (Fz) channels. Subsequent analyses indicate that treatmentrelated change in F4 theta power (AUC=.81, $p=.03$) was significantly predictive of TNS treatment response, suggesting this is a biomarker, and potentially part of the neural mechanism mediating treatment response. In the current presentation, we examine posttreatment resting state functional connectivity and clinical correlates to more fully characterize the neural network underlying TNS treatment related improvements in ADHD.
Methods: 62 children aged 8-12 years, with KSADS-diagnosed ADHD were randomly assigned to four weeks of nightly active or sham TNS treatment. Primary outcomes were clinician rated ADHD Rating Scale (ADHD-RS) and Clinical Global Impression (CGI) scales. Secondary outcomes included baseline cognitive measures, weekly ratings of behavioral executive functions (BRIEF), and electroencephalography (EEG) measures at baseline and posttreatment. To estimate resting state functional connectivity, the following procedures were used: 1. EEG data are decomposed using independent components analyses, 2. Dipole density was calculated for 76 regions of interest (ROIs), 3. Information flow between ROIs based on contribution of each dipole source, 4. Between-group, pixelwise t-tests were performed for each connection between ROIs, 5. Run permutation test to perform cluster-level correction to control for multiple comparisons.
Results: After 4-weeks of TNS treatment, the active group exhibited significantly decreased functional connectivity along the midline, particularly between mid-and right-frontal (i.e., right superior frontal gyrus, anterior cingulate) connections with parietal (i.e., precuneus, right/left superior parietal) and occipital (i.e., calcarine, right/left superior occipital) nodes. In addition, the right frontal to superior parietal connection was significantly negatively correlated with right frontal (F4) EEG theta power ($r=-.51$, $p=.004$) and trended toward significance with ADHD inattentive symptoms ($r=.28$, $p=.14$), indicating that lower connectivity is associated with higher F4 theta power and lower inattention symptoms. The right frontal to left cuneus connection was correlated with BRIEF Initiate ($r=.41$, $p=.03$) and Working Memory ($r=.35$, $p=.07$) scores, indicating lower connectivity is associated with better executive functioning. These data suggest that right frontal (F4) EEG power modulation is a biomarker for putative changes in fronto-parietal (FP) network connectivity, both of which are associated with improved executive function and reduced ADHD symptoms.
Conclusions: The neural mechanism underlying TNS treatment effects in ADHD is activation of the fronto-parietal network resulting in increased EEG power in the mid-and right-frontal electrodes and subsequent improvement in executive functions and ADHD behaviors

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Neuropsychopharmacology. 2021;46:147.
CHARACTERIZING DE NOVO DAMAGING CODING VARIANTS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Olfson E, Cappi C, Farhat L, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable psychiatric condition. Identifying genes that contribute to ADHD risk is a critical step in understanding underlying mechanisms and developing novel treatments. However, decades of candidate gene studies have not identified reproducible

findings, and only recently have the first genome-wide significant common variants been identified in a large genome-wide association study. Similar to other childhood-onset neuropsychiatric conditions, it is likely that rare genetic variants with larger effects also play an important role in the etiology of ADHD. In the largest case-control DNA sequencing study, a similar burden of ultra-rare protein truncating variants in evolutionary constrained genes was observed in individuals with autism spectrum disorder (ASD) and ADHD, suggesting that study designs that have led to risk gene identification in ASD may also be successful in ADHD. In the field of autism, DNA sequencing studies of parent-child trios with de novo variant detection have identified a plethora of highconfidence risk genes, which are already impacting clinical care. This approach has also been successful in discovering risk genes in Tourette's disorder and obsessive-compulsive disorder but has yet to be leveraged to find risk genes for ADHD. This is because the only published DNA sequencing studies of parent-child trios with ADHD have small sample sizes. Here, we address this gap in the field by conducting whole-exome DNA sequencing in a larger cohort of parent-child trios impacted by ADHD to shed light on the etiology of this impairing condition.

Methods: Whole-exome DNA sequencing was performed in 80 parent-child trios (240 individuals total) where the child had a primary diagnosis of ADHD. Exclusion criteria included a diagnosis of ASD, intellectual disability, psychosis, mood disorder, or clinically significant medical or neurological disease. Exome capture was performed using the IDT xGen Exome Panel, followed by whole-exome sequencing on the Illumina NovaSeq with 80x coverage. These results were compared to 225 previously sequenced unaffected parent-child trios. After quality control, we examined 73 ADHD trios and 224 control trios for de novo single nucleotide variants and indels following the Genome Analysis Toolkit (GATK) best practice guidelines. We focused on variants that were rare in reference databases and that were either likely gene disrupting (including variants causing premature stopcodons, altered splice sites, and frameshifts) or missense variants that were predicted to be damaging based on a missense badness, PolyPhen-2, constraint (MPC) score >2. We then explored overlap with high-confidence risk genes for other conditions and conducted exploratory pathway analyses.

Results: Our results show a trend towards an increased rate of de novo likely gene disrupting variants and missense variants predicted to be damaging in ADHD cases compared with controls (Rate ratio= 1.6, p=0.13), suggesting that further study of de novo variation in larger cohorts may lead to risk gene discovery. Furthermore, we found that genes harboring de novo damaging variants in the ADHD cases overlap with known risk genes for other disorders. Of note, two unrelated individuals with ADHD have de novo likely gene disrupting variants in the lysine demethylase 5B gene (KDM5B), which is a previously identified high-confidence risk gene for ASD. This highlights the potential role of pleiotropy in these childhood neuropsychiatric conditions. Exploratory network analyses show enrichment of genes with de novo damaging variants in several canonical biologic pathways. Given these promising findings, we are currently sequencing an additional 70 parent-child trios impacted by ADHD. We will plan to present these combined sequencing results examining de novo and rare inherited variants in 150 ADHD parentchild trios at ACNP.

Conclusions: Whole-exome DNA sequencing of parent-child trios with ADHD can be used to identify de novo damaging variants. These damaging variants occur in genes that overlap with risk genes for other related neuropsychiatric conditions and are enriched for canonical biological pathways. Overall, our results demonstrate that whole-exome DNA sequencing with de novo variant detection provides a powerful and previously unexplored path for identifying new risk genes for ADHD and relevant biologic pathways. By increasing our sample size, we hope to provide additional insights into the underlying biology of this common and impairing condition

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Neuropsychopharmacology. 2021;46:123-24.

PARENT COGNITION AND BEHAVIOR PREDICT VARIABLE OUTCOMES IN CHILDREN WITH RAS/MITOGEN-ACTIVATED PROTEIN KINASE (RMK) PATHWAY PATHOGENIC MUTATIONS.

Bruno J, Green T.

Background: Mounting evidence supports the role of the Ras/ mitogen-activated protein kinase (RMK) pathway in neurodevelopmental disorders. RMK pathogenic mutations affect physical, cognitive, and behavioral phenotypes, resulting in specific neurogenetic disorders collectively termed RASopathies. Noonan syndrome (NS) is the most common RASopathy. Despite knowledge of specific genetic mutations that cause NS, there is significant phenotypic variability in cognition and behavior traits. Here we examine

the correspondence between non-carrier parents and children (probands) with NS across and within cognitive and behavioral phenotypic traits. We also examine how RMK pathogenetic mutations modify trait correspondence.

Methods: Participants included 45 families of children age 4-12 years with NS and either PTPN11 (N = 33) or SOS1 (N = 10) mutation. Parent (one per family) and proband cognition were assessed with Weschler full-scale IQ (FSIQ). IQ subtest data were examined to understand parent/proband correspondence patterns across verbal and performance domains. Parent/proband behavior was assessed with the Achenbach scales for depression, anxiety, somatic, and attention deficit hyperactivity (ADHD) problems. Most families (N = 37) provided behavioral data from both parents, which was averaged. Five families provided behavioral data from one parent, and three families were missing parent behavioral data. For each trait, we used effect sizes to assess offsets (parent -proband scores), stepwise regressions to examine how trait correspondence is modified by RMK mutation, slopes to estimate variable penetrance within a trait.

Results: Offsets indicated that proband cognition (FSIQ scores) was shifted down relative to parent scores: mean difference = 12.535, $p < 0.001$, Cohen's $d = 1.04$. For behavior, proband scores were shifted up (indicating greater levels of behavior problems) relative to parent scores for depression ($d = -0.82$), anxiety ($d = -0.82$), and ADHD problems ($d = -0.82$, all p's < 0.001, survive Bonferroni correction) but not somatic problems $p > 0.10$, $d = -0.57$). Regression results indicate that parent FSIQ was a significant predictor of proband IQ after controlling for proband gene mutation (PTPN11 or SOS1, $F = 3.270$, $+f = 0.344$, $p = 0.048$, +öR2 = 109, $p = 0.030$). Upon examination of verbal and performance subtests subtest data, the model and change in R2 were significant only for block design ($F = 6.361$, $+f = 0.471$, $p = 0.004$, +öR2 = 0.206, $p = 0.002$). Subsequent regression results indicated that parent behavior was a significant predictor of proband behavior after controlling for proband gene mutation (PTPN11 or SOS1) and parent FSIQ. Results were significant for depression ($F = 7.643$, $+f = 0.607$, $p < 0.001$, +öR2 = 0.363, $p < 0.001$), anxiety ($F = 3.971$, $+f = 0.421$, $p = 0.015$, +öR2 = 0.165, $p = 0.008$) and ADHD problems ($F = 4.153$, $+ f = 0.395$, $p = 0.013$, +öR2 = 0.154, $p = 0.01$). Specifically, parent FSIQ did not account for a significant proportion of variance in proband behavior (ADHD problems +öR2 = 0.075, $p = 0.064$, anxiety and depression problems p's > 0.10).

Conclusions: We demonstrate that parent cognition and behavior are useful in predicting proband outcomes, specifically in children with NS. First, the offsets or differences between parent and proband scores indicate that the penetrance of NS varies depending upon the trait examined (between traits). Offsets and corresponding effect sizes were greatest for FSIQ, yet most traits examined (FSIQ, depression, anxiety, and ADHD) demonstrated large effect sizes. Regression results demonstrate significant relationships between parent and proband traits and variable penetrance within traits after accounting for gene mutation. Slopes for cognition (FSIQ and block design) were significantly less than 1, indicating variable penetrance; higher parent scores were associated with a greater difference between parent and proband scores. IQ subtest data revealed a significant predictive relationship between parent/proband block design and lack of significant relationships with parent/proband verbal subtests. This result contrasts with previous findings in other neurogenetic syndromes and the general population, which indicate significant relationships across IQ domains and stronger relationships between verbal relative to performance domains. The present results may indicate that, in addition to shifting IQ below expected based on age-norms, NS also disrupts the parent/child heritability of verbal IQ domains. Parent depression, anxiety, and ADHD were significant predictors of proband behavior. Furthermore, parent behavior traits may hold a unique role in understanding proband behavior that is over and beyond the contribution of parental IQ. For behavior traits, the slopes were not significantly different from 1, suggesting that the difference between parent and proband behavior does not vary with parent scores (no evidence for variable penetrance). Our results demonstrate that a variety of parent traits are useful in estimating variable penetrance in NS. Utilizing parent traits in a predictive framework affords control for various environmental and genetic factors and thus provides a more individualized estimate of expected proband outcomes. Further refinement of predictive modeling to estimate penetrance will advance a precision medicine approach to treating NS and other neurogenetic syndromes

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FUNCTIONAL NETWORK CONNECTOME ABNORMALITIES ASSOCIATED WITH FAMILIAL RISK FOR DEVELOPING BIPOLAR I DISORDER IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Qin K, Lei D, Zhu Z, et al.

Background: Comorbid attention-deficit/hyperactivity disorder (ADHD) is highly prevalent in youth with bipolar I disorder (BDI), and ADHD symptoms commonly precede the initial onset of mania and reduce the age at onset of mood symptoms. Having a first-degree relative with BD-I substantially increases the risk of developing BD-I, and there is a high prevalence of ADHD in youth with a first-degree relative with BD-I. Although youth with a firstdegree relative with BD-I and ADHD symptoms are at elevated risk for developing BD-I, associated central pathophysiological mechanisms are poorly understood. The initial onset of BD-I frequently occurs during adolescence, a developmental period associated with robust maturational changes in prefrontal cortex structural and functional connectivity. Graph theory analysis is increasingly being used to characterize topological properties of brain network organization and connectivity. In this crosssectional resting-state MRI study, we characterized the topology of the functional connectome in ADHD youth with (high-risk) and without (mid-risk) a first-degree relative with BD-I and a healthy comparison group (low-risk). Exploratory analyses evaluated associations between functional topological metrics and clinical measures of ADHD and mood symptom severity.

Methods: Resting-state MRI scans were acquired from n = 37 adolescents with ADHD and at least one biological parent or sibling with BD-I (high-risk), n = 45 ADHD adolescents with no first- or second-degree relative with a mood or psychotic disorder (mid-risk), and n = 32 healthy adolescents with no personal or family history of a DSM-5 Axis I psychiatric disorder (HC, low-risk). All ADHD patients met DSM-5 criteria for ADHD (all types), had no exposure to psychostimulants for at least 3 months prior to scanning, and had no comorbid mood, anxiety, conduct, eating or psychotic disorders. Whole-brain functional connectivity network was constructed for each participant. Global- and nodal-level network topological properties were calculated based on individual functional networks using graph theoretical analysis. Global topological metrics included global efficiency (Eglob), local efficiency (Eloc), clustering coefficient (Cp), characteristic path length (Lp), normalized clustering coefficient (+¡), normalized characteristic path length (++) and small-worldness scalar (¤â). The nodal topological metrics reflecting centrality included degree, betweenness, and efficiency. The comparison of network topological metrics across groups and post-hoc analyses were conducted using the non-parametric permutation analysis (10000 permutations) with a one-way ANOVA model. Bonferroni correction was applied for subsequent post-hoc pairwise comparisons. Correlation analyses evaluated associations between significantly different functional topological metrics and clinical measures of mood and ADHD symptom severity, and FDR correction was applied to control for false positives.

Results: A total of n = 114 psychostimulant-free adolescents were included in the functional connectome analysis, and there were no group differences in age, sex, or BMI. Significant group differences were observed for the global topological metrics Eglob (p = 0.026) and Lp (p = 0.028). Eglob was significantly decreased (p = 0.005) and Lp (p = 0.003) increased in mid-risk ADHD adolescents compared to low-risk HC subjects. Brain regions with significant group differences in at least two of three nodal topological metrics included the left dorsolateral superior frontal gyrus (SFG), right middle orbitofrontal cortex (OFC), right hippocampus, left amygdala, left inferior parietal lobule (IPL) and right middle temporal pole (MTG). Compared with low-risk HC subjects, high-risk ADHD adolescents exhibited abnormal nodal topological centralities in the left dorsolateral SFG, right hippocampus and right MTG, whereas mid-risk ADHD adolescents exhibited abnormalities in the right middle OFC, right hippocampus, and left amygdala. Significant differences between high-risk and mid-risk ADHD groups were found in the left IPL. Among all ADHD subjects, the degree (r = -0.28, p = 0.002) and efficiency (r = -0.27, p = 0.003) of the right hippocampus, and the degree (r = -0.27, p = 0.003) and efficiency (r = -0.27, p = 0.003) of the right middle OFC, were inversely correlated with ADHD-RS total score. Hyperactive/impulsive scores were inversely correlated with global efficiency (r = -0.25, p = 0.007) and right hippocampus degree (r = -0.29, p = 0.002), and positively correlated with characteristic path length (r = 0.26, p = 0.005) and betweenness (r = 0.29, p = 0.001) of left dorsolateral SFG. The degree (r = 0.27, p = 0.004) and betweenness (r = 0.25, p = 0.007) of the left dorsolateral SFG was positively correlated with YMRS total scores.

Conclusions: This cross-sectional analysis found that youth at midand high-risk for developing BD-I exhibit patterns of functional network abnormalities compared with low-risk youth. Common abnormal regional centralities were observed in the right hippocampus for all ADHD adolescents regardless of risk for

developing BD-I, whereas high-risk subjects exhibited unique abnormalities in topological metrics in the inferior parietal gyrus. These findings suggest that familial risk for BD-I in conjunction with ADHD is associated with a pattern of regional functional network topological abnormalities that may represent a unique prodromal phenotype

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ATTENTION TRAINING IN ANXIETY DISORDERS ALTERS CINGULO-OPERCULAR NETWORK SIGNAL.

Drysdale A, Myers M, Harper J, et al.

Background: Altered attention may be a core cognitive feature of anxiety disorders. Extensive research has shown that anxiety disorders in children and adults are linked with biases in threatrelated attention. Recent work implicates additional aspects of attention and its underlying neural networks in pediatric anxiety disorders. Our laboratory found that increased anxiety positively correlated with increased stimulus-driven attention and brain activity within the ventral attention network. We designed a novel treatment to see if targeting these processes could reduce clinical anxiety, completing a small clinical trial in pediatric anxiety disorders. At ACNP 2020, we presented the initial results of this clinical trial. Cognitive training successfully lowered anxiety and decreases in anxiety correlated with changes in goal-directed attention. Here, we analyze how cognitive training affected the cingulo-opercular network (CON) and the relationship of network changes to anxiety improvements.

Methods: In a small (n = 18, 12 female, ages 8-12) clinical trial (Clinicaltrials.gov, ID # NCT03790696), we recruited children with generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder. Subjects were initially screened using validated measures (SCARED and Mood and Feelings Questionnaire) and then diagnosed using a semi-structured interview (KSADS-PL). We excluded subjects with diagnoses of attention deficit hyperactivity disorder, developmental disorders, or schizophrenia. Participants underwent twice weekly cognitive attention training for eight (8), forty-five (45) minute sessions. In the training task, participants received cues indicating the side of the screen on which the target would appear after a variable cue-target interval. We measured anxiety before, during, and after training using the SCARED-parent report as our primary measure. Participants completed pre-and post-training neuroimaging including fMRI of an attention task. We analyzed BOLD signal within inferior frontal gyrus (IFG) regions of interest, segmented by their involvement in specific attention-related cognitive networks. We modeled the effects of training and anxiety on BOLD signal. We examined the relationship of CON signals to anxiety changes by correlating task-related signals in an IFG CON node to anxiety at baseline and after training.

Results: Participants' anxiety decreased significantly after training as measured by the SCARED-parent report (mean change [95% CI]:-22.44 [-16.96-27.92], $p < 0.001$). BOLD signals in a CON node showed a significant main effect of training, decreasing after training ($p < 0.02$). We also found a significant interactive effect of training and anxiety on this CON node ($p < 0.01$). Prior to training, there is no significant correlation between CON node signal and anxiety ($r = -0.45$, $p = 0.14$). After training, there is a significant positive correlation between the CON node and anxiety ($r = 0.68$, $p < 0.015$).

Conclusions: We completed a small clinical trial using cognitive attention training to treat pediatric anxiety disorders. After training, we observed reduced anxiety, altered attention, and signal changes within neural attention networks. We specifically focused on how training affected a node of the cingulo-opercular network. This network is involved in executive function including stable task-level control. We found that attention training lowered signals in a CON node. Further, there was a shift in the relationship between this node's activity and anxiety after attention training. While there was no relationship between anxiety and signal in this CON node at baseline, signal within this node after training was positively related to anxiety. Participants whose signal remained elevated showed higher levels of residual anxiety. Taken together, these findings implicate successful reduction in CON signal as a key aspect of successful treatment via attention training. This work highlights the fundamental role of attention and its related networks in anxiety disorders. We plan to expand on this work by characterizing individual attention profiles in the search for personalized intervention targets

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BRAIN NETWORK STRUCTURAL CONNECTOME ABNORMALITIES IN ADOLESCENTS AT VARYING RISK FOR BIPOLAR I DISORDER: A CROSS-SECTIONAL MRI STUDY.

Zhu Z, Lei D, Qin K, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that significantly increases risk for developing other psychiatric disorders including bipolar I disorder (BD-I). Comorbid ADHD is highly prevalent in youth with BD-I, and ADHD symptoms commonly precede the initial onset of mania and reduce the age at onset of mood symptoms. Having a first-degree relative with BD-I also significantly increases the risk for developing BD-I, and there is high prevalence of ADHD in youth with a firstdegree relative with BD-I. Furthermore, the initial onset of mania, and by definition BD-I, frequently occurs during adolescence, a developmental period associated with robust maturational changes in prefrontal cortex structural and functional connectivity. Previous structural MRI studies have found that youth with BD-I or ADHD exhibit morphological abnormalities in prefrontal brain regions compared with healthy typically developing youth. However, the majority of prior studies did not control for familial risk of BD-I, ADHD comorbidity, and/or psychostimulant exposure, and there have been no studies that have directly compared psychostimulant-free ADHD youth with and without a first-degree relative with BD-I. In this crosssectional study, we used graph-based network analysis based on structural MRI data to interrogate topological properties of brain networks in ADHD adolescents with and without a first-degree relative with BD-I and a healthy control group. We additionally evaluated relationships between topological metrics and mood and ADHD symptom ratings.

Methods: Three groups of psychostimulant-free adolescents (10-18 years) were recruited: adolescents with ADHD and at least one biological parent or sibling with BD-I (high-risk), adolescents with ADHD and no first- or second-degree relative with a mood or psychotic disorder (mid-risk), and healthy adolescents with no personal or family history of psychiatric illness (HC, low-risk). Highresolution 3D T1-weighted images were collected using a Philips 3.0 T MR scanner. Brain networks were constructed based on the similarity of morphological features across regions and analyzed using a graph theory approach. Network metrics, which include seven global-level graph metrics (characteristic path length, clustering coefficient, normalized clustering coefficient, normalized characteristic path length, small-worldness, global efficiency, and local efficiency) and three nodal-level properties (degree, efficiency and betweenness) were calculated. We used ANOVA models to compare the structural connectome characteristics across groups, and post hoc pairwise permutation tests were conducted for measures that differed between groups. Significant topological metrics with $p < 0.05$ were reported. Partial correlation analysis was used to assess the relationships between each topological metric and clinical measures of mood and ADHD symptom severity variables. The potential confounding effects of age and sex were controlled for in the models, and the threshold for results were set to an expected FDR of 5% to correct for multiple comparisons.

Results: A total of n = 149 adolescents (mean age: 14.1 -¦ 2.5 years, 36% female) were included in the analysis (low-risk, n = 49; mid-risk, n = 50; high-risk, n = 50). No significant group differences were observed for age, sex, or BMI. The mid-risk and highrisk ADHD groups exhibited similar differences when compared with low-risk HC subjects, mainly in the default-mode network (DMN) and central executive network (CEN), including bilateral gyrus rectus, right superior parietal gyrus, and right triangular inferior frontal gyrus. Topological alterations in the salience network (SN), including right opercular inferior frontal gyrus and right pallidum, were found between the high-risk group and both mid- and low-risk groups. Significant abnormalities in global network properties were found only in the high-risk group when compared with low-risk HC group, which included reduced characteristic path length ($p = 0.008$), increased global efficiency ($p = 0.008$), and increased local efficiency ($p = 0.041$). ADHD-RS hyperactivity/impulsivity subscale scores were positively correlated with the degree ($r = 0.34$, $p = 0.001$) and nodal efficiency ($r = 0.27$, $p = 0.008$) of right triangular inferior frontal gyrus. There were no significant correlations between topological metrics and mood symptom ratings after correcting for multiple comparisons.

Conclusions: Both high- and mid-risk ADHD adolescents exhibit topological alterations in three major intrinsic connectivity networks (i.e., CEN, DMN and SN) compared to low-risk HC subjects. However, topological alterations in the SN were only observed in the high-risk group. These findings suggest that familial risk for BD-I in conjunction with ADHD is associated with different regional structural network

abnormalities compared with ADHD alone and may represent a unique prodromal phenotype relevant to the risk for developing BD-I

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NEURAL ACTIVATION DURING RESPONSE INHIBITION, BUT NOT ERROR PROCESSING, DIFFERENTIATED DISTINCT SYMPTOM PROFILES OF IRRITABILITY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE ABCD STUDY.

Tseng WL, Shu Lee K, Xiao J, et al.

Background: Irritability, characterized by developmentally inappropriate temper outbursts and low frustration tolerance (Leibenluft, 2017), is a hallmark symptom of disruptive mood dysregulation disorder (DMDD) in the DSM-5. Irritability commonly co-occurs with attention-deficit/hyperactivity disorder (ADHD; Shaw et al., 2014). It is estimated that >35% of youths in the community samples, and >70% in the clinical samples, have both chronic irritability/DMDD and ADHD (Shaw et al., 2014; Leibenluft and Kircanski, 2021). While individual differences exist in the symptom manifestations of irritability and ADHD, the shared and nonshared neurobiological pathways underlying these differential symptom profiles are not well-understood. Here, we used a latent phenotyping approach to identify youths with distinct phenotypic profiles of irritability and ADHD symptoms. Next, we examined differences between these phenotypic profiles in behavioral performance and neural responses during a Stop Signal Task that probed response inhibition and error processing-two neurocognitive processes central to both irritability and ADHD (Kessel et al., 2016; Shaw et al., 2014; Walcott and Landau, 2004).

Methods: Data were from the Adolescent Brain and Cognitive Development (ABCD) study at baseline (N=11,875, mean age=9.9 years, female=47.8%). Irritability symptoms were assessed using 4 items from the parent reports of the computerized Kiddie-Structure Assessment of Affective Disorders and Schizophrenia (KSADS). These included 1 item from the DMDD module (i.e., temper outbursts ГёÑ 3 times/week), 2 items from the oppositional defiant disorder module (i.e., often touchy or easily annoyed; often loses temper), and 1 item from the major depressive disorder module (i.e., irritability). ADHD symptoms were assessed using 18 items from the ADHD module of the parent-reported KSADS. Behavioral responses and neural activations during the Stop Signal fMRI Task (Casey et al., 2018) were measured. The main behavioral measure was the Stop Signal reaction time. Neural measures were the beta coefficients representing BOLD (blood-oxygen-level-dependent) signal changes during two contrasts of interest: Correct Stop vs. Correct Go (response inhibition) and Incorrect Stop vs. Correct Go (error processing). We focused on 29 brain regions that showed good test-retest reliability (i.e., intra-class correlation [ICC] > .60; Korucuoglu et al., 2021) during this task. Taking a latent modeling approach, we first conducted latent class analysis (LCA) to identify unique irritability and ADHD symptom profiles. We then conducted exploratory factor analysis and then confirmatory factor analysis across the 29 brain regions to derive networks of regions with coherent coactivation patterns. Next, we examined whether the task behavioral measure (i.e., Stop Signal reaction time) and neural activations differed across the LCA-derived groups with distinct symptom profiles.

Results: Using LCA, we identified four groups of youths based on irritability and ADHD symptoms; Akaike Information Criterion (AIC) = 56111.24, Bayesian Information Criterion (BIC) = 56782.04, sample-size adjusted BIC (ABIC) = 56492.85, Entropy = .97, bootstrapped parametric likelihood ratio test (BLRT) < .001, smallest class proportion = 2.4%. These four groups are: (1) high irritability and low ADHD (n = 279, 2.4%); (2) high ADHD and low irritability (n = 901, 7.7%); (3) high ADHD and high irritability (n = 787, 6.7%); (4) and low irritability and low ADHD symptoms (n = 9,781, 83.3%). Exploratory factor analysis and subsequent confirmatory factor analysis revealed two distinct yet correlated networks - a response inhibition network that included the left supramarginal gyrus, left inferior parietal cortex, and left pars orbitalis and an error processing network that included the left and right lateral orbital-frontal cortex and left pars orbitalis. The four LCA groups did not differ in Stop Signal reaction time ($F_{3, 5246} = 1.08$, $p > .05$). The four groups differed in neural activations during response inhibition but not error processing. Specifically, during response inhibition, relative to those with low irritability and low ADHD (Intercept = 0), those with high ADHD and high irritability showed increased activation (Intercept = .21), whereas those with high irritability and low ADHD (Intercept = -.54) and those with high ADHD and low irritability (Intercept = -.15) both showed decreased activation (especially so for those with high irritability and low ADHD). Results adjusted for potential confounds such as age, sex, sociodemographic variables (e.g., caregiver education, marital status, and total household income), and scanning sites.

Conclusions: Using latent modeling, this study showed that neural activation during response inhibition, but not error processing, differentiated distinct symptom profiles of irritability and ADHD in youths. Specifically, the co-occurrence of irritability and ADHD symptoms was characterized by heightened activation in the response inhibition network, whereas the presence of irritability or ADHD alone was characterized by decreased activation in the same network. Dissociable neurobiological pathways across distinct symptom profiles of irritability and ADHD may provide novel insights into the potential neural mechanisms for change that are specific to unique symptom profile, paving the way for transdiagnostic interventions and precision medicine

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ARTIFICIAL INTELLIGENCE-BASED PREDICTION OF AGGRESSIVE BEHAVIOR IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mishra R, Park C, Atique M, et al.

Background: Attention deficit hyperactivity disorder (ADHD) can be associated with disruptive behavior, including aggression. Episodes of aggressive behavior, whether verbal or physical, may occur without noticeable triggers. This study aims to develop an artificial intelligence (AI)-based model to predict aggressive behavior by monitoring physical activity. We used decision treebased AI model as its predictions are interpretable similar to human decision making.

Methods: Physical activity was continuously monitored in a home setting in 11 children (Age = 8.5 -¦ 1.0 years, Female = 27.3%) with ADHD showing frequent aggressive behavior. The wearable sensor (ActiGraph GT3X +, Pensacola, FL, USA) was attached to the waist for a week. A decision tree was trained with collected physical activity data, with the caregiver reporting the time and nature of the aggressive events. The identified parameters were used as the input features for the decision tree-based AI model, which was trained to recognize aggressive events labelled by the caregiver.

Results: Energy expenditure ($p < 0.01$, Cohen's $d = 0.23$), percent of light activity ($p < 0.01$, $d = 0.5$), and step count ($p < 0.01$, $d = 0.4$) were distinguished an event of aggression from nonaggressive behavior. The decision tree-based model showed 75% accuracy, 74% specificity, 90% sensitivity and 20% precision.

Conclusions: This study provides initial support for a decisiontree based classification model to predict aggressive behaviors in children with ADHD. Overall, the combination of energy expenditure, percent of light of activity, and step count can predict aggressive behavior. Future work must seek to improve precision, allowing broad clinical application

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CROSS-SECTIONAL EVALUATION OF PREFRONTAL NEUROCHEMISTRY AND PRODROMAL MOOD SYMPTOMS IN YOUTH AT VARYING RISK FOR BIPOLAR I DISORDER.

Chen C, Tallman M, Cecil K, et al.

Background: The initial onset of bipolar I disorder (BD-I) frequently occurs during adolescence, and having a first-degree relative with BD-I substantially increases the risk of developing BDI. Additionally, attention deficit/hyperactivity disorder (ADHD) is a risk factor for psychopathology including BD-I, and there is a high prevalence of ADHD in youth with BD-I or a first-degree relative with BD-I. Furthermore, ADHD symptoms commonly precede the initial onset of BD-I and are associated with an earlier onset of mood symptoms. Although adolescents with ADHD and a firstdegree relative with BD-I are at elevated risk for developing mood disorders, associated prodromal clinical and neurophysiological features remain poorly understood. Proton magnetic resonance spectroscopy (1H MRS) studies have previously found that youth with BD-I or ADHD exhibit abnormalities in prefrontal neurochemistry compared with healthy typically developing youth. However, the majority of prior studies did not control for familial risk of BD-I, ADHD comorbidity, and/or psychostimulant exposure, and there have been no studies that have directly compared psychostimulant-free ADHD youth with and without a firstdegree relative with BD-I. In this cross-sectional study, we characterized mood and cognitive symptoms and used 1H MRS to investigate bilateral ventrolateral prefrontal cortex (VLPFC) neurochemistry in ADHD youth with (high-risk) and without (midrisk) a first-degree

relative with BD-I and a healthy comparison group (low-risk). Exploratory analyses evaluated associations between VLPFC neurochemistry and mood and ADHD symptom severity.
Methods: A total of n = 150 male and female (65% male) psychostimulant-free adolescents (mean age: 14.1 -¦ 2.5 years) were enrolled into three groups: adolescents with ADHD and at least one biological parent or sibling with BD-I (high-risk, n = 50), adolescents with ADHD and no first- or second-degree relative with a mood or psychotic disorder (mid-risk, n = 51), and healthy adolescents with no personal or family history of a DSM-5 Axis I psychiatric disorder (low-risk, n = 49). All ADHD patients met DSM- 5 criteria for ADHD (all types), had no exposure to psychostimulants for at least 3 months prior to scanning, and had no comorbid mood, anxiety, conduct, eating or psychotic disorders. ADHD (ADHD-RS), mania (YMRS), depression (CDRS-R), and global functioning (CGAS) ratings were determined, and 1H MRS scans performed using a Philips 3.0 T MR scanner. MRS voxels (20 +ù 20 +ù 20 mm) were positioned in the right and left VLPFC, and glutamate (Glu), glutamate+glutamine (Glx), myo-inositol (mI), choline (Cho), N-acetyl aspartate (NAA), and phosphocreatine plus creatine (PCr + Cr) concentrations determined.
Results: There were no significant group differences in age (p = 0.25), sex (p = 0.83), race (p = 0.28), or BMI (p = 0.40). Significant group differences were observed for ADHD-RS total score (p < 0.0001), as well as inattentive (p < 0.0001) and hyperactivity/ impulsivity (p < 0.0001) subscores, YMRS total score (p < 0.0001), CDRS-R total score (p < 0.0001), and CGAS total score (p < 0.0001). Pairwise comparisons found that both high-risk and mid-risk groups differed significantly from low-risk on all rating measures, and high-risk subjects had significantly higher hyperactivity/ impulsivity subscores (p = 0.004), YMRS total scores (p = 0.0006), and CDRS-R total scores (p = 0.006) compared with low-risk subjects. For the 1H MRS analysis, a total of n = 143 subjects were included: high-risk, n = 47; mid-risk, n = 48; low-risk, n = 48. For the right VLPFC, no significant group differences were observed for Glu (p = 0.27), Glx (p = 0.24), mI (p = 0.19), Cho (p = 0.84), NAA (p = 0.63), or PCr + Cr (p = 0.55). For the left VLPFC, no significant group differences were observed for Glu (p = 0.84), Glx (p = 0.82), mI (p = 0.15), Cho (p = 0.53), NAA (p = 0.53), and PCr + Cr (p = 0.69). Among all subjects (n = 143), CDRS-R (r = 0.18, p = 0.03) and YMRS (r = 0.19, p = 0.03) total scores were positively correlated with right VLPFC NAA. CDRS-R scores were inversely correlated with left VLPFC Cho (r = -0.18, p = 0.03) and Glx (r = -0.18, p = 0.03), and YMRS scores were inversely correlated with left VLPFC Glx (r = -0.21, p = 0.04).
Conclusions: This cross-sectional analysis found that youth at high-risk for developing BD-I exhibit greater depression and manic symptom severity, as well as greater hyperactivity/impulsivity symptoms, compared with mid- and low-risk youth. These prodromal symptoms may represent early indices of progressive mood symptom dysregulation that could facilitate risk assessment and management. Although neither high-risk nor mid-risk youth exhibited significant abnormalities in prefrontal neurochemistry, associations between mood symptoms and prefrontal NAA, Cho, and Glx warrant additional investigation

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Pakistan Journal of Medical and Health Sciences. 2021;15:1666-68.

THE RELATIONSHIP BETWEEN MOTOR SELF-MOTIVATION AND SYMPTOMS OF ATTENTION-DEFICIT HYPERACTIVITY IN ADHD CHILDREN.

Dana A, Salehian MH, Asadi TB, et al.

Background: The growth and development of the child are essential and inevitable, and the growth of every child requires motor development.
Purpose: This study examines the relationship between motor self-motivation and attention-deficit hyperactivity disorder's symptoms in children with attention-deficit hyperactivity disorder. 40 people were selected by the convenience sampling method from the psychology centers of the province. The research method was descriptive-correlational. A questionnaire was used to collect data. Data were analyzed using Pearson correlation and linear regression.
Results: The results showed that there is a significant negative relationship between motor self-motivation and symptoms of attention-deficit hyperactivity disorder. The results of regression analysis also showed that motor self-motivation is able to predict the symptoms of attention-deficit hyperactivity disorder in children.
Conclusion: In general, the more children's motor motivation, the more minor attention-deficit hyperactivity disorder's symptoms

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Pediatr Res. 2021.

VISUAL TRACKING AT 4 MONTHS IN PRETERM INFANTS PREDICTS 6.5-YEAR COGNITION AND ATTENTION.

Kaul YF, Rosander K, von Hofsten C, et al.

Background: Visual tracking of moving objects requires sustained attention and prediction of the objectΓÇÖs trajectory. We tested the hypothesis that measures of eye-head tracking of moving objects are associated to long-term neurodevelopment in very preterm infants.

Methods: Visual tracking performance was assessed at 4 month's corrected age in 57 infants with gestational age <32 weeks. An object moved in front of the infant with sinusoidal or triangular (i.e. abrupt) turns of the direction. Gaze gain, smooth pursuit gain, and timing of gaze to object motion were analyzed. At 6.5 years the Wechsler Intelligence Scale for Children (WISC-IV), the Brown Attention Deficit Disorder (Brown ADD), and visual examination were performed.

Results: Gaze gain and smooth pursuit gain at 4 months were strongly related to all WISC-IV parameters at 6.5 years. Gaze gain for the triangular and sinusoidal motion patterns related similarly to the cognitive scores. For the sinusoidal motion pattern, timing related to most Brown ADD parameters. There were no statistically significant differences in associations dependent on motion pattern. Visual function did not influence the results.

Conclusion: The ability to attend to and smoothly track a moving object in infancy is an early marker of cognition and attention at 6.5 years. Impact: Potential long-term implications of infant visual tracking of moving objects for school-age neurodevelopment has not been previously studied in very preterm infants.Early coordination of eye and head movements in gaze gain, smooth pursuit, and timing of gaze to object motion are closely associated with cognition and attention at 6.5 years.As related functions at 6.5 years include perceptual and verbal skills, working memory, processing speed and attention, predictive elements in gaze tracking of moving objects might be a suitable target for future intervention studies

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Pediatrics. 2017;140:S206.

ASSOCIATION BETWEEN ATOPIC DERMATITIS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN U.S. CHILDREN AND ADULTS.

Anon.

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Pharmacoepidemiol Drug Saf. 2021;30:1380-90.

PRENATAL EXPOSURE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A FOLLOW-UP STUDY IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT.

Hjorth S, Lupattelli A, Handal M, et al.

Purpose: To estimate the association between Attention-Deficit/Hyperactivity Disorder (ADHD) in children in preschool and primary school, and prenatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) by timing and duration.

Methods: This study was based on the Norwegian Mother, Father and Child Cohort Study linked to the Medical Birth Registry of Norway, the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NSAID exposure was identified by maternal self-report in pregnancy. Child diagnosis of ADHD was obtained from NPR and NorPD. Symptoms of ADHD at age 5 years were measured using Conners' Parent Rating Scale-Revised, where higher scores correspond to more symptoms. To account for time-varying exposure and confounders, marginal structural models were fitted to estimate hazard ratios and mean difference in z-scores.

Results: The analyses on ADHD diagnosis and ADHD symptoms included 56 340 and 34 961 children respectively. Children exposed to NSAIDs prenatally had no increased risk of ADHD diagnosis (first trimester: HR 1.12, 95% CI 0.86;1.45, second trimester: HR 0.98, 95% CI 0.69;1.38, third trimester: HR 0.68, 95% CI 0.31; 1.46) or ADHD symptoms (first trimester: standardized mean difference 0.03, 95% CI ΓêÆ0.03;0.09, second trimester: standardized mean difference 0.03, 95% CI 0.04;0.11, third trimester: standardized mean difference 0.11, 95% CI ΓêÆ0.03; 0.25). There was no duration-response relationship for either outcome.

Conclusion: Though non-differential misclassification of the exposure may have attenuated results, these findings are reassuring and suggest no substantially increased risk of ADHD diagnosis or symptoms in children prenatally exposed to NSAIDs, regardless of timing or duration

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PLoS ONE. 2021;16.

CANCELLATION OF OUTPATIENT APPOINTMENTS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Nomura K, Tarumi R, Yoshida K, et al.

Background Regular visit to psychiatric clinic is essential for successful treatment of any psychiatric condition including attention-deficit/hyperactivity disorder (AD/HD). However, cancellation of outpatient appointments in patients with AD/HD, which represents a significant medical loss, has not been systematically investigated to our knowledge.

Methods A systematic chart review was conducted for patients visiting the Shimada Ryoiku medical Center for Challenged Children in Japan at the age of 15 years from January to December 2013. The primary outcome measure was the cancellation rate, defined as the number of missed visits divided by the number of scheduled visits. The cancellation rates during 24 months after the first visit were compared between outpatients with AD/HD and other psychiatric disorders, including pervasive developmental disorders (PDD), and developmental coordination disorders and/or communication disorders (DCD-CD). A generalized linear model with binomial distribution was used to examine factors associated with cancellation rates exclusively in the AD/HD group.

Results We included 589 patients (mean -¦ SD age, 5.6 -¦ 3.4 years; 432 males) in the analysis. The cancellation rate in patients with AD/HD was 12.3% (95% confidence interval [CI]: 10.0ΓÇô15.1), which was significantly higher than in those with PDD (5.6%, 95% CI: 3.8ΓÇô8.3) and DCD-CD (5.3%, 95% CI: 3.6ΓÇô7.8). Prescriptions of osmotic-release oral system-methylphenidate (OROS-MPH) and antipsychotics were associated with fewer cancellations in AD/HD patients (odds ratios: 0.61, 95% CI: 0.39ΓÇô0.95 and 0.49, 95% CI: 0.25ΓÇô0.95, respectively), although these significances did not find in the subgroup analysis including only patients with 6 years old.

Conclusions Patients with AD/HD were more likely to miss appointments compared to those with other psychiatric disorders. The impact of AD/HD medications as well as potential psychiatric symptoms of their parents or caregivers on appointment cancellations needs to be evaluated in more detail in future investigations

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PLoS ONE. 2021;16.

RATIONALE AND VALIDATION OF A NOVEL MOBILE APPLICATION PROBING MOTOR INHIBITION: PROOF OF CONCEPT OF CALM-IT.

Cardinale EM, Naim R, Haller SP, et al.

Identification of behavioral mechanisms underlying psychopathology is essential for the development of novel targeted therapeutics. However, this work relies on rigorous, timeintensive, clinic-based laboratory research, making it difficult to translate research paradigms into tools that can be used by clinicians in the community. The broad adoption of smartphone technology provides a promising opportunity to bridge the gap between the mechanisms identified in the laboratory and the clinical interventions targeting them in the community. The goal of the current study is to develop a developmentally appropriate, engaging, novel mobile application called CALM-IT that probes a narrow biologically informed process, inhibitory control. We aim to leverage the rigorous and robust methods traditionally used in laboratory settings to validate this novel mechanism-driven but easily disseminatable tool that can be used by clinicians to probe inhibitory control in the community. The development of CALM-IT has significant implications for the ability to screen for inhibitory control deficits in the community by both clinicians and researchers. By facilitating assessment of inhibitory control outside of the laboratory setting, researchers could have access to larger and more diverse samples. Additionally, in the clinical setting, CALM-IT represents a novel clinical screening measure that could be used to determine personalized courses of treatment based on the presence of inhibitory control deficits

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PLoS ONE. 2021;16.

CURRENT USE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) MEDICATIONS AND CLINICAL CHARACTERISTICS OF CHILD AND ADOLESCENT PSYCHIATRIC OUTPATIENTS PRESCRIBED MULTIPLE ADHD MEDICATIONS IN JAPAN.

Sasaki Y, Tsujii N, Sasaki S, et al.

Background/aim Patients with attention-deficit hyperactivity disorder (ADHD) manifest symptoms of hyperactivity, impulsivity, and/or inattention. ADHD medications available in Japan are limited compared with those in Western countries. Prescribing status has not been sufficiently evaluated in clinical settings in Japan. This study investigated the current use of ADHD medications and characteristics of patients who received multiple ADHD medications in a clinical setting in Japan.

Methods Study participants were those who visited the Department of Child and Adolescent Psychiatry, Kohnodai Hospital between April 2015 and March 2020. We investigated patients who received osmotic-controlled release oral delivery system methylphenidate, atomoxetine, or guanfacine. A retrospective case-control design was used to evaluate the characteristics of patients who received multiple ADHD medications. Patients who were given three ADHD medications were defined as the case group. Randomly sampled sex- and age-matched patients diagnosed with ADHD were defined as the control group. We compared data for child-to-parent violence, antisocial behavior, suicide attempt or self-harm, abuse history, refusal to attend school, and two psychological rating scales (the ADHD-Rating Scale and Tokyo Autistic Behavior Scale).

Results Among the 878 patients who were prescribed any ADHD medications, 43 (4.9%) received three ADHD medications. Logistic regression revealed that children with severe ADHD symptoms, autistic characteristics, or tendency of child-to-parent violence were more likely to have been prescribed three medications during their treatment.

Conclusions Our findings suggest the approach to prevent the use of multiple ADHD medications. A prospective study to investigate the causality between prescribing status and clinical characteristics is warranted

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PLoS ONE. 2021;16.

DIFFERENTIAL STRUCTURE-FUNCTION NETWORK COUPLING IN THE INATTENTIVE AND COMBINED TYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lee D, Knight EQ, Song H, et al.

The heterogeneous presentation of inattentive and hyperactive-impulsive core symptoms in attention deficit hyperactivity disorder (ADHD) warrants further investigation into brain network connectivity as a basis for subtype divisions in this prevalent disorder. With diffusion and resting-state functional magnetic resonance imaging data from the Healthy Brain Network database, we analyzed both structural and functional network efficiency and structurefunctional network (SC-FC) coupling at the default mode (DMN), executive control (ECN), and salience (SAN) intrinsic networks in 201 children diagnosed with the inattentive subtype (ADHD-I), the combined subtype (ADHD-C), and typically developing children (TDC) to characterize ADHD symptoms relative to TDC and to test differences between ADHD subtypes. Relative to TDC, children with ADHD had lower structural connectivity and network efficiency in the DMN, without significant group differences in functional networks. Children with ADHD-C had higher SC-FC coupling, a finding consistent with diminished cognitive flexibility, for all subnetworks compared to TDC. The ADHD-C group also demonstrated increased SC-FC coupling in the DMN compared to the ADHD-I group. The correlation between SC-FC coupling and hyperactivity scores was negative in the ADHD-I, but not in the ADHD-C group. The current study suggests that ADHD-C and ADHD-I may differ with respect to their underlying neuronal connectivity and that the added dimensionality of hyperactivity may not explain this distinction

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Psychol Med. 2021 Oct;51:2274-86.

INSIGHTS INTO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FROM RECENT GENETIC STUDIES.

Brikell I, Burton C, Mota NR, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder (NDD). In this narrative review, we summarize recent advances in quantitative and molecular genetic

research from the past 5–10 years. Combined with large-scale international collaboration, these advances have resulted in fast-paced progress in understanding the etiology of ADHD and how genetic risk factors map on to clinical heterogeneity. Studies are converging on a number of key insights. First, ADHD is a highly polygenic NDD with a complex genetic architecture encompassing risk variants across the spectrum of allelic frequencies, which are implicated in neurobiological processes. Second, genetic studies strongly suggest that ADHD diagnosis shares a large proportion of genetic risks with continuously distributed traits of ADHD in the population, with shared genetic risks also seen across development and sex. Third, ADHD genetic risks are shared with those implicated in many other neurodevelopmental, psychiatric and somatic phenotypes. As sample sizes and the diversity of genetic studies continue to increase through international collaborative efforts, we anticipate further success with gene discovery, characterization of how the ADHD phenotype relates to other human traits and growing potential to use genomic risk factors for understanding clinical trajectories and for precision medicine approaches

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Psychoneuroendocrinology. 2021;131.

MOTHER'S HAIR CORTISOL AND SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN HER PRESCHOOL CHILD.

Cosan AS, Schlo S, Vasen Z, et al.

Children with attention deficit hyperactivity disorder (ADHD) require increased caregiver assistance and supervision, and their parents have shown high perceived parenting stress. Hence, physiological adjustment processes in the caregivers, involving the hypothalamic-pituitary-adrenal axis, seem plausible. We analyzed the association between maternal hair cortisol concentration (HCC) and symptoms of ADHD in preschool-aged children. 150 mothers of 4-5 year-old children participated in the study. To determine the HCC, the first scalp-near 3 cm hair segment was used. ADHD symptoms of the child were measured using teacher- and parent-report questionnaires and a clinical interview with the mother. When controlling for several putative confounders, teacher-reported ADHD symptoms were significantly positively associated with mothersΓÇÖ HCC. No associations of HCC with the mother-reported ADHD symptoms of the child emerged. It is possible that teacher-reported ADHD symptoms of the child reflect relevant ADHD symptoms more validly. As our study is the first on this issue, cross-validation is needed

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Psychopharmacology. 2021;238:3055-62.

ANTIBIOTIC EXPOSURE AND CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SYSTEMATIC REVIEW AND META-ANALYSIS.

Ai Y, Zhao J, Shi J, et al.

Background: Disturbances of gastrointestinal microbiome may result in the development of attention-deficit/hyperactivity disorder (ADHD). Antibiotic therapy is commonly known to influence the gastrointestinal microbiome. However, results from studies on the association between antibiotic exposure and ADHD have been inconsistent.

Methods: Several databases (PubMed, PsychInfo, EMBASE) were searched on January 1, 2021, to identify relevant studies. A random effects model was used to calculate the pooled risk estimate. Statistical heterogeneity was tested using the chi-square test and the I2 statistic.

Results: There were four risk estimates on antibiotic intake during pregnancy and eight risk estimates on antibiotic intake after birth. The pooled odds ratio for ADHD comparing antibiotic exposure with non-exposure during pregnancy was 1.14 (95% confidence interval [CI], 1.10ΓÇô1.18). The pooled odds ratio with postnatal antibiotic exposure was 1.12 (95% CI, 0.99-1.26). Substantial heterogeneity existed among these analyses. The timing of antibiotic exposure, type of antibiotic, and number of antibiotic intakes might influence the association between antibiotic exposure and ADHD.

Conclusions: Our findings suggest that maternal antibiotic intake during pregnancy may be associated with an increased risk of ADHD in the offspring. However, there was insufficient evidence for the association between antibiotic intake after birth and ADHD risk. Further studies should be performed before a definitive conclusion can be established

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Research on Child and Adolescent Psychopathology. 2021 Dec;49:1567-79.

DEVELOPMENTAL RELATIONS BETWEEN INTERNALISING PROBLEMS AND ADHD IN CHILDHOOD: A SYMPTOM LEVEL PERSPECTIVE.

Speyer LG, Eisner M, Ribeaud D, et al.

ADHD and internalising problems commonly co-occur with up to 50% of children diagnosed with ADHD also suffering from anxiety or depression. However, their developmental relations are currently not well understood. Longitudinal symptom level analyses can provide valuable insights into how difficulties in these areas of psychosocial functioning affect each other. Using Gaussian Graphical Models and Graphical Vector Autoregression Models, this study estimated cross-sectional and longitudinal networks of ADHD and internalising symptoms in 1387 children using parent- and teacher-reported Social Behaviour Questionnaires (SBQ) when children were aged 7, 9 and 11. Cross-sectional and longitudinal networks suggested that ADHD shares reciprocal relations with internalising symptoms through a number of potential bridge symptoms that are primarily connected to anxiety symptoms. High scores on child cannot sit still, is restless, or hyperactive were found to be the strongest bridge symptom acting as an antecedent to higher internalising symptoms whereas child is worried was the strongest antecedent for higher ADHD symptoms. Findings of this study highlight several potential bridge symptoms that may serve as key intervention targets and further emphasise the need for clinicians to assess children presenting with ADHD symptoms for internalising problems and vice versa

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Scientific World Journal. 2021;2021.

SENSORY BEHAVIOURS AND RESTING PARASYMPATHETIC FUNCTIONS AMONG CHILDREN WITH AND WITHOUT ADHD.

Gomez IN, Domondon LM, Tsang HWH, et al.

Previous studies suggest that parasympathetic functions support sensory behaviours. However, the relationship between sensory behaviours and parasympathetic functions remain inconclusive and inconsistent among children with and without attention-deficit hyperactivity disorder (ADHD). This research aims to examine the sensory behaviours and resting parasympathetic functions among children with and without ADHD. We compared sensory behaviours and baseline parasympathetic functions of 64 participants, with 42 typically developing and 24 ADHD male children aged 7-12 years. Sensory behaviours were evaluated using the sensory profile. Baseline parasympathetic functions were indexed using the normalized unit of heart rate variability high-frequency bands (HF n.u.). Children underwent an experimental protocol consisting of watching a silent cartoon movie while HF n.u. is continuously monitored, within a controlled environment. The results of this research showed significantly lower HF n.u. ($t(64) = 7.84$, $p<0.01$) and sensory processing total score ($t(64) = 14.13 = p<0.01$) among children with ADHD compared to their typically developing peers. Likewise, a significant moderate positive correlation ($r = 0.36$, $p<0.05$) was found between the HF n.u. and sensory profile total scores among children with ADHD. Children with ADHD have significantly lower resting state parasympathetic functions compared to their typically developing peers

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Tijdschr Psychiatr. 2021;63:868-74.

ADOLESCENTS WITH CONCURRENT ADHD AND SUBSTANCE USE DISORDER; INTERNATIONAL CONSENSUS.

Spijkerman R, Crunelle CL, Ã–zgen MH, et al.

BACKGROUND: Substance use disorder (SUD) is common among youths with attention-deficit/hyperactivity disorder (ADHD). Co-morbid ADHD and SUD in youths complicates screening, diagnosis, and treatment of both disorders and is associated with worse treatment prognosis. Limited research in youths with SUD and co-morbid ADHD provides insufficient basis for firm recommendations. To offer clinicians some guidance on this topic, we present the results of an international consensus procedure.

AIM: To summarize an international consensus on diagnosis and treatment of young people with comorbid ADHD and SUD.

METHOD: In a modified Delphi-study, a multidisciplinary, international group of 55 experts strived to reach consensus on 37 recommendations.

RESULTS: Consensus was reached on 36 recommendations. Routine screening of ADHD and/or SUD is important. For the treatment of co-morbid SUD and ADHD in youths, both psychosocial and pharmacological treatment should be considered. Psychosocial treatment should preferably consist of psychoeducation, motivational interviewing (MI), and cognitive behavioral therapy (CBT) focused on SUD or both disorders. Long-acting stimulants are recommended as first choice pharmacotherapy, preferably embedded in psychosocial treatment. Experts did not agree on the precondition that patients need to be abstinent before starting stimulant treatment.
CONCLUSION: Clinicians and youths with co-morbid SUD and ADHD can use this international consensus to choose the best possible treatment

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Traditional Medicine and Modern Medicine. 2018;1:21-26.

IS COMBINED CBT THERAPY MORE EFFECTIVE THAN DRUG THERAPY ALONE FOR ADHD IN CHILDREN? A META-ANALYSIS.

Ding Q, Li M, Zhu D.

Based on published research on the combined cognitive behavioral therapy (CBT) versus drug therapy alone in children with attention deficit/hyperactivity disorder (ADHD), we systematically reviewed and analyzed the efficacy of two treatment methods in children with ADHD. The literature as at the end of 10 July 2017 in multiple databases was systematically searched. Standardized mean differences (SMD) and 95% confidence intervals (CIs) were calculated. The results indicated that combined CBT therapy was efficacious in reducing symptoms of ADHD (SDM -0.48, 95% CI -0.80 to -0.17). The executive function scores were not improved more in the combined CBT (SMD -0.34; 95% CI -0.71 to 0.03). This study suggests that combined CBT seems more efficacious in some domains affecting children with ADHD, but further evaluation is needed

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Transl Psychiatry. 2021;11.

INTERSTAARS: ATTENTION TRAINING FOR INFANTS WITH ELEVATED LIKELIHOOD OF DEVELOPING ADHD: A PROOF-OF-CONCEPT RANDOMISED CONTROLLED TRIAL.

Goodwin A, Jones EJH, Salomone S, et al.

Attention-deficit/hyperactivity disorder (ADHD) is first diagnosed during middle childhood, when patterns of difficulty are often established. Pre-emptive approaches that strengthen developing cognitive systems could offer an alternative to post-diagnostic interventions. This proof-of-concept randomised controlled trial (RCT) tested whether computerised gaze-based attention training is feasible and improves attention in infants liable to develop ADHD. Forty-three 9- to 16-month-old infants with a first-degree relative with ADHD were recruited (11/2015-11/2018) at two UK sites and randomised with minimisation by site and sex to receive 9 weekly sessions of either (a) gaze-contingent attention training (intervention; n = 20); or (b) infant-friendly passive viewing of videos (control, n = 23). Sessions were delivered at home with blinded outcome assessments. The primary outcome was a composite of attention measures jointly analysed via a multivariate ANCOVA with a combined effect size (ES) from coefficients at baseline, midpoint and endpoint (Registration: ISRCTN37683928). Uptake and compliance was good but intention-to-treat analysis showed no significant differences between 20 intervention and 23 control infants on primary (ES 0.4, 95% CI 0.9 to 0.2; Complier-Average-Causal Effect ES 0.6, 95% CI 1.6 to 0.5) or secondary outcomes (behavioural attention). There were no adverse effects on sleep but a small increase in post-intervention session fussiness. Although feasible, there was no support for short-term effects of gaze-based attention training on attention skills in early ADHD. Longer-term outcomes remain to be assessed. The study highlights challenges and opportunities for pre-emptive intervention approaches to the management of ADHD

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Trends Psychiatry Psychother. 2021 Jul;43:235-39.

DISABILITY IN CHILDREN AND ADOLESCENTS: THE EXTENT OF THE IMPACT ON PSYCHIATRIC DISORDERS AND EDUCATIONAL DEFICITS.

Zaqueu L, Teixeira MCTV, Lowenthal R, et al.

INTRODUCTION: Most children/adolescents with disability live in low and middle-income countries and, worldwide, they are more likely to have mental health problems and achieve worse academic performance compared to those with typical development.

OBJECTIVE: To assess whether Brazilian children/adolescents with four types of disabilities are more likely to have psychiatric disorders and educational deficits than children/adolescents with typical development.

METHOD: A multicenter cross-sectional study involving a school-based probabilistic sample of second to sixth graders (N = 1,674) from public schools in four Brazilian regions. The four types of disabilities (intellectual, visual, hearing, and motor) were assessed using the Ten Questions Questionnaire. Psychiatric disorders were measured with the Schedule for Affective Disorders/Schizophrenia for School-Age Children (K-SADS-PL), and academic performance was evaluated using the Teste de Desempenho AcadÃªmico - TDE (the academic performance test).

RESULTS: A logistic regression model with cluster-robust errors identified the following statistically significant associations with three of the four types of disability (the exception was hearing). Intellectual disability was associated with anxiety ($p < 0.01$), depression ($p < 0.01$), attention deficit hyperactivity disorder (ADHD) ($p < 0.001$), school failure ($p < 0.01$), and poor academic performance ($p < 0.01$). Visual disability was associated with depression ($p < 0.01$). Motor disability was marginally associated with ADHD ($p = 0.08$).

CONCLUSIONS: Presence of disabilities (intellectual, visual, and motor) in children/adolescents was associated with psychiatric disorders, school failure, and academic performance. It is therefore important to identify presence of disabilities and plan and deliver specific interventions and specialized educational care for the needs presented by these children/adolescents. This is particularly important in low and middle-income countries, where these disabilities are frequent among children/adolescents

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Turk Psikiyatri Derg. 2021;32:261-66.

VALIDITY AND RELIABILITY OF THE TURKISH VERSION OF THE WEISS FUNCTIONAL IMPAIRMENT RATING SCALE-SELF REPORT FORM.

Yalin-Sapmaz Å, Ergin D, Åžen-Celasin N, et al.

OBJECTIVE: The aim of this study was to demonstrate the validity and reliability of the WFIRS-S-TR, Turkish version of the Weiss Functional Impairment Rating Scale-Self Report form.

METHOD: The study comprised two groups of participants of 15-18 years of age, one consisting of 35 children diagnosed with attention deficit and hyperativity disorder (ADHD) based on the DSM-IV criteria and the other, 510 healthy volunteers attending high school. Apart from the WFIRS-S-TR, the Health Questionnaire for Children and Adolescents (KIDSCREEN-10 Index) which is a general quality of life and functionality measurement instrument, was used to check the concurrent validity of the WFIRS-S-TR.

RESULTS: The Cronbach's alpha coefficient for the total scale was 0.939. The test-retest reliability assessed by repeated measurements two weeks apart gave a high correlation between the results ($r=0.804$, $p<0.0001$). Total mean score of the WFIRS-S-TR showed significant correlation with the KIDSCREEN-10 Index total mean score ($r= -0.467$, $p<0.0001$). Confirmatory factor analysis was carried out for the construct validity of the WFIRS-S-TR. The RMSEA and the CFI values were found to be 0.065 and 0.68, respectively.

CONCLUSION: The WFIRS-S-TR can be used as a valid and reliable tool both in clinical practice and for research purposes

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Turk Klin Pediatr. 2021;30:219-28.

EVALUATION OF STRESS COPING STRATEGIES IN ADOLESCENTS WITH ATTENTION DEFICIENCY HYPERACTIVITY DISORDER: CASE-CONTROL STUDY.

Taƒ Torun Y, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood, characterized by difficulties in academic field, peer relationships and family life. The aim of this

study is to determine the strategies for coping with stress in adolescents diagnosed with ADHD and to evaluate the relationship between the coping strategies they used and the problems they encounter in daily life.

Material and Methods: The sample of the study consists of patients with ADHD (n=40) between the ages of 12-17 and a healthy control group (n=26). As data collection tools; sociodemographic data form, Conners-Wells adolescent self-report scale long form and coping strategies short form were used.

Results: It was determined that dysfunctional coping total scores were higher in the ADHD group than the control group. When the subscales were examined, it was determined that the denial and behavioral disengagement subscale scores were significantly higher in the ADHD group. Planning was found to be lower in the ADHD group. With the emotionally centered coping score/revealing emotions method, the total scores of family problems, ADHD Index, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Hyperactivity/Impulsivity and DSM-IV were positive and moderate; A positive, high-intensity relationship was found between emotional problems.

Conclusion: It was concluded that adolescents diagnosed with ADHD used more emotionally focused and dysfunctional coping strategies compared to the control group, and the relationship between the coping methods used and symptoms of inattention, hyperactivity and impulsivity was different from each other

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frontiers in Neuroscience

ORIGINAL RESEARCH
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Autistic Traits and Empathy in Children With Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder and Co-occurring Attention Deficit Hyperactivity Disorder/Autism Spectrum Disorder

Stefania Aiello[1†], David Vagni[1†], Antonio Cerasa[1,2,3], Elisa Leonardi[1], Cristina Carrozza[1], Francesca Famà[1], Agrippina Campisi[1], Flavia Marino[1], Rosamaria Siracusano[4], Maria Ausilia Alquino[5], Francesco Mainiero[6], Eva Germano[5], Gennaro Tartarisco[1], Giovanni Pioggia[1‡], Antonella Gagliano[7‡] and Liliana Ruta[1‡]*

[1] Institute for Biomedical Research and Innovation (IRIB), National Research Council of Italy (CNR), Messina, Italy, [2] S. Anna Institute, Crotone, Italy, [3] Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health Science and Nutrition, University of Calabria, Arcavacata, Italy, [4] Division of Child Neurology and Psychiatry, Federico II University Hospital Naples, Naples, Italy, [5] Division of Child Neurology and Psychiatry, Department of the Adult and Developmental Age Human Pathology, University of Messina, Messina, Italy, [6] Department of Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy, [7] Child and Adolescent Neuropsychiatry Unit, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) are two of the most represented neurodevelopmental conditions in childhood. The diagnostic shift introduced by the DSM-5, allowing a combined diagnosis of ADHD and ASD, poses different clinical challenges related to diagnostic overshadowing, accuracy of clinical judgment and potential delay in an ASD diagnosis in children presenting with ADHD. Here we tried to disentangle the clinical phenotype and specificity of the two co-occurring conditions in relation to autism traits and empathy, by comparing children with ASD with and without comorbid ADHD with children presenting ADHD only and children with typical development. The child versions of the Autism Quotient (C-AQ) and Empathy Quotient (C-EQ) were administered to a total sample of 198 male children between 6 and 14 years old with age appropriate language skills and normal intelligence. Univariate analysis demonstrated no significant differences in the C-AQ total and subscale scores as well as the C-EQ between children with ASD and children with ASD + ADHD, while children with ADHD alone presented an intermediate phenotype between ASD and TD. Furthermore, a receiver operating characteristic (ROC) analysis was applied to discriminate among the different phenotypes. We found that the C-AQ and C-EQ were accurate at distinguishing with satisfactory reliability between: (a) ASD vs. non- ASD (N-ASD) groups comprising both ADHD and TD children (Area Under the Curve AUC 88% for C-AQ and 81% for C-EQ); (b) ASD and TD (AUC 92% for C-AQ

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Francesca Felicia Operto, University of Salerno, Italy

***Correspondence:**
Liliana Ruta
liliana.ruta@cnr.it

[†] These authors have contributed equally to this work and share first authorship

[‡] These authors have contributed equally to this work and share last authorship

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and 95% for C-EQ); (c) ASD and ADHD (AUC 80% for C-AQ and 68% for C-EQ). Our data confirm the reliability of the C-AQ and C-EQ as behavioral markers to differentiate ASD (regardless of comorbid ADHD) from an ADHD condition and TD. Interestingly, in our sample an ADHD condition does not increase the severity of the clinical phenotype in terms of autism traits distribution and empathy, suggesting that the psychological measures detected by the two quantitative instruments are independent of ADHD traits. This evidence will contribute to the translational efforts in developing better tailored treatments and preventive strategies.

Keywords: autistic traits, empathy, ADHD, ASD, gender

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) (American Psychiatric Association [APA], 2013) introduced a new conceptualization of Neurodevelopmental Disorders, providing a fundamental shift from a categorical to a dimensional system of diagnosis (Hudziak et al., 2007; Jones, 2012). In the DSM-5, remarkable modifications affected one of the currently most represented neurodevelopmental conditions in childhood: Autism Spectrum Disorder (ASD).

The major changes in the ASD diagnostic category were: (i) the rearrangement of the three core domains down to two core domains (social communication and restricted and repetitive behaviors); (ii) the removal of sub-diagnoses (Autistic Disorder, Asperger Syndrome, Pervasive Developmental Disorder Not Otherwise Specified, Disintegrative Disorder) in favor of a dimensional approach of symptoms' severity; and (iii) the possibility of a comorbid diagnosis of ADHD.

Within the autism phenotype, restricted repetitive behaviors have been linked to cognitive rigidity (South et al., 2007; Lemonda et al., 2012; Faja and Nelson Darling, 2019), hyperfocus and difficulties in predictive coding (van de Cruys et al., 2014). Different studies have replicated an impairment in executive functions (EF) such as verbal working memory, inhibition and quick visual scanning in the ASD population (Rommelse et al., 2015; Operto et al., 2021). Furthermore, EF is known to self-regulate emotional and empathic abilities, also referred to as "Hot Executive functions" (Yang et al., 2011), which result impaired in children with autism (Harmsen, 2019), with significantly higher deficits in emotional regulation (ER) than other neurodevelopmental and psychiatric disorders (Samson et al., 2012; Joshi et al., 2018). Additionally, difficulties in controlling emotions often result in internalizing problems such as anxiety and depression (Gadow et al., 2012; Operto et al., 2021).

Impairments in EF and self-regulation represent core neuropsychological features of ADHD. Interestingly, poor quality of social perspective's assumptions, impaired social cognition, lack of pragmatic language and empathy have also been observed in children with ADHD (Marton et al., 2009; Bora and Pantelis, 2016; Lasmono et al., 2021). With respect to empathy subdomains, it has been reported that ADHD is mainly characterized by a deficit in affective empathy (sharing and responding to another individual's emotions) rather than to its cognitive domain (understanding another person's perspective) (Abdel-Hamid et al., 2019; Cristofani et al., 2020; Fantozzi et al., 2021) as it is usually observed in ASD (Rueda et al., 2015). The emotional and behavioral profile in ADHD children results in both internalizing and externalizing problems such as mood and anxiety disorders, aggressive and/or oppositional behaviors, with consequent difficult peer relationships (Nijmeijer et al., 2008; Harkins et al., 2021). Furthermore, many children with ADHD also show hyperfocus on topics that meet their personal interests (Groen et al., 2020) and demonstrate difficulties in processing speed and working memory (Molavi et al., 2020; Operto et al., 2021).

Previous evidence confirmed the symptoms overlap between ADHD and ASD, with 18–50% of children with ADHD presenting with clinical levels of ASD symptoms (Ronald et al., 2008; Kochhar et al., 2011; Van Der Meer et al., 2012; Grzadzinski et al., 2016) and conversely, 40–70% of children with ASD displaying co-occurring ADHD (Salazar et al., 2015; Joshi et al., 2017; Antshel and Russo, 2019).

Diagnostic accuracy may be even more challenging when ASD and ADHD co-occur. In fact, the neuropsychological and behavioral overlapping between the two conditions poses important questions related to diagnostic overshadowing and need to be in depth investigated to explain possible shared etiologies (Antshel and Russo, 2019). Furthermore, studying the co-occurrence of the two conditions at early stages is crucial to be aware of how they evolve and, consequently, how their pathways vary along with child development. This longitudinal perspective is fundamental to enhancing targeted treatment. Previous findings suggest that, in the socio-communicative domain, ADHD lies intermediately between ASD and control groups (Grzadzinski et al., 2011; van de Cruys et al., 2014; Salley et al., 2015; Groen et al., 2018). ADHD and ASD could then belong to the same continuum and represent two different manifestations of a common spectrum disorder. A recent study showed that compared to only ASD, an ADHD comorbidity was associated with reduced cognitive task performance (Mansour et al., 2021). Other studies demonstrated that an ASD + ADHD condition increased deficits in social interaction and was associated with lower adaptive functioning, higher anxiety, lower empathy (Colombi and Ghaziuddin, 2017; Shephard et al., 2019; Dellapiazza et al., 2021) and a poorer quality of life (Gadow et al., 2009; Sikora et al., 2012; Joshi et al., 2017). Furthermore, with regard to their emotional and behavioral profile, a recent study has demonstrated that children with comorbid ASD and ADHD

result with higher externalizing problems than ASD alone, and lower externalizing symptoms than children with ADHD alone (Carta et al., 2020). Similarly, children with a diagnosis of ADHD who displayed higher autistic traits showed lower cognitive and social skills and the presence of autistic traits determined a more severe outcome (Kotte et al., 2013; Green et al., 2016; Joshi et al., 2020; Sesso et al., 2020).

Based on existing literature we aimed to disentangle the clinical phenotype and specificity of the two co-occurring conditions in relation to autistic traits and empathy, by comparing children with mild to moderate ASD, with normal intelligence and functional language, with and without comorbid ADHD, with children presenting with ADHD only and typically developing (TD) children. Specifically, we intend to explore if comorbid ADHD is associated with an increase in the expression of autistic traits and a decrease of empathy as detected by two dimensional measures such as the child versions of the Autism-Spectrum Quotient (C-AQ) (Auyeung et al., 2008; Ruta et al., 2012) and the Empathy Quotient (C-EQ) (Auyeung et al., 2009). In particular, we are interested in investigating whether the C-AQ and C-EQ are able to distinguish between ASD with or without ADHD and ADHD alone, as well as against typical development.

MATERIALS AND METHODS

Subjects

All the children presenting a clinical diagnosis of ADHD and/or ASD were assessed at the clinical facilities of the National Research Council of Italy (IRIB—CNR) and the Polyclinic University Hospital "AOU G. Martino" both located in Messina, Italy, while TD children were recruited in three big mainstream schools in the metropolitan area of Messina. Clinical diagnosis was examined by medical records and was then confirmed by an experienced child neuropsychiatrist (A.G., E.G., and R.S.) and a chartered clinical psychologist of the team (S.A., E.L.) according to the DSM-5 criteria, with the support of the Autism Diagnostic Observation Schedule-2nd edition (ADOS-2, Module 3) and the parent version of the Conners scale-3rd edition, respectively. All the ASD children included in the study, received a diagnosis of ASD without disorder of intellectual development and with no impairment of functional language (6A02.0) according to ICD-11. All the children had an IQ between 70 and 130 (mean = 98.7, *SD* = 14), assessed using the Wechsler Intelligence Scale for Children-4th edition (WISC-IV).

Exclusion criteria included children with (1) intellectual disability; (2) syndromic (secondary) autism; (3) no fluent language; (4) level 3 (severe) at the DSM-5 severity classification, because for those children many questions on the C-AQ and C-EQ were not applicable or a positive answer would capture difficulties collateral to ASD and not nuclear to it (e.g., "when my child talks on the phone, he doesn't know when it's his turn to talk").

The study was reviewed and approved by the Ethics Committees of CNR (ethical clearance, 01.08.2018) and parents of the children included in the study provided their written informed consent.

Behavioral Measures

The child version of the Autism Spectrum Quotient (C-AQ) and Empathy Quotient (C-EQ) were used to assess Autistic Traits (ATs) and empathy in all the children. The C-AQ and C-EQ were originally developed to study dimensional autistic traits and empathy as a continuum. The C-AQ (Auyeung et al., 2008; Ruta et al., 2012) is a 50-items parent-report questionnaire to assess five areas associated with autism: social skills, communication, imagination, attention switching, and attention to details. It is an adapted version of the AQ for adults, a reliable tool able to identify autistic traits in the general population also at a subthreshold level, discriminating high functioning autism from non-autistic individuals. Items specifically map into the clinical features of autism (ex. She/he prefers to do things the same way repeatedly). Answers are measured with a Likert scale, from 1 to 4 (Definitely Disagree, Slightly Disagree, Slightly Agree, Definitely Agree) with higher scores indicating more autistic traits and behaviors.

The C-EQ (Auyeung et al., 2009) is a 27-items parent-report questionnaire to measure the degree of empathy expressed in real life situations, experiences, and interests. It is an adapted version of the EQ for adults, a trustworthy instrument to evaluate individual behaviors into situations where empathizing skills are required (ex. My child often doesn't understand why some things upset other people so much). Items are presented with a Likert format from 1 to 4 (Definitely Disagree, Slightly Disagree, Slightly Agree, Definitely Agree) with higher scores indicating higher empathic skills. The EQ demonstrated a significant sex difference in the general population (with boys usually resulting as less empathizing than girls) and a negative correlation with autistic traits.

Statistical Analyses

All statistical analyses were conducted using the SPSS Statistics Release 26.0 (IBM SPSS, New York, NY). A two-way ANOVA was performed separately for the C-AQ and the C-EQ. We performed a univariate analysis of variance (ANOVA) to verify between-group differences in the total scores of the C-AQ and C-EQ; the four diagnostic groups were used as dependent variables, the C-AQ and C-EQ were used as independent variables. Levene's Test was used in ANOVA and Box's Test in MANOVA to test the equality of error variances. Given that the groups size was uneven, in case of unequal variances a robust Bias-corrected accelerated (BCa) Bootstrap with 1,000 samples, stratified by group, will be used (Krishnamoorthy et al., 2007). Age and IQ were not matched across all the groups, hence all the analyses were controlled for these measures.

Furthermore, we executed a MANOVA, with the same factors and covariates, to analyze between-group differences in AQ subscales. Multiple comparisons were performed by applying Sidak correction. Pillai's Trace was used to test the null hypothesis.

A receiver operating characteristic (ROC) curve of the C-AQ and C-EQ total scores was calculated to plot sensitivity and 1-specificity in the whole ASD group (ASD+ and ASD−) vs. N-ASD group (ADHD and TD together). The area under the

curve (AUC) is a measure of the overall predictive validity, where an AUC = 0.50 indicates a random prediction of the independent variable, AUC > 0.70 indicates fair validity and AUC > 0.90 indicates excellent validity. Potential cut-off scores on the AQ and EQ for differentiating between children with and without ASD were also evaluated using ROC analysis to determine the cut-point corresponding to the best combination of sensitivity and specificity.

RESULTS

Group Differences on the Child Versions of the Autism Quotient and Empathy Quotient Total Scores

A total sample of 198 male children aged between 6 and 14 years old (mean = 8.8, *SD* = 2.2) has been recruited and tested in the study. *N* = 77 children presented a diagnosis of ASD only (ASD−); *n* = 24 children received a diagnosis of ASD and ADHD (ASD+); *n* = 33 children had ADHD only and *n* = 64 children had typical development (TD) (see **Table 1**).

Equality of variance conditions were not met for C-AQ. Therefore, we decided to use a stratified BCa for both outcome measures to have more robust error ranges. We detected a main effect of group for both the C-AQ [$F_{(3,192)} = 60.0$, $p < 0.001$ $\eta_p^2 = 0.448$] and C-EQ [$F_{(3,\ 149)} = 32.1$, $p < 0.001$, $\eta_p^2 = 0.393$]. We found neither the age effect [$F_{(1,\ 192)} = 0.60$, $p = 0.438$] nor the IQ effect [$F_{(1,\ 192)} = 1.21$, $p = 0.272$] on C-AQ and C-EQ [$F_{(1,\ 149)} = 0.253$, $p = 0.616$ and $F_{(1,\ 149)} = 3.10$, $p = 0.081$, respectively].

On both measures, pairwise comparisons showed that the ASD+ and ASD− groups had comparable scores, with, a mean difference of 5.18 [−2.93, 14.27], $p = 0.237$, for the C-AQ and −0.52 [−5.25, 4.22], $p = 0.787$ for the C-EQ (**Figure 1**).

Furthermore, ASD− scores were significantly different from both the ADHD (−19.54 [−25.95, 13.25], $p = 0.001$ for the C-AQ; 5.16 [8.20, 2.07], $p = 0.001$ for the C-EQ) and the TD group (−34.17 [−40.01, −27.96], $p = 0.001$ for the C-AQ and 14.94 [11.94, 18.13], $p = 0.001$ for the C-EQ), respectively. Children with ADHD, in turn, displayed, on both the C-AQ and C-EQ, intermediate mean scores, but significantly different than TD children (14.63 [8.36, 20.61], $p = 0.001$ for the C-AQ and −9.78 [−14.84, −4.71], $p = 0.001$ for the C-EQ).

Group Differences in Child Versions of the Autism Quotient Subscales Scores

Equality of variance conditions were not met for the social and the attention to details subscales. As before, we performed a stratified BCa. The main effect of the group, reported on the C-AQ total score, was confirmed by the multivariate analysis [$F_{(15,570)} = 8.49$, $p < 0.001$, $\eta_p^2 = 0.183$]. We found no effect of age [$F_{(5,188)} = 0.719$, $p = 0.610$], while IQ had a significant effect [$F_{(5,188)} = 4.20$, $p = 0.001$, $\eta_p^2 = 0.100$]. Univariate analysis led to a main effect of group for communication [$F_{(3,\ 192)} = 44.5$, $p < 0.001$, $\eta_p^2 = 0.410$], social [$F_{(3,192)} = 57.5$, $p < 0.001$, $\eta_p^2 = 0.437$], attention switching [$F_{(3,192)} = 24.5$ $p < 0.001$, $\eta_p^2 = 0.277$], and imagination [$F_{(3,192)} = 29.4$ $p < 0.001$,

TABLE 1 | Demographic data and explored variable comparison for the sample.

Variable	ASD− (*N* = 77)	ASD+ (*N* = 24)	ADHD (*N* = 33)	TD (*N* = 64)	Statistics	*Post hoc*
Age (95% C.I.)	9.11 (8.64, 9.60)	8.46 (7.98, 8.89)	8.51 (7.95, 9.09)	9.83 (9.41, 10.23)	$F_{(3,197)} = 5.631, p = 0.001$	ASD− = TD; TD > ASD+ = ADHD
IQ (95% C.I.)	97.6 (94.5, 100.8)	106.6 (100.7, 111.9)	101.0 (96.4, 105.7)	96.6 (93.3, 99.8)	$F_{(3,197)} = 3.676, p = 0.013$	ASD + > TD; ASD− = ADHD = TD
AQ tot (95% C.I.)	88.2 (83.1, 93.1)	94.0 (87.7, 100.0)	68.7 (64.3, 72.6)	54.4 (50.6, 57.9)	$F_{(3,\ 192)} = 52.0, p < 0.001, \eta_p^2 = 0.448$	ASD + = ASD− > > ADHD > > TD
AQ soc (95% C.I.)	17.7 (16.6, 18.8)	18.6 (16.6, 20.6)	11.2 (9.5, 12.9)	7.79 (6.55, 9.02)	$F_{(3,\ 192)} = 57.5, p < 0.001, \eta_p^2 = 0.473$	ASD + = ASD− > > ADHD > TD
AQ att (95% C.I.)	18.3 (17.2, 19.4)	18.9 (16.9, 21.0)	15.0 (13.3, 16.7)	11.6 (10.4, 12.9)	$F_{(3,\ 192)} = 24.5, p < 0.001, \eta_p^2 = 0.277$	ASD + = ASD− > ADHD > TD
AQ det (95% C.I.)	16.4 (15.1, 17.6)	17.1 (14.9, 19.4)	15.3 (13.4, 17.2)	15.9 (14.5, 17.3)	$F_{(3,\ 192)} = 0.573, p = 0.634, \eta_p^2 = 0.009$	ASD + = ASD− = TD = ADHD
AQ com (95% C.I.)	19.1 (17.8, 20.3)	21.4 (19.1, 23.8)	14.6 (12.7, 16.6)	9.14 (7.72, 10.55)	$F_{(3,\ 192)} = 44.5, p < 0.001, \eta_p^2 = 0.410$	ASD + = ASD− > > ADHD > > TD
AQ imm (95% C.I.)	16.8 (15.6, 17.9)	17.5 (15.6, 19.5)	12.7 (11.0, 14.3)	9.81 (8.60, 11.02)	$F_{(3,\ 192)} = 29.4, p < 0.001, \eta_p^2 = 0.315$	ASD− = ASD+ > > ADHD > TD
EQ tot (95% C.I.)*	20.6 (18.7, 22.4)	20.0 (17.3, 22.5)	25.7 (23.6, 27.9)	35.5 (33.3, 40.0)	$F_{(149)} = 32.1, p < 0.001, \eta_p^2 = 0.393$	ASD− = ASD+ < ADHD < < TD

*Covariates and estimates appearing in the model are evaluated at the following values: Age = 9.17, IQ = 98.9. Bootstrap results are based on 1,000 bootstrap samples stratified by group and computed using Bias-correction. *EQ participants: ASD+ = 24, ASD− = 70, ADHD = 32, TD = 29.*

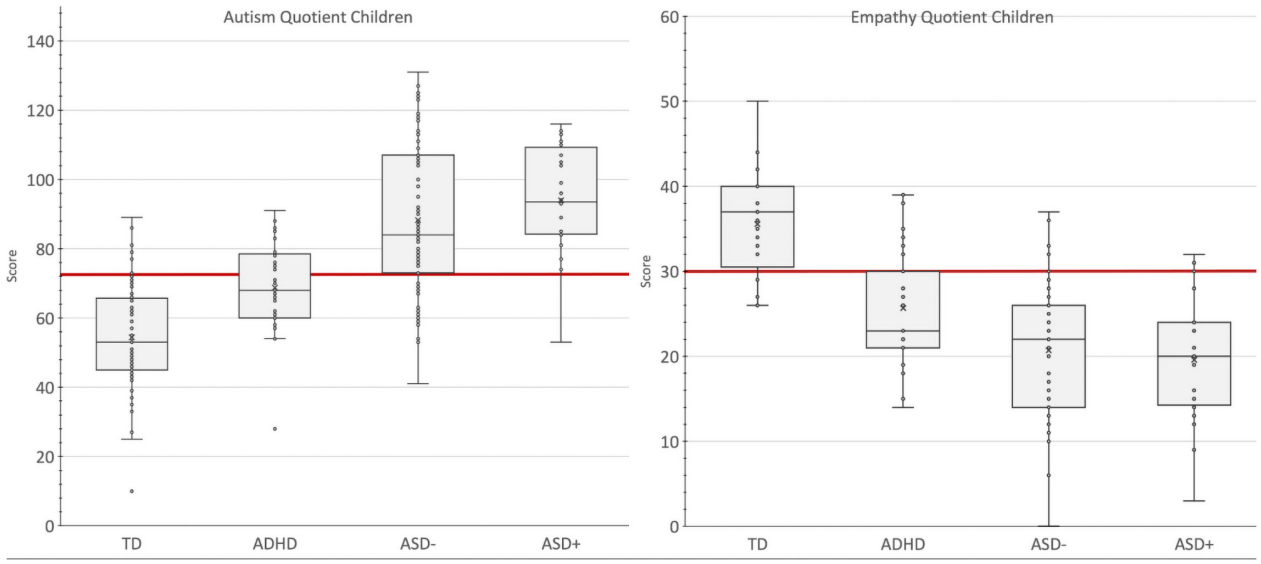

FIGURE 1 | Group comparison on the C-AQ and C-EQ total scores. Box and Whisker Plot. A box is drawn from the first quartile to the third quartile, while a line is drawn at the median and the cross is the mean value. The whiskers extend from each quartile to the minimum or maximum. The Red Line is the Cut-off Value with the Highest Accuracy in Discriminating Autism Spectrum Disorder. TD, Typical Development Group; ADHD, Attention Deficit and Hyperactivity Group; ASD–, Autism Spectrum Disorder Group; ASD+, ASD with comorbid ADHD group.

$\eta_p{}^2 = 0.315$] subscales. There was no group effect for the attention to details subscale [$F_{(3,192)} = 0.57$ $p = 0.634$, $\eta_p{}^2 = 0.009$)]. The effect of IQ was significant for the social skills and attention to details subscales [$F_{(1,192)} = 5.81$ $p = 0.017$, $\eta_p{}^2 = 0.029$ and $F_{(1,192)} = 4.02$ $p = 0.046$, $\eta_p{}^2 = 0.021$, respectively].

Pairwise comparisons showed that, on the social, communication, imagination and attention switching subscales, ASD+ and ASD− groups had comparable scores (all p-values > 0.386), both groups scored higher than the ADHD only and TD group (all p-values < 0.021), and in turn, ADHD scores were higher than the control group (all p-values < 0.045). There were no significant differences among the four groups on the attention to detail score (all p-values > 0.787). **Figure 2** displays the group differences on the C-AQ subscales scores.

Accuracy of the Child Versions of the Autism Quotient and Empathy Quotient in Predicting Group Differences

Using ROC curve analysis for a positive ASD diagnosis (ASD vs. N-ASD), independent of the ADHD status, the AUC was 0.877 [0.830, 0.923] for C-AQ, and 0.806 [0.737, 0.874] for C-EQ (**Figure 3**).

We also determined the best threshold able to discriminate between ASD and N-ASD with maximum accuracy. The cut-off was 73 (equal or higher) for the C-AQ and 26 (equal or less) for the C-EQ. Using those values, for C-AQ the sensitivity was 82% and the specificity was 79% leading to an overall accuracy of 81%, while for C-EQ the sensitivity was 75% and the specificity was 72%, with an accuracy of 73% (**Table 2**).

A comparison between ASD and TD, led to an AUC of 0.918 [0.877, 0.959] with a cut-off of 73 for AQ-C scores, corresponding to a sensitivity of 82% and a specificity of 89% with an accuracy of 86%. On the C-EQ, AUC was 0.945 [0.907, 0.983] with a cut-off of 26, a sensitivity of 75%, a specificity of 100% and an accuracy of 87%.

Finally, the direct comparison of the whole ASD group (ASD+ and ASD−) vs. the ADHD group, led, for the C-AQ, to an AUC of 0.795 [0.719, 0.872] with a cut-off of 77 corresponding to a sensitivity of 72% and a specificity of 73% with an accuracy of 73%. For the C-EQ, AUC was 0.680 [0.581, 0.779] using a cut-off of 18, sensitivity was 36% and specificity was 94% leading to an accuracy of 65%.

DISCUSSION

Recent literature is posing specific attention to the clinical implications of having a comorbid ASD and ADHD with a focus on investigating the extension to which the two co-occurring conditions contribute to a different phenotype expression compared to ASD and ADHD alone. Although clinical data support the presence of a more severe outcome and impairment in the quality of life, evidence from the current standardized clinical measures is still inconsistent in detecting, with sufficient accuracy, the neuropsychological differences between individuals with ASD, individuals with a comorbid ADHD (ASD+) and individuals with an ADHD alone. One of the reasons for this clinical challenge, is that, for example, many individuals with ADHD, as well as individuals with ASD, show significant impairments in the social interaction and communication area, as displayed by higher scores on the social affect domain at the Ados Diagnostic Observation Schedule, second edition (ADOS-2), and the main domain that allows to distinguishing between

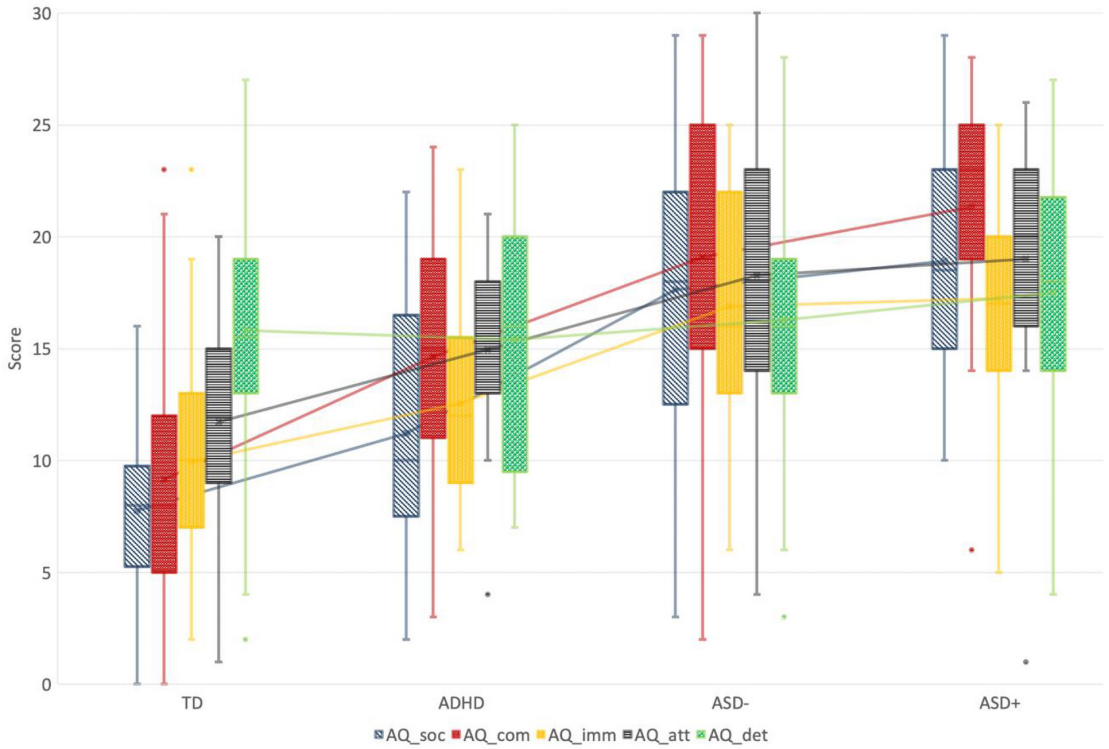

FIGURE 2 | Group differences on the C-AQ subscales scores. TD, Typical Development Group; ADHD, Attention Deficit and Hyperactivity Group; ASD–, Autism Spectrum Disorder Group; ASD+, ASD with comorbid ADHD group; AAQ_soc, Autism Quotient Children—Social Skills Subscale; AQ_com, Autism Quotient Children—Communication Subscale; AQ_soc, Autism Quotient Children—Imagination Subscale; AQ_imm, Autism Quotient Children—Attention Shifting Subscale; AQ_soc, Autism Quotient Children—Attention to Details Subscale.

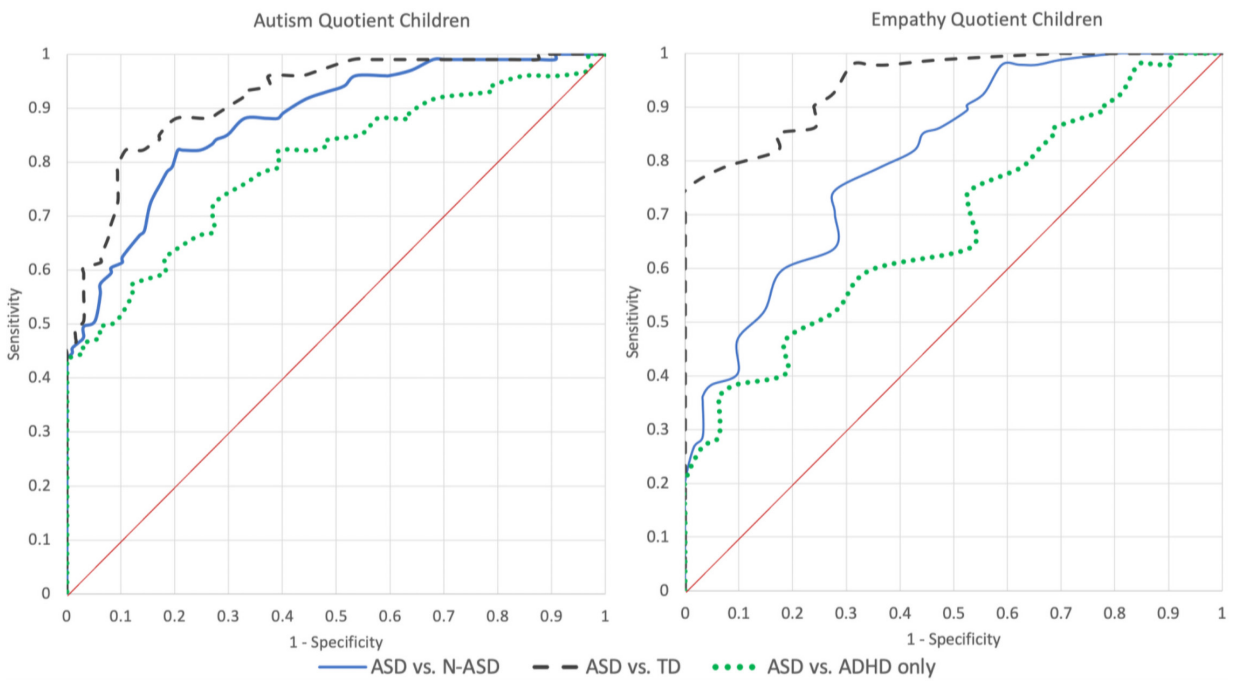

FIGURE 3 | ROC curves of the C-AQ and C-EQ for different combinations of groups. TD, Typical Development Group; ADHD, Attention Deficit and Hyperactivity Group; ASD, Autism Spectrum Disorder with or without comorbid ADHD Group; N-ASD, TD and ADHD grouped together.

TABLE 2 | ROC analysis and accuracy for different combination of groups.

Comparison	Scale	# Pos.	# Neg.	AUC	S.E.	Sig.	95% C.I.	Cut-off	Sensibility	Specificity	Accuracy
ASD vs. N-ASD	AQ	101	97	0.877	0.024	<0.001	0.830–0.923	73	0.822	0.794	0.808
	EQ	94	61	0.806	0.035	<0.001	0.737–0.874	26	0.745	0.721	0.733
ASD vs. ADHD	AQ	101	33	0.795	0.039	<0.001	0.719–0.872	77	0.723	0.727	0.725
	EQ	94	32	0.680	0.051	0.002	0.581–0.779	18	0.362	0.937	0.650
ASD vs. TD	AQ	101	64	0.918	0.021	<0.001	0.877–0.959	73	0.822	0.891	0.857
	EQ	94	29	0.945	0.019	<0.001	0.907–0.983	26	0.745	1.000	0.873

ASD and ADHD individuals at the ADOS-2 is based on the repetitive and restricted behaviors that remain a specific core domain for ASD (Grzadzinski et al., 2016). Similar findings have been reported when individuals with ASD and ASD+ have been compared in their social affect profile at the ADOS-2 (Harkins et al., 2021). However, other measures, based on parent-reports, such as the Social Responsiveness Scale, 2nd Edition (SRS-2) (Constantino and Gruber, 2012), demonstrated a significant group difference between children with ASD and children with ASD+, the latter group scoring significantly higher. Overall, these findings underline that there is still inconsistency in the psychological measures sensitivity and specificity to disentangle the behavioral phenotype of the two conditions both separately and even more, when associated.

To address this gap, in our study, we explored whether two quantitative measures of autism traits and empathy such as the C-AQ and C-EQ were able to distinguish children with ASD with or without ADHD, from children with ADHD alone, and children with typical development. For this reason, we used a ROC analysis to determine the threshold score that maximized classification accuracy among the conditions for each measure (**Figure 3**). We found that the C-AQ has good accuracy at distinguishing between ASD and N-ASD children (80%), and between ASD and TD (86%) and a satisfactory accuracy at discriminating between ASD and ADHD (73%). Our results confirm that the C-AQ is a reliable quantitative measure not only to discriminate between an ASD vs. a non-ASD condition as well as a typical development, but is also able to put apart, with a satisfactory discriminative power, an ASD from an ADHD condition. Furthermore, a cut-off of 73 was able to reliably distinguish between ASD from non-ASD conditions, while a cut-point value of 77 was the best score for discriminating ASD from ADHD. These threshold values are very similar to those reported by Auyeung et al. (2008) (cut-off of 76 for ASD vs. TD groups) confirming the cross-cultural stability of the instrument.

Conversely, the C-EQ demonstrated good accuracy at distinguishing between ASD and TD (87%) but not a sufficient accuracy in the distinction between ASD and ADHD (65%). In line with previous evidence, one possible explanation for the latter finding is that also children with ADHD may show a specific deficit in empathy (especially the affective component) as it has been reported by several studies (Abdel-Hamid et al., 2019; Harmsen, 2019; Cristofani et al., 2020; Fantozzi et al., 2021; Lasmono et al., 2021). Furthermore, this result is not unexpected, being that empathy is a trans-categorical psychological trait, which implies many aspects of social cognition, prosocial behavior, emotion regulation and morality, and is involved in different neurodevelopmental and psychiatric conditions (Henry et al., 2016; Lamm et al., 2016; Cotter et al., 2018). To account for this potential bias, from a clinical perspective, it might be considered that the cut-off of 18 (see **Supplementary Table 1**), maximizes specificity (94%) to the detriment of sensitivity (36%). Another possible explanation for a reduced accuracy of the C-EQ in discriminating between ASD and ADHD is that within the autism heterogeneity, a subgroup of children and individuals with ASD, for their specific clinical profile or different mechanisms of compensation and masking, do not actually score significantly lower at the empathy tasks, compared with neurotypical individuals (Rueda et al., 2015; Alkire et al., 2021; Rieffe et al., 2021). Indeed, to reach a sensibility for ASD of 90%, the cut-off on C-EQ should be raised to 32, leading to a specificity of 76% compared to TD and 22% compared to ADHD. As for the C-AQ, we also confirmed for the C-EQ good cross-cultural stability (Baron-Cohen and Wheelwright, 2004).

Univariate analysis (**Figures 1**, **2**) revealed significant group differences between ASD, scoring the highest, ADHD, presenting intermediate scores and TD scoring the lower. This finding supports the robustness of the two measures to detect ASD traits not only in relation to typical development but also vs. other clinical conditions sharing common traits, such as ADHD. Interestingly, in our sample, children with ASD+ did not score significantly higher than children with ASD alone. A recent study by Pehlivanidis et al. (2021) reported similar findings at the AQ, showing that adults with ASD+ and ASD− had comparable scores, in turn significantly higher than the ADHD group. It means that the effect of comorbid ADHD seemed not to be additive in the reported severity of ASD and the reasons should be examined in future studies. We hypothesized two possible reasons, as follows: it might be that within the autism spectrum the psychological measures detected by the two quantitative instruments are fairly independent of ADHD traits; alternatively it could be related to a behavioral overshadowing of ASD on ADHD (for instance, if a child has difficulties in making friends due to impulsivity, but has also due to major social-communication difficulties, the latter can overshadow the first one).

Limitations

The study has some limitations. The first limitation concerns the demographic characteristics of the sample. Furthermore, average IQ in ASD+ children was higher than in the other groups. Previous studies demonstrated that C-AQ and C-EQ

are independent of age and IQ (Baron-Cohen et al., 2001, 2006; Chapman et al., 2006; Auyeung et al., 2008), Also a *post hoc* stratified boot-strapped analysis led to similar results. Secondly, we have not been able to collect ADHD-related specific measures, therefore, for the purpose of the study, we focused on the discriminative ability of quantitative, parent-report, quick screening measures such as the C-AQ and the C-EQ to detect, relatively early, an ASD condition vs. other clinical overlapping conditions such as ADHD. Furthermore, in future larger studies, cluster analysis and single item resolution analysis would be worthy to explore the specificity and transdiagnostic domains of autism traits distribution and empathy in a hybrid dimensional approach.

CONCLUSION

In our study we found that the C-AQ and C-EQ are reliable and robust instruments to quantify ASD traits and empathy in children with normal intelligence and fluent language with and without comorbid ADHD as compared to children with an ADHD condition alone and TD children. Specifically, within the autism spectrum, the presence of a comorbid ADHD does not influence the severity and distribution of autistic traits and empathy, while children with a diagnosis of ADHD displayed an intermediate phenotype, with higher levels of autistic traits and lower empathy compared to TD children. The results of our study will also contribute to the translational efforts in developing better tailored treatments and preventive strategies.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of CNR (ethical clearance, 01.08.2018). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SA contributed to the study design and to the manuscript draft. DV conducted the statistical analysis and statistical data interpretations and participated in the manuscript draft. ACe contributed with statistical data interpretations and to the manuscript draft. EL, CC, FF, ACa, and FlM enrolled and tested the ASD+, ASD−, and TD participants. RS, MA, and EG enrolled and tested the ADHD participants. FrM and GT contributed with statistical analysis and statistical data interpretations. GP contributed to the coordination of the study. AG participated in the study design, coordinated the enrollment of ADHD participants and contributed to the manuscript draft. LR designed and supervised the study and drafted the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Article

Morphing Task: The Emotion Recognition Process in Children with Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder

Cristina Greco [1], Maria Romani [1], Anna Berardi [1], Gloria De Vita [1], Giovanni Galeoto [1,2], Federica Giovannone [1], Miriam Vigliante [1] and Carla Sogos [1,*]

[1] Department of Human Neurosciences, Sapienza University of Rome, 00185 Rome, Italy; cristinagreco.npi@gmail.com (C.G.); maria.romani@uniroma1.it (M.R.); anna.berardi@uniroma1.it (A.B.); gloria.devita@uniroma1.it (G.D.V.); giovanni.galeoto@uniroma1.it (G.G.); federica.giovannone@uniroma1.it (F.G.); miriam.vigliante@uniroma1.it (M.V.)
[2] Istituto Neurologico Mediterraneo Neuromed IRCCS, 86077 Pozzilli, Italy
* Correspondence: carla.sogos@uniroma1.it

Abstract: Recognizing a person's identity is a fundamental social ability; facial expressions, in particular, are extremely important in social cognition. Individuals affected by autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) display impairment in the recognition of emotions and, consequently, in recognizing expressions related to emotions, and even their identity. The aim of our study was to compare the performance of participants with ADHD, ASD, and typical development (TD) with regard to both accuracy and speed in the morphing task and to determine whether the use of pictures of digitized cartoon faces could significantly facilitate the process of emotion recognition in ASD patients (particularly for disgust). This study investigated the emotion recognition process through the use of dynamic pictures (human faces vs. cartoon faces) created with the morphing technique in three pediatric populations (7–12 years old): ADHD patients, ASD patients, and an age-matched control sample (TD). The Chi-square test was used to compare response latency and accuracy between the three groups in order to determine if there were statistically significant differences ($p < 0.05$) in the recognition of basic emotions. The results demonstrated a faster response time in neurotypical children compared to ASD and ADHD children, with ADHD participants performing better than ASD participants on the same task. The overall accuracy parameter between the ADHD and ASD groups did not significantly differ.

Keywords: autism spectrum disorder (ASD); attention deficit hyperactivity disorder (ADHD); emotion recognition; facial expression; pediatric

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1. Introduction

Faces are complex stimuli that convey social and affective information; recognizing a person's identity is a fundamental social ability [1]. In fact, people deduce personality traits from the similarity between the morphological features of a person's face and emotional expressions [2,3]. Individuals affected by autism spectrum disorder (ASD) display impairment in the recognition of emotions and, consequently, also in the recognition of expressions related to emotions, even their identity.

This is one of the reasons that the practical and clinical applications of automatic emotion recognition have been extensively tested and validated in some neurodevelopmental disorders [4–6], particularly in participants with ASD and attention deficit hyperactivity disorder (ADHD).

Facial expression recognition involves dynamic and multimodal phenomena. Facial transformation from a neutral expression sends complex signals, which are converted into emotions [7]. The practical and clinical applications of automatic emotion recognition have been extensively tested and validated [8–12].

ASD is known to be associated with difficulties in using facial expressions to convey emotions and deficits in emotional reciprocity [13–17]. Difficulties in understanding emotions through facial expressions affect a person's ability to appropriately respond to different situations [18–22]. Since the 1970s, impaired emotion recognition has been described in people with ASD. The six basic emotions (happiness, sadness, fear, disgust, anger, and surprise) identified by Ekman have been investigated [23]. However, emotion recognition findings have been inconsistent to date. Some authors have linked ASD to deficits in the recognition of specific subsets of emotions, which have variously included fear, anger, disgust, and sadness [24–27], while others observed specific deficits in the recognition of anger or surprise [28,29]. Finally, other studies found no evidence of emotion recognition impairments compared to the general population [30]. It appears that the performance of ASD participants on emotion recognition tasks is influenced by different variables, including age. Some authors found that emotion recognition deficits in children aged 5–7 years decreased in late childhood, but no further improvement has been detected during adolescence or adulthood [31]. A meta-analysis carried out by Lozier and colleagues [32] confirmed that ASD was associated with face-emotion recognition deficits, and that the magnitude of these deficits increased with age.

ADHD is a neurodevelopmental disorder characterized by attention deficit, hyperactivity, and impulsivity (for a more in-depth view, see the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5)) [14]. A number of studies found that, in addition to impaired executive functions and problematic behavior [33], emotion recognition deficits associated with interpersonal difficulties may be present, similar to those found in ASD [34].

Children with ADHD are less accepted and often rejected by their peers [35–37]. These social difficulties are likely to persist into adulthood. Although some theories assume that emotion recognition deficits are explained by general attentional deficits, increasing evidence suggests that they may actually constitute a distinct impairment. Schönenberg et al. [38] found that individuals with ADHD exhibited impaired recognition of sad and fearful facial expressions, while Schwenck et al. [39] did not find significant differences in emotion recognition between children with ADHD and matched controls. Finally, Jusyte et al. [8] found that, compared to controls, children with ADHD exhibited lower accuracy rates across all basic emotional expressions. Although emotion recognition abilities have been investigated in both ADHD and ASD, few studies have directly compared the performance obtained by individuals with the aforementioned disorders. Furthermore, existing studies have measured expression recognition abilities by employing static images of expressions at their highest intensity. For instance, Berggren et al. [40] used the Frankfurt Test for Facial Affect Recognition to compare matched samples of children with ADHD and ASD. They found that the ADHD group responded faster than the ASD group, but they did not find any difference in accuracy between the two groups. The same test was used by Sinzig et al. [41], who reported facial affect recognition deficits in children suffering from ADHD and in children suffering from both ASD and ADHD when compared to healthy controls. Demopoulos et al. [42] compared the social cognitive profiles of children and adolescents with ASD and ADHD using the Diagnostic Assessment of Nonverbal Accuracy-2 (DANVA-2) to measure effects on facial and vocal identification abilities. Both groups performed significantly worse than the normative sample.

The recognition of facial expression involves dynamic and multimodal phenomena. The transformation of the face from a neutral expression sends complex signals, which are converted into emotions [7–43].

The morphing task has been used since 2001 to evaluate children with ADHD and ASD [44], and it is still used today [45–47]. However, studies in the literature have primarily focused on visual updating; studies comparing the two clinical groups (ADHD and ASD) with a control group through human and animated morphing tasks are scarce.

We aimed to investigate the performance of ADHD, ASD, and TD participants with regard to both accuracy and speed in the morphing task and to determine whether the use

of dynamic pictures representing cartoon faces could significantly facilitate the process of recognizing emotions in ASD participants.

We hypothesized that children with ADHD would respond faster than ASD participants due to their executive and attention deficits [40], which is in contrast to the findings of Swenck et al. in 2013, who demonstrated no difference in response accuracy or speed between the ADHD and control groups [39]. We also expected that response accuracy would be reduced, particularly for negative emotions [32–48]. Finally, based on the results obtained in 2015 by Brosnan with ASD participants [49], we hypothesized that the use of cartoon faces may facilitate the recognition of emotions as compared to stimuli representing human faces.

Our study aimed to provide a watershed in the understanding of the emotion recognition process. While many studies have investigated this process in ADHD and ASD populations, comparative studies between the two clinical populations are scarce and results have been conflicting, especially when conducted using tasks with dynamic images (representing cartoon faces). Therefore, we used dynamic images of cartoon faces in emotion recognition, with the perspective of using the morphing task as a tool to enhance the expression recognition process at the rehabilitation level.

2. Methods

2.1. Participants

Sixty-two children in the age range 7–12 years were recruited and assigned to one of three groups: (1) an ADHD combined type (ADHD-C) group; (2) an ASD group; and (3) an age-matched control group.

All children and parents recruited for the first two groups were referred to the Department of Human Neurosciences at Policlinico Umberto I clinic in Rome for a follow-up evaluation, which included recruitment to our study between May and September 2019. The 21 children in the ADHD group and the 20 children in the ASD group were included after meeting the DSM-5 diagnostic criteria for ADHD-C or ASD, respectively [14], and after scoring $\geq$85 on the Full-Scale Intelligence Quotient (FSIQ). Participants were excluded if their first language was not Italian, in order to avoid bias related to linguistic difficulties, or if they had comorbid medical or psychiatric disorders detected through a review of their medical record, in order to avoid the risk of bias due to the associated diagnosis. The control participants were 21 children with typical development (TD) recruited from a primary school in Rome. The inclusion criteria for this group were an age range of 7–12 years and an average score on the Raven's Coloured Progressive Matrices (CPM) [50] or Standard Progressive Matrices (SPM) [51] (above the 25th percentile). The exclusion criteria were visual or auditory impairment or neurodevelopmental, neurological, or organic disorders, as determined through an interview with the parents. The study was approved by the ethics committee of Sapienza University of Rome and performed in compliance with the Declaration of Helsinki (2000). Written informed consent was obtained from the participants' parents.

2.2. Morphing Task

All participants were evaluated using a morphing task. The morphing technique is an image processing technique commonly used to metamorphosize from one image to another (e.g., an initial image of a child gradually turns into an image of an adult).

In our study, 24 videoclips with neutral faces gradually developed basic emotions (sadness, anger, surprise, happiness, disgust, and fear). Videoclips were built using FantaMorph (version 5, Abrosoft Co., Eden Prairie, MN, USA), a software used to create morphing images and sophisticated animation effects, including the transformation of the images used.

It should be emphasized that the group of complex emotions (i.e., pride, embarrassment, jealousy) was excluded since these emotions imply the attribution of a cognitive state as well as an emotion and are more dependent on context and culture [52]. They can also

be based on belief [53]. Children with TD begin to recognize and verbally label complex emotions, such as embarrassment, pride, and jealousy, at age 7 [54]. Golan et al. [55] suggested that recognition of complex emotions is also impaired in children with ASD.

These videoclips were split into two conditions to compare emotion recognition in human and cartoon faces. These two conditions were chosen on the basis of studies carried out by Jusyte in 2017 [8] and Brosnan et al. in 2015 [49], which analyzed emotion recognition through human animated stimuli (in the first case) and through human and digital animated stimuli (in the second). Our task included a training session and two different conditions (Figures 1 and 2) [56,57].

Figure 1. Example of a frame of a human face without distracting elements (adapted from Fantamorph). ©Jeffrey Cohn, S52.

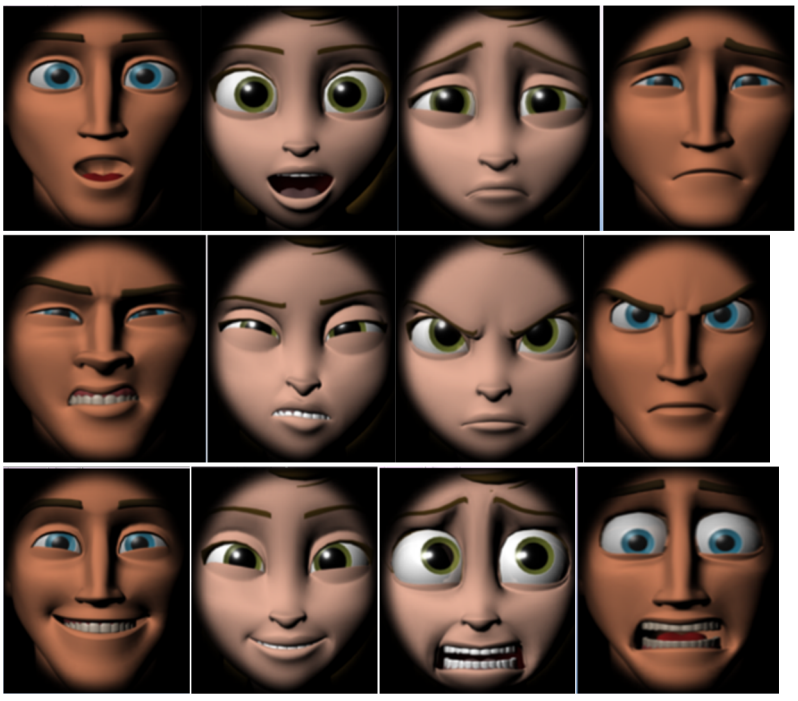

Figure 2. Frames of cartoon faces without distracting elements.

2.3. Training Session

During the training session, participants watched two videoclips in which a neutral expression turned into a sad or happy expression in order to introduce children to the task. All children passed the initial trial and were then admitted to the experiment.

2.4. First Condition

In the first condition, we presented greyscale images representing 12 young adults, six females and six males, selected from the Cohn-Kanade database [56,57]. We removed potentially distracting details, such as hair or body parts, in order to focus attention on the faces.

2.5. Second Condition

In the second condition, we used colored pictures showing cartoon faces of six females and six males. These images were included in the Facial Expression Research Group Database (FERG-DB) [58]. They were digitally generated using Maya software (version 1, Autodesk, Mill Valley, CA, USA) and the images were created using a 2D renderer (version 7.1.8, Unity, San Francisco, CA, USA) [58].

2.6. Procedure

Participants and their parents were informed about the study procedures and all parents provided written informed consent to participate. The administration room, which was the same for the two clinical groups, was located within the school for the control group. The room had a table with a notebook and two chairs (one for the participant and one for the doctor) and no distracting elements such as posters, billboards, or games.

In the training session, participants were instructed by the child neuropsychiatrist to press a button on the keyboard as soon as a face corresponding to the lexical label appeared on the screen.

Each videoclip lasted 7 s and included 60 frames. We recorded answers and response latency on the appropriate answer sheet. In both conditions, videoclips were presented in the same random order obtained by pseudo-randomization for each child. The experiment was conducted using a Microsoft Office PowerPoint presentation (total time about 20 min), shown on a computer with a 10-inch screen and at a distance of 50 cm.

For statistical analysis, SPSS 19 software (International Business Machines Corporation, Armonk, NY, USA) was used. In order to compare the performance obtained by ADHD, ASD, and TD participants with regard to both accuracy and speed on the morphing task, we performed the following analyses:

- The Chi-square test (χ^2) was performed to investigate potential relationships between the number of errors (as categorial variables) and the six emotions in the two conditions (human and cartoon faces);
- Multivariate analysis of variance (MANOVA) was used to investigate group differences with regard to response latency (speed in seconds).

3. Results

The clinical participants were 20 children with ADHD combined type (ADHD-C) in the age range 7–12 years old (mean age: 10.12 years; 15 males and 5 females), 21 children with ASD in the age range 7–12 years old (mean age: 10.21 years; 18 males and 3 females), and 21 children in the control group (TD) in the age range 7–12 years old (mean age: 9.33 years; 13 males and 8 females). Demographic characteristics are reported in Table 1.

Table 1. Demographic characteristics of the included participants: 21 children with typical development (TD), 20 children with attention deficit hyperactivity disorder (ADHD), and 20 children with autism spectrum disorder (ASD). The clinical participants were 20 children with ADHD.

	ASD	ADHD	TD
Mean age (range)	9.33 (7–12)	10.12 (7–12)	10.12 (712)
Female (number (%))	8 (38)	5 (25)	3 (15)

The Chi-square test was used to compare response accuracy between the three groups in order to determine if there were statistically significant differences ($p < 0.05$; $p < 0.01$) in

the recognition of basic emotions. In condition 1 (human faces), ASD children exhibited a significantly higher error frequency as compared to TD participants when they were asked to recognize disgusted faces (0.3% ADHD, 0.4% ASD, 0.2%TD; $\chi^2 = 7.612$; $p = 0.022$). With regard to surprise, the ADHD group exhibited the highest error frequency compared to the other two groups (0.6% ADHD, 0.2 % ASD, 0.2% TD; $\chi^2 = 6.025$; $p = 0.049$).

In condition 2 (cartoon faces), we found a significant difference in error frequency distribution relative to the emotion of sadness between the ADHD group and the other two groups (1.0% ADHD, 0.0% ASD, 0.0% TD; $\chi^2 = 6.620$; $p = 0.037$). With regard to disgust, the ADHD group had the highest percentage of errors (0.4% ADHD, 0.3% ASD, 0.2% TD; $\chi^2 = 9.371$; $p = 0.009$).

We compared the response accuracy for the aforementioned emotions between the two clinical groups (ADHD and ASD). The results were similar to those obtained in the previous phases of this study. In particular, in condition 1 (human faces) we found no significant differences between the ADHD and ASD groups in identifying the emotion of disgust, while the error frequency distribution for surprise was significantly higher in the ADHD group (0.8% ADHD, 0.2% ASD; $\chi^2 = 3.881$; $p = 0.049$). In condition 2 (cartoon faces), the percentage of error in identifying the emotion of disgust was higher in the ADHD group relative to the ASD group (0.6% ADHD, 0.4% ASD; $\chi^2 = 4.020$; $p = 0.045$), and the error frequency for sadness was higher in the ADHD group (1.0% ADHD, 0.0% ASD; $\chi^2 = 3.399$; $p = 0.065$).

3.1. Misidentified Emotions

In condition 1, the emotion disgust was more frequently confused with anger in both clinical groups compared to the control group (0.4% ADHD, 0.4% ASD, 0.2% TD; $\chi^2 = 15.899$; $p = 0.045$). The ADHD and TD groups tended to confuse fear and the facial expression of sadness more frequently than the ASD group, while the ASD group more often confused fear and surprise compared to the other two groups (sadness: 0.3% ADHD, 0.1% ASD, 0.5% TD; surprise: 0.0% ADHD, 1.0% ASD, 0.0% TD; $\chi^2 = 22.579$; $p = 0.032$). In condition 2, the ADHD group more frequently confused disgust and anger as compared with the TD group, which confused these emotions less frequently (0.4% ADHD, 0.3% ASD, 0.2% TD; $\chi^2 = 13.592$; $p = 0.035$).

3.2. Response Latency

In order to explore the presence of significant differences between the three groups regarding response latency (parameter speed in seconds), we conducted a multivariate analysis of variance (MANOVA). Wilks' multivariate Lambda test suggested the existence of statistically relevant differences in response latency between the three groups ($\lambda_{Wilks} = 0.220$, $F = 1.701$, $\eta^2 = 0.531$, $p = 0.020$). To report these results, we report the name of the emotion followed by M (male face) or F (female face) to indicate the gender of the stimulus presented. In the post hoc comparison in condition 1 (Table 2) for the emotion happiness F and disgust M, the TD group responded faster than the ASD and ADHD groups. For the emotions surprise M and F, anger and happiness M, and disgust F, the ASD group responded slower than the ADHD and TD groups. Concerning the emotion fear F, response latency in the ASD group was longer than in the TD group, while the ADHD group responded faster than the ASD group for anger M (Table 2).

In condition 2, the post hoc comparison in Table 3 showed slower response times in the ASD group compared to the other two groups. For the emotions surprise F and sadness M, the ASD group responded slower than only the TD group (Table 3).

Table 2. Post hoc comparison: diagnostic groups × latency morphing human faces.

Feeling of Human Face	Groups			Comparison		χ^2
	ADHD Mean ± SD	ASD Mean ± SD	TD Mean ± SD	ASD vs. TD	ADHD vs. TD	
Happiness_Female Face	4.57 ± 1.764	5.24 ± 1.44	3.24 ± 1.31	$p < 0.01$	$p < 0.05$	0.243
Disgust_Male Face	5.09 ± 1.05	5.23 ± 1.72	4.14 ± 1.55	$p < 0.05$	$p < 0.05$	0.104
Surprise_Male Face	4.73 ± 1.43	5.56 ± 0.86	4.75 ± 1.19	$p < 0.05$	Not significant	0.103
Anger_Female Face	4.71 ± 1.43	5.83 ± 1.13	4.54 ± 1.30	$p < 0.01$	$p < 0.05$	0.173
Fear_Female Face	5.66 ± 1.56	6.62 ± 0.75	5.31 ± 1.43	$p < 0.01$	Not significant	0.161
Happiness_Male Face	4.01 ± 1.06	5.09 ± 1.24	4.22 ± 0.82	$p < 0.01$	$p < 0.05$	0.170
Anger_Male Face	4.86 ± 1.66	5.95 ± 1.07	5.14 ± 1.11	$p < 0.05$	$p < 0.05$	0.115
Surprise_Female Face	3.66 ± 1.01	4.54 ± 1.41	3.61 ± 0.83	$p < 0.05$	Not significant	0.136
Disgust_Female Face	4.39 ± 1.15	5.29 ± 1.44	4.06 ± 1.06	$p < 0.01$	$p < 0.05$	0.159

Note. ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; TD = typical development; χ^2 = Chi-square test.

Table 3. Post hoc comparison: diagnostic groups × morphing latency cartoon faces.

Feeling of Cartoon Face	Groups			Comparison		χ^2
	ADHD Mean ± SD	ASD Mean ± SD	TD Mean ± SD	ASD vs. TD	ADHD vs. TD	
Fear_Male Face	3.56 ± 1.49	4.711 ± 1.823	3.13 ± 1.43	$p < 0.01$	$p < 0.05$	0.157
Sadness_Female Face	3.42 ± 1.09	4.14 ± 1.3	2.97 ± 0.65	$p < 0.01$	$p < 0.05$	0.184
Anger_Female Face	3.04 ± 0.93	4.46 ± 2.17	3.09 ± 1.07	$p < 0.01$	Not significant	0.167
Happiness_Male Face	2.73 ± 0.8	3.71 ± 2	2.35 ± 0.49	$p < 0.01$	$p < 0.05$	0.176
Disgust_Female Face	3.57 ± 1.54	4.7 ± 2.12	3.07 ± 1.24	$p < 0.01$	$p < 0.05$	0.149
Surprise _Female Face	3.46 ± 1.05	4.07 ± 1.91	2.97 ± 0.65	$p < 0.01$	$p < 0.05$	0.111
Sadness_Male Face	3.54 ± 1.4	4.1 ± 1.91	2.8 ± 0.542	$p < 0.01$	$p < 0.05$	0.132

Note ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; TD = typical development; χ^2 = Chi-square test.

4. Discussion

In this study, we investigated the behavior (in terms of speed and accuracy) of ADHD and ASD individuals in response to dynamic emotional images in a morphing task. When compared to the ASD and ADHD groups, children with TD performed better in terms of speed, while the ADHD group performed better than the ASD group. In terms of accuracy, there was no significant difference between the ADHD and ASD groups.

The findings in our analysis confirm previous studies that found a deficit in the emotion recognition process in subjects with ASD and ADHD. Our study shows that the poor performance of the ASD group, particularly for the emotion disgust, is consistent with literature data, especially in regard to Lozier's meta-analysis [32]. Meta-analyses have mainly involved sets of pictures representing faces and have excluded other kinds of tasks (e.g., cartoon faces). In the study by Brosnan et al. [49], a population of teenagers with ASD was tested using dynamic and static stimuli representing both human and digital faces. Digital stimuli facilitated the ASD group in identifying emotions, both dynamic and static, similar to the control sample. The performance of the ASD group in response to the dynamic and static stimuli of human faces remained low compared to the control group. A similar result was shown in our study. We found that digital stimuli facilitated the ASD group in identifying emotions, such as disgust, compared to both the TD and ADHD groups. Our data differ from Berggen et al. [40], who found a quicker response

time for identifying emotions in the ADHD vs. ASD group compared to the control group, and no significant difference with respect to the performance of the TD group.

Specifically, in condition 1 (human faces), the emotion disgust was least recognized by the ASD group, while the emotion surprise was least recognized by the ADHD group. In condition 2 (cartoon faces), the highest error frequency was shown for the emotions sadness and disgust, in both cases by the ADHD group vs. the TD and ASD groups.

These results suggest that digital faces/cartoons may facilitate recognition for participants in these groups. The ASD group made fewer mistakes recognizing disgust, one of the hardest emotions to perceive, in condition 2. This facilitation suggests that the ASD group may be able to use atypical strategies to recognize emotions. This hypothesis originated from previous studies [30–59] in which "exaggerated" facial expressions were perceived as "typical" expressions in static stimuli animated by participants with ASD [60]. Animated stimuli resulted in an extreme representation of emotion in the details of the face, which leads to easier emotion recognition for these participants. The mistakes in emotion recognition were analyzed. The ASD and ADHD groups confused disgust and fear in human faces, and fear was significantly confused with sadness (TD > ADHD > ASD) and surprise (ASD > other groups). In condition 2, disgust was confused with anger (ADHD > TD). These results confirm the emotional profiles of these two disorders and the tendency, mainly in ADHD subjects, for easy recognition of negative emotions, such as anger. Furthermore, ASD participants better recognized emotions in cartoons.

A qualitative observation showed that in our sample there was a lower error rate in cartoon emotion recognition than in human faces. Happiness is the easiest emotion to recognize. Disgust and fear, especially in condition 1, were the most difficult to recognize. This is consistent with literature stating that fear is easier to perceive than recognize. Of the six basic emotions, fear may be defined as the one that conveys the strongest multisensorial signals. These signals, such as environmental threats, may play an important role in decoding emotions [61].

Disgust, after fear, was the most difficult emotion to identify, and was recognized better in the oldest neurotypical participants (similar to fear). Conversely, in ASD, the recognition deficit increased with age, especially for disgust, fear, and sadness [32]. The variability of results for different emotions reflects differences in emotion recognition development by age [62]. For the speed parameter in the "human faces" condition, a longer response latency of the ASD group was shown for both negative and positive emotions. Furthermore, the ADHD group had a shorter response time for anger M compared to participants with TD and ASD. The cartoon condition showed a significantly longer response latency in the ASD group, as compared to the ADHD and TD groups, in negative emotions such as fear M, sadness M/F, anger F, and disgust F, and in only two positive emotions, happiness M and surprise F. These response latency results confirmed the hypothesis that both clinical groups had difficulty in emotion recognition that seems to be related to inherent social difficulties in communication and atypical interactions.

In brief, the difficulty in complex emotion recognition in these participants was evident by:

- Major latency in emotion recognition for both clinical groups;
- Greater emotion recognition error rate compared to the control group;
- Tendency to confuse some emotions (see fear/sadness, anger/disgust).

We hypothesized that there would be an emotion recognition deficit in children with ASD and ADHD compared to the control TD group when using a dynamic stimulus, such as the morphing test. Overall, a faster response time was detected in the group of children with TD compared to the ASD and ADHD groups. The ADHD group, in turn, had a faster response time than the ASD group. Regarding the accuracy of the overall performance, the ADHD and ASD groups did not show a significant difference, and mostly seemed to be superimposable, while the performance of the TD group was qualitatively better. Our data confirm previous studies in the literature. The advantages of the morphing technique have been proven by evidence. Dynamic stimuli may somehow facilitate the emotion recognition

process in both groups because a "dynamic picture" impersonalizes human interactions in a more realistic way. In everyday life, facial expressions are rarely transmitted and decoded as static snapshots of internal states [7]. Dynamic faces represent a richer and more valid view of the way in which emotions and facial expressions are identified [60–63]. The morphing technique is used in many fields, from healing processes and surgery dynamics [59–64] to the emotion recognition process in psychiatric pathologies [65]. Our data also show that the use of digitalized faces/cartoons may represent a means to facilitate recognition in ASD participants.

Considering the remarkable facilitation and improved response to dynamic pictures, we hypothesize that the morphing technique could be a valuable aid to reinforce the bases of mind theory and may support the improvement of social reciprocity in ADHD [66] and ASD participants in a therapeutic context.

Several studies have been performed in order to better understand the utility of computer-based interventions (CBIs) in teaching social and emotional skills to subjects with ASD [67,68].

Ramdoss et al. [69], in a systematic review, concluded that CBIs showed mild effects on social and emotional skills in ASD, and that CBIs may represent a promising practice to improve these abilities. However, the authors underlined several limitations, including the heterogeneity of subjects in terms of age and cognitive capacities. Furthermore, the literature reports have stressed the difficulties that individuals with ASD may have in applying the abilities acquired in CBIs to real-life situations, and has suggested combining this approach with a group activity or face-to-face instruction with an adult tutor in order to improve generalization in ASD individuals.

Consistent with these studies, the findings of the present study evidenced the possibility that the morphing task might be a way to simplify emotion recognition in these populations, allowing them to understand the internal states of others, enhance their empathy, and, hypothetically, reduce their gaps in social relationships. In our study, this improvement occurred above all for disgust. However, it can be hypothesized that an improvement for other emotions could be achieved by perfecting the videos through the contextualization of cartoon faces.

This study has some limitations. First, the clinical sample included children of a specific age (7–12 years old). Extending the sample from preschool to adulthood would allow the emotion recognition process to be evaluated throughout life and would allow the accuracy and response latency to be associated with age in these populations, as Richoz showed for the normotypical population [7].

Second, the visual attention parameter (using eye tracking or configurable face processing skills) was not assessed, and consequently the differences in face perception could represent a bias of the study.

Third, all participants included in the study had a pure diagnosis of ASD or ADHD; none had an overlap of the two diagnoses. In addition, all participants had an FISQ of 85 or more. While there is no evidence that these factors influenced the results obtained, we cannot rule out this possibility.

Fourth, the images used in condition 1 were grayscale images of young adults. This could represent a bias with respect to the use of color cartoon images in condition 2. In fact, it has been suggested in the literature, despite the scarcity of studies, that the use of color images of child and adolescent faces may represent a more realistic confirmation of the ability to recognize emotions in the pediatric population.

Additional aspects of interest may be represented by functional Magnetic Resonance Imaging (MRI) studies and the activation of specific brain structures during the emotion recognition process through dynamic tasks [70] and eye-tracking studies with different setting patterns identified [1]. Finally, we used grayscale images in the static task and colored images in the cartoon task, which may have biased our results. The better performance of our participants may be due to the colorfulness of the stimuli. Future studies should evaluate these variables.

This study demonstrates that emotion recognition was facilitated through the use of cartoon faces in ASD and ADHD populations, and that the quality of emotion recognition was comparable between ASD and ADHD participants. This is the first study to compare facial recognition in participants with ADHD, ASD, and TD using a morphing task.

5. Conclusions

The findings of this study may have clinical implications in the planning of alternative strategies for rehabilitation settings for children with neurodevelopmental disabilities. The theoretical implications include a better understanding of the maturational changes underlying social skill deficits. We believe that the morphing task has proven to be useful in behavioral investigations and that its use in a more natural or ecological assessment setting is promising. Finally, these results are important for future research evaluating the emotion recognition process as a therapy goal and the morphing task as a rehabilitation tool in order to improve the social and empathy skills of children with ASD and ADHD.

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Review

The Effects of Physical Exercise on Mental Health: From Cognitive Improvements to Risk of Addiction

Pasquale Caponnetto [1,2,3,*], Mirko Casu [1,*], Miriam Amato [1], Dario Cocuzza [1], Valeria Galofaro [1], Alessandra La Morella [1], Sara Paladino [1], Kamil Pulino [1], Nicoletta Raia [1], Flavia Recupero [1], Cristian Resina [1], Samuele Russo [1], Laura Maria Terranova [1], Jennifer Tiralongo [1] and Maria Chiara Vella [1]

[1] Department of Educational Sciences, University of Catania, 95123 Catania, Italy; miriam.amato1998@gmail.com (M.A.); dariococuzza01@gmail.com (D.C.); galofaro.valeria@tiscali.it (V.G.); alessandralamorella@gmail.com (A.L.M.); sara_paladino@hotmail.com (S.P.); kamilpulino17@gmail.com (K.P.); Nikoxx22@gmail.com (N.R.); flarecupero92@gmail.com (F.R.); cristian97ct@gmail.com (C.R.); SamRush190398@gmail.com (S.R.); Terranova-laura@virgilio.it (L.M.T.); jennitiralongo@icloud.com (J.T.); chiaravella15@gmail.com (M.C.V.)
[2] Department of Clinical and Experimental Medicine, Center of Excellence for the Acceleration of Harm Reduction (CoEHAR), University of Catania, 95123 Catania, Italy
[3] Center for Tobacco Prevention and Treatment, University Hospital "Policlinico G.Rodolico-San Marco", University of Catania, 95123 Catania, Italy
* Correspondence: p.caponnetto@unict.it (P.C.); mirko.casu@live.it (M.C.)

Abstract: (1) *Background*: we aimed to investigate the effects of physical activity on cognitive functions and deficits of healthy population and other needy groups. Secondly, we investigated the relation between healthy habits and psychopathological risks. Finally, we investigated the impact of COVID-19 pandemic on exercise addiction and possible associated disorders. (2) *Methods*: From April 2021 to October 2021, we conducted a review aimed at identifying the effects of physical exercise on mental health, from cognitive improvements to risk of addiction; we searched for relevant studies on PubMed, Web of Science, EMBASE, PsycINFO and CINHAL. (3) *Results*: For the first purpose, results indicated multiple effects such as better precision and response speed in information processing tasks on healthy populations; improvement of executive functions, cognitive flexibility and school performance in children; improvement of attention and executive functions and less hyperactivity and impulsiveness on children with attention deficit hyperactivity disorder (ADHD); improvement of executive and global functions on adults; improvement of overall cognitive functioning on patients with schizophrenic spectrum disorder or bipolar disorder. Data also demonstrated that exercise addiction seems to be related to low levels of education, low self-esteem, eating disorders and body dysmorphisms. Eventually, it was found that people with lower traits and intolerance of uncertainty show a strong association between COVID-19 anxiety and compulsive exercise and eating disorder. (4) *Conclusions*: these findings underline on one side the beneficial effects of physical activity on cognitive function in healthy individuals in a preventive and curative key, while on the other side the importance of an adequate evaluation of psychological distress and personality characteristics associated with exercise addiction.

Keywords: physical activity; exercise addiction; sport addiction; cognitive functions; executive functions

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1. Introduction

According to the World Health Organization (WHO) definition, physical exercise is "any body movement made by skeletal muscles which requires waste of energy": this last one includes whatever everyday physical activity, and it is considered a determinant of a healthy lifestyle. Differently, "sport training" represents a lower-ranking classification compared to physical exercise, characterized by planning, organization, temporal repetitiveness and a final or intermediate aim to improve, or maintain, one or many physical

well-being factors. Physical exercise is an important element which leads to beneficial effects in terms of physical and cognitive human being functioning [1].

"Cognitive processes" are defined as specific mental functions such as: memory (conceived in its different forms), attention (both general and selective), language, praxis functions (which is the capacity of making finalized movements to reach a result) and gnostic functions (namely being able to perceive and recognize). Lastly, there are the so-called "executive functions": the ability to plan, control and coordinate thoughts and actions [2].

Health professionals should promote sport as an element of cognitive stimulation but at the same time also identify those rare cases in which a sport addiction can occur.

The aim of this review is to investigate the relationship between physical activity and cognitive functions by putting the stress on both positive effects and negative ones too (if there are any); such an objective was achieved.

There are several beneficial effects of physical activity: for instance, exercise helps to avoid physical and mental issues in children and adults by promoting neuronal plasticity, [3], making the cognitive decline in the elderly slower and improving deficient conditions in the youth who suffer from development disorders [4]. Moreover, another positive aspect may well be the strengthening of social and relational skills [5]. Furthermore, physical exercise can be considered as a possible form of therapy both in the treatment of psychopathologies and neurodegenerative illnesses [6] and as an alternative and complementary therapy too [4]. Recent studies have shown the importance of physical activity thanks to its capacity of protecting the immune system during the COVID-19 pandemic [7]. In addition, physical exercise can attenuate anxiety, stress, and depression symptoms, improving sleep disorders [8]. Nevertheless, anxiety and depression can be associated to compulsive physical exercise [9] since there is a weak boundary between sport positive aspects and the risk of determining dependence: the actual research, indeed, also underlines the cons of doing sport (for instance, the exercise addiction might cause relevant psychophysical consequences) [10].

Exercise addiction is a psychological disorder characterized by a compulsive engagement in any form of physical exercise, despite negative consequences. While regular exercise is generally a healthy activity, exercise addiction generally involves performing excessive amounts of exercise to the detriment of physical health, spending too much time exercising to the detriment of personal and professional life, and exercising regardless of physical injury [11–13]. It may also involve a state of dependence upon regular exercise which involves the occurrence of severe withdrawal symptoms when the individual is unable to exercise [11]. In fact, Aidman and Woolard suggested that the symptoms that appear in athletes 24–36 h after missing a planned training session when it is impossible or canceled should be used as the criteria for the diagnosis of exercise addiction. These withdrawal signs include anxiety; restlessness; a feeling of guilt, tension, and discomfort; apathy; sluggishness; lack of appetite; sleeplessness; and headaches [14]. Exercise addiction also shows a high comorbidity with eating disorders [12].

This type of addiction can be classified under a behavioral addiction in which a person's behavior becomes obsessive, compulsive, and/or causes dysfunction in a person's life [14]. Among DSM-5 criteria for exercise addiction there are: an increase in tolerance, withdrawal symptoms, loss of control, doing physical exercise for too much time, reduction of other activities, continuation of physical activity even if there are physical, psychological, and relational problems [15]. Concerning scientific literature, previous studies highlighted correlations between personal traits and personality [16], and behavioral disorders linked to exercise addiction [17], also analyzing both genetic and environmental causes [18].

Other meta-analyses and systematic reviews focused on the cognitive benefits of physical activity and other meta-analyses and systematic reviews focused on the physical activity addiction. To the best of our knowledge, no reviews were conducted specifically on the effects of physical exercise on mental health and explore the direction from cognitive improvements to risk of addiction. Our aim is to focus specifically on effects of physical

exercise providing an updated view of the current spectrum of knowledges about sport, health benefits and potential risks.

This review led to delineate different aspects of the relationship between sport and cognitive function. On the one hand, its benefits, on the other, the risks that can arise when sports practice leads to addiction.

In addition, the ongoing COVID-19 pandemic has changed many aspects of daily life; during the first global lockdown in March 2020, numerous people were forced to stay at home to prevent further contagion of the virus. Research studies were carried out on physical activity during that period [19], with particular focus on implementing it to provide immune protection against long-term SARS-CoV-2 virus infection [20,21] and to avoid excessive sedentary lifestyle [19]. With the imposition of staying at home and the consequent stress of the global situation, an increased use of physical activity and physical exercise as a form of psychophysical release has been hypothesized, especially to combat boredom and reduce stress [22]; this could have led to the development of compulsive use of physical exercise, also resulting in the development of exercise addiction [15]. We have, therefore, dealt with comparing the few studies in the literature that have investigated the impact of the pandemic on exercise addiction and possible associated disorders.

From now on such topics will be examined in depth in the attempt of providing a clear and schematic recap of materials, methods, and results in order to discuss and find new future perspective research.

2. Materials and Methods

2.1. Search Strategies

From April 2021 until the date of submission of the article (October 2021), the reviewers A.L., C.R., D.C., F.R., J.T., K.P., L.M.T., M.A., M.C., M.C.V., N.R., S.P., S.R. and V.G. (please see section Author Contributions) searched first the databases PubMed, Web of Science, EMBASE, PsycINFO and CINHAL for relevant studies using the following search terms string: ("physical activity" OR "sport") AND ("cognitive functions" OR "cognitive deficits"). Later the same reviewers searched all the databases for relevant studies using the following search terms strings: ("exercise addiction") AND ("COVID-19 pandemic"). The electronic searching was supplemented by hand-searching of reference lists of the included review articles to identify any additional source. This review was fully conducted according to PRISMA guidelines 2020 for Systematic Reviews [23].

2.2. Eligibility Criteria

We included every article meeting the following criteria:

(a) All studies and review published on indexed journals and indexed in PubMed, Web of Science, EMBASE, PsycINFO and CINHAL.
(b) Studies related to:
    i Effects of PA and PE on cognitive functions or deficits.
    ii Exercise addiction, risks, symptomatology, and consequences, also in relation to COVID-19 pandemic.
(c) Written in English.
(d) Published from 2011 until the date of submission of the article.

3. Results

3.1. Characteristics of the Included Studies

The database search identified a total of 3842 articles. After excluding duplicates, we found 2733 unique records, which were initially screened by reviewers S.P., J.T., S.R., A.L., M.C.V. and L.M.T. (please see section Author Contributions), based on title and abstract data. The screening has selected 307 articles to assess for eligibility criteria, 2426 records have been excluded because not matching with the intent of the present review. Three-hundred-and-seven full-text articles were assessed for eligibility, thirty out of these met the

inclusion criteria and were included in the review and 277 were excluded because they did not meet the inclusion criteria (flow diagram, Figure 1).

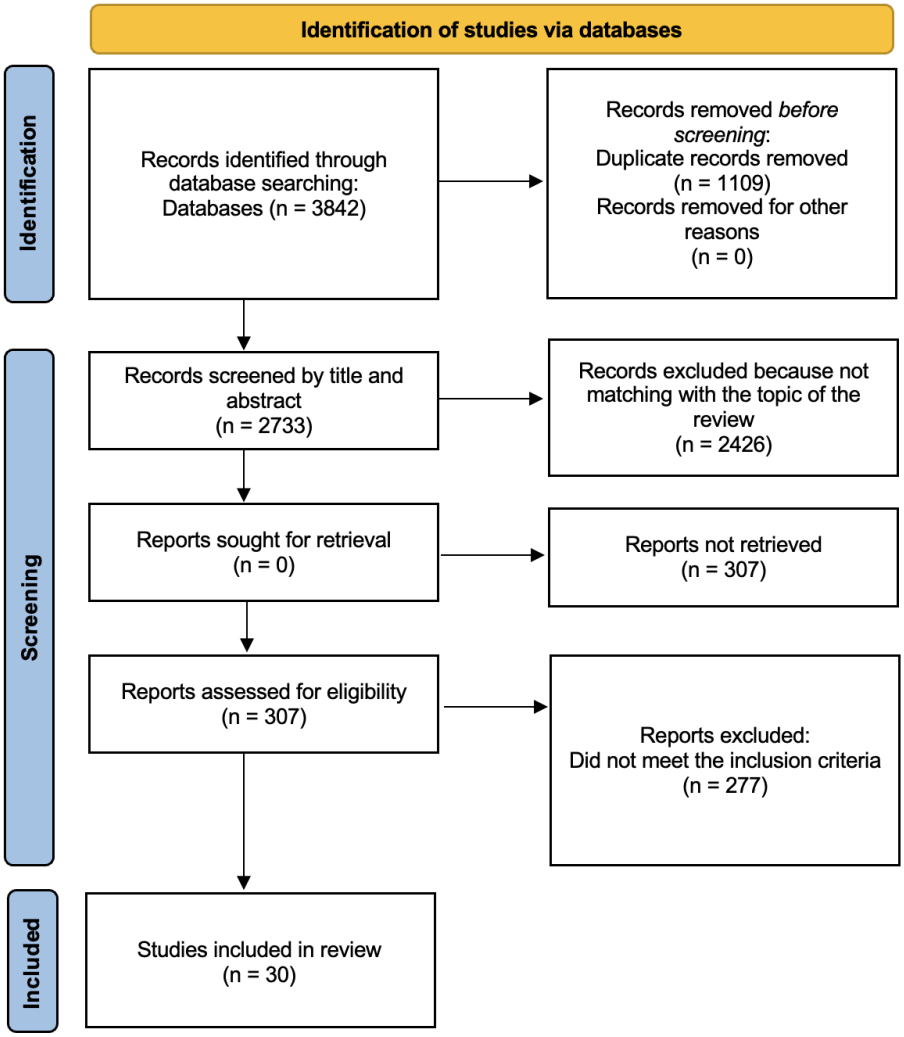

Figure 1. PRISMA (2020) Flow Diagram.

3.2. Benefits of Physical Exercise on Cognitive Functions

The analysis of several research from scientific literature confirmed the positive influence of physical exercise on cognitive functions.

The phenomenon of positive influence of physical exercise on cognitive functions is evident in a randomized study conducted by Chiu et al. [24] in which the sample consisted in thirty-one participants recruited from National Central University, Taiwan. Twelve of these were in the exercise group, who regularly engaged in running or swimming, 11 were members of the university volleyball teams, and 8 were controls. For each, height, weight, and gender were recorded, and fitness was evaluated using a standard measure, the Progressive Aerobic Cardiovascular Endurance Run (PACER) test, a measure of maximal oxygen uptake (VO_{2max}) and an indicator of aerobic physical fitness. A between-subjects design was used with repeated measures of flanker task accuracy and response times (for each of three different time limits for making a response) as within-subject factors. The flanker task measures information processing skill in different time constraints. Response times were used in diffusion model analysis to allow assessment of further relevant within subject parameters. Each participant performed blocks of the flanker task with a fixed response time limit (of which they were informed) for each block, with block orders (and hence the order of presentation of the time limits) being randomized across participants.

Results showed that sporting participation, and more specifically, playing volleyball, was associated with better performance on the flanker task, primarily in terms of accuracy on the task but also with a trend toward faster responding. Additionally, time pressure was associated with reduced accuracy on the task. Response times also showed the expected reduction with the shorter time limits. The pattern of the effects on accuracy for the sporting groups showed more accurate performance for the volleyball group for the shortest time limit compared to controls, with seemingly intermediate performance for the exercise group. The response time data pointed out a trend toward faster responding for the volleyball group for the 1000 ms (intermediate) and 3000 ms (longest time limit) conditions.

3.2.1. Effects of Physical Activity on Cognitive Functions in Relation to Age

Erickson et al. [25] also showed that physical activity (PA) improves cognitive functions in many age ranges. In their general review, they found out that both acute and chronic moderate-to-vigorous PA interventions improved brain structure and function, as well as cognition, and academic outcomes, in children from 6 to 13 years old. They refer to chronic PA behavior as PA that is repeated and lasts longer than a single session or episode. Thus, acute PA research reflects the immediate (transient) response to a single bout of PA, while chronic PA reflects a true change in an individual's baseline (i.e., a prolonged/permanent shift in activity). In the case of chronic PA, the change is not as tightly coupled in time to the last bout of PA. Anyway, moderate evidence from randomized controlled trials (RCTs) indicated an association between moderate-to-vigorous intensity PA and improvements in cognition, including performance on academic achievement and neuropsychological tests, such as those measuring processing speed, memory, and executive function. Two systematic reviews reported by Erickson et al. have described differences in brain structure and function as a result of PA in RCTs, with additional support from cross-sectional comparisons of higher and lower fit groups of preadolescents. Briefly, findings have demonstrated differences in brain structure including greater integrity in specific white matter tracts following PA interventions. Functional brain changes resulting from PA interventions have also been noted in preadolescent children. Such studies have indicated PA intervention-induced benefits to the neuroelectric system as well as changes in functional magnetic resonance imaging (fMRI) signals. Collectively, there is moderate evidence that PA is beneficial to cognition and brain structure and function during preadolescence.

A systematic review by Bidzan-Bluma et al. [3] considered the effect of physical activity on children's cognitive functions. The authors pointed out morphological modifications of cerebral structures and improvements of cognition abilities in children, after physical exercise, analyzing data from 58 articles. Positive influence on selective attention, development of better lexical accomplishment, effective linguistic comprehension and improved syntactical and orthographical skills were also observed. The domains in which the positive effect of physical exercise is more pronounced—in the period between childhood and preadolescence—are working memory, cognitive flexibility, and inhibition control, with consequent pursuit of objectives capability. Moreover, research suggested that physical activity positively influences verbal functions, which facilitates the learning of words in a new language, leading to richer networks of words and their meanings, and also improves spelling performance, language understanding, and the detection of syntactic errors.

Available data in literature suggest that physical exercise also positively affects cognitive domains of ADHD (attention deficit hyperactivity disorder) children [8]. Specifically, a meta-analysis conducted by Cerrillo-Urbina et al. [26] examinated five trials grouped according to the intervention program: aerobic and yoga exercise. The meta-analysis included a total of 249 children diagnosed with ADHD. Of these, 230 participated in aerobic exercises and 19 in yoga exercises. The average sample size of all groups was 31.13 subjects. The meta-analysis suggests that aerobic exercise had a moderate to large effect on core symptoms such as attention, hyperactivity and impulsivity and related symptoms such as anxiety, executive function, and social disorders in children with ADHD. Yoga exercise

suggests an improvement in the core symptoms of ADHD. The main cumulative evidence indicates that short-term aerobic exercise, based on several aerobic intervention formats, seems to be effective for mitigating symptoms such as attention, hyperactivity, impulsivity, anxiety, executive function and social disorders in children with ADHD.

Regarding people over 50 years old, literature showed that acute and long-term PA improves brain structures, functions, and cognition, reducing risks connected to cognitive impairment and lowering the possibility of developing dementia [25]. In a meta-analysis of 39 randomized controlled trials conducted by Barha et al. [27], training showed to improve executive functions, episodic memory, visuo-spatial functions, words fluidity, speed processing and global cognitive functions. In specific, results suggest evidence that a larger amount of PA is associated to lower risks of cognitive decline and dementia, including Alzheimer's disease. Another meta-analysis by Sofi et al. [28] concerning 15 prospective studies which lasted from 1 to 12 years, with a total of more than 33.000 participants, revealed that larger amounts of PA were associated to a 38% lower risk of cognitive decline. A meta-analysis conducted by Beckett et al. [29] involving 10 prospective studies—which included more than 20.000 participants—showed that larger amounts of PA were associated to a 40% lower risk of developing Alzheimer's disease.

Furthermore, regarding the prevention of age-related cognitive decline in elderly with mild cognitive impairment (MCI), a randomized trial conducted by Bisbe et al. [30] explored cognitive effects of choreographic exercise and of a multimodal physical therapy program, with two elderly parallel groups from 65 to 85 years old with amnestic MCI, which are the subjects with highest risk of developing dementia. Participants were assigned to the choreography or physical therapy group and performed exercises twice a week, of which the duration was 60 min, for a period of 12 weeks. The 36 participants were assessed at baseline and after the 12 training weeks, through physical and neuropsychological standardized evaluations. The main result of the study was an improvement in verbal memory performance, measured with the word list learning test from the Wechsler Memory Scale—Third Edition (WMS-III). Changes in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) visual memory subtest and other cognitive scores were considered as secondary results. The comparison between groups showed the following effects: the choreography group obtained more statistically significant benefits in verbal-recognition memory than physical therapy group ($p = 0.003$). Both groups showed better performance in retarded visual recall from RBANS (choreography group: $p = 0.022$; physical therapy group: $p = 0.030$). Eventually, there have been no statistically significant worsening of any neuropsychological aspect.

3.2.2. Effects of Physical Activity on Cognitive Functions in Patients with Mental Disorders

Concerning the psychiatric area, Aas et al. [6] demonstrated that physical activity leads to cognitive functions improvement in patients with severe mental disorders. This was demonstrated by dividing a sample composed of 306 participants with schizophrenia or bipolar disorder and considering two groups: patients that performed physical activity for $\geq$90 min a week and patients that performed physical activity for <90 min a week. Through neuropsychological evaluation, it emerged that the group which performed physical activity for $\geq$90 min a week had better global functioning (GAF scores; $p < 0.001$). This one group also obtained higher scores in working memory ($p < 0.001$), executive functioning ($p < 0.001$), verbal memory ($p = 0.04$) and general intellectual skills ($p = 0.02$). A multiple regression analysis was executed to investigate the relation between physical exercise (as continue variable) with cognitive function, considering age, sex, and psychiatric diagnosis. There was a positive association between physical exercise and working memory ($p = 0.006$) and executive functioning ($p = 0.006$). In addition, a significant association was observed between messenger ribonucleic acid (mRNA) of brain-derived neurotrophic factor (BDNF) levels, measured in plasma through standardized procedures, and general intellectual skills, measured by Wechsler Abbreviated Scale of Intelligence (WASI; $p = 0.037$), showing a higher mRNA of BDNF level in patients with better cognitive performance.

Moreover, this study highlighted a significant association between physical exercise and mRNA of BDNF levels ($p = 0.046$).

Eventually, a meta-review by Chamberlain and Grant [16] confirmed that global cognition of subjects with schizophrenia can be improved through aerobic exercises. Particularly, a systematic review and meta-analysis by Firth et al. [31] focused on seven randomized controlled trials—which involved 292 subjects with schizophrenia—revealed that aerobic exercise improves global cognitive functioning more than control conditions, which included: only table soccer, occupational therapy and treatment as usual ($p < 0.001$).

We were able to note, therefore, how the performance of physical activity produces numerous benefits on cognitive functions on all types of analyzed samples (Table 1).

Table 1. Positive effects of physical activity on cognitive functions.

PARTICIPANTS	BENEFITS OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTIONS
GENERAL POPULATION	Better precision and response speed in information processing tasks
CHILDREN	Improvement of executive functions Improvement selective attention Wider lexical network Improvement of linguistic understanding Improvement of syntactic ability Improvement of spelling skills Improved working memory Improvement of cognitive flexibility Improved inhibition control Improvement of school performance
CHILDREN WITH ADHD	Improvement of attention Less hyperactivity Less impulsiveness Improvement of executive functions
ADULTS OVER 50 YEARS OLD	Lower risk of cognitive decline and dementia Improvement of executive functions Improvement of visual-spatial functions Improvement of episodic memory Improved fluency of words Improvement of processing speed Improvement of global cognitive functions
PATIENTS WITH SCHIZOPHRENIC SPECTRUM DISORDER OR BIPOLAR DISORDER	Improvement of overall cognitive functioning Improvement of general intellectual skills Improvement of verbal memory Improved working memory

3.3. Risk Factors in the Development of Exercise Addiction

Exercise Addiction was conceptualized by Morgan [32] as a behavioral dysfunction and, therefore, as addiction that takes negative connotation. He assumed that excessive physical exercise could lead to physical damage and to neglect many everyday life contexts (e.g., family, job). There are two key-aspects of this condition: firstly, sport becomes a daily need; secondly, the presence of withdrawal symptoms in case of abstention from training.

Lukács et al. [33] explored exercise addiction in amateur runners through multidimensional approach, underlying some risk predictors of develop this addiction. The sample consisted in 257 runners with at least 2 consecutive years of practice. Risk prevalence of exercise addiction (EA) was 8.6%, while 53.6% of respondents was characterized as symptomatic non-addicted and 37.8% asymptomatic non-addicted. Likelihood ratio tests indicated that five factors have contributed in a significant way: time spent running weekly ($p < 0.001$); childhood activity $p = 0.008$); level of education ($p = 0.006$); anxiety ($p = 0.023$);

loneliness ($p = 0.004$). It was observed that the risk group obtained a higher score in "lack of control" subscale; these runners were, in fact, less able to manage the urge of doing or to stop exercising. The results support the theory that assumes lonely athletes use sport activity as source of joy and happiness—to cope for anxiety and loneliness—increasing time or quantity of physical activities, because they need more and more of it to achieve these emotions.

A new and interesting discovery is that a lower level of education may predict the probability of exercise addiction. Studying at better universities or colleges may improve the capability to deal with emotional distress and develop coping strategies which, in their turn, can prevent behavioral disorders and presumably numerous other problems. In fact, the level of education seemed to be a protective factor, as resulted in Menczel's research [34]: 65% of the sample—1743 subjects, 58.6% of which were female, the mean age was 31.7 (SD = 8.491), the youngest person was 18, and the oldest one was 61-year-old—had a university or college degree. The subjects were administered questionnaires consisted of different parts, namely, demographic questions, e.g., age, gender, residency, weight and height. In the second part, sporting habits were assessed, such as the frequency, the kind of sport they practiced. Menczel also measured the existence of eating disorders. As the final part of the survey, fitness users were asked to fill in two standardized questionnaires, the Exercise Addiction Inventory (EAI) and the Exercise Dependence Scale-21 (EDS). Additionally, to these scales—self-esteem, well-being and sensation seeking were also measured. Furthermore, body dissatisfaction was measured with the Eating Disorder Inventory and the SCOFF scale. In terms of education, the higher level of studies, the lower scores people obtained on exercise dependence (ED) (rs, 0.094, $p \leq 0.001$; rs, 0.148, $p \leq 0.001$). As Menczel suggests, addictive exercising may link to having worse coping mechanisms, poorer ways to deal with stress. One way to improve in it is to study in higher education.

3.3.1. Exercise Addiction, Behavioral Disorders and Psychological Distress

Exercise addiction can also be related to certain personality characteristics and/or psychological distress. In a cross-sectional survey by Guidi et al. [35], a total of 79 participants (recruited in five gyms) completed the following self-report questionnaires: Exercise Dependence Questionnaire (EDQ), Eating Disorder Inventory II (EDI-2), Temperament and Character Inventory (TCI), Attitude Toward Self Scale (ATS), Muscle Dysmorphia Questionnaire (MDQ) and Symptom Questionnaire (SQ). In the sample, exercise addicted subjects were 32, who were compared with control subjects (n = 47). From the results, it was observed significant differences between genres in EDI-2 total score, where women have obtained higher scores than men ($p = 0.048$). Participants with primary exercise addiction showed more dysfunctional eating patterns than control group; in fact, significant differences emerged in EDI-2 total score ($p < 0.001$). Other differences between these groups are associated to behavioral aspects: participants with primary exercise addiction reached higher scores than control group in these TCI subscales: damage avoidance ($p = 0.038$), persistence ($p = 0.024$), self-directivity ($p = 0.002$). In contrast, lower scores were reached in matureness character index ($p = 0.033$). In SQ total score ($p = 0.002$) and in anxiety ($p = 0.001$) and hostility subscales ($p < 0.001$), better scores were found in participants with primary exercise addiction. Considering the issue of body dysmorphia related to exercise addiction, significant differences in ATS dysmorphophobia subscale ($p = 0.010$) emerged, with higher scores in participants with primary exercise addiction. Primary exercise addiction resulted significantly associated with higher scores in muscular dysmorphia, evaluated by MDQ ($p < 0.001$). Data provided further support to the idea that exercise addiction could be a specific clinical condition associated with psychological symptoms and personality characteristics. These evidences report a relation between excessive physical activity and eating behavioral disorders. Regarding personality characteristics, these results are consistent with those of other studies, in which a negative association between self-esteem and excessive physical activity was highlighted. The results also indicate difficulty in assumption of

responsibility and lack of objectives. Finally, the presence of primary exercise addiction is associated with significant higher scores in muscular and body dysmorphia, anxiety and hostility.

In Hausenblas e Giacobbi's hypothesis [22], some people could start to perform physical activity as a coping strategy towards psychological distress. The researchers therefore examined the relationship between personality and exercise dependence symptoms; participants of the study were 390 university students who completed multidimensional assessments of personality, exercise dependence, and exercise behavior. To examine the predictive relationship of personality for exercise dependence symptoms hierarchical regressions with forced block entry were undertaken. In Block 1, exercise dependence was regressed on exercise behavior. In Block 2, the personality subscales (neuroticism, extraversion, conscientiousness, agreeableness, openness) were entered into the regression. Results showed that extraversion, neuroticism, and agreeableness predicted exercise dependence symptoms.

3.3.2. Exercise Addiction during COVID-19 Pandemic

The current COVID-19 pandemic has changed many aspects of everyday life. We have compared the few studies in literature which investigated the impact of the pandemic on exercise addiction and possible associated disorders. As a result, two studies—centered on predictors—are presented.

In a study conducted by Scharmer et al. [36], psychological consequences due to current pandemic situation were explored, intended as predictors to develop compulsive practices (e.g., eating disorders). Particularly, the objective of this study was to explore the association among anxiety caused by COVID-19, trait intolerance of uncertainty, COVID-19 intolerance of uncertainty, eating disorder and exercise addiction. Participants were 295 university students (M:19.7 years; SD: 2.0). The following tools were administrated: EDE—Q (Eating Disorder Examination Questionnaire); STAI—T (State—Trait Anxiety Inventory—Trait subscale); CET (Compulsive Exercise Test); IUS—12 (COVID-19 intolerance—uncertainty); GLETQ (Gordon Leisure—Time Exercise Questionnaire). CET high scores emerged and positively correlated only with the trait intolerance of uncertainty. People with lower traits and intolerance of uncertainty showed a strong association between COVID-19 anxiety and CET and EDE-Q scores. In fact, this study shows that trait intolerance of uncertainty is the strongest predictor of compulsive exercise, while anxiety trait is the strongest predictor of eating disorder.

In an experimental study [37], possible consequences that physical activity restraint during current COVID-19 pandemic can have on people with exercise addiction were investigated. The study was conducted using a sample of 1079 participants from eight Spanish language countries. To test the relation between risk of EA and weekly exercise variation, a bivariate correlation was calculated, which was weak but statistically significant ($r = -0.127$, $p < 0.001$), showing the existence of a weak correlation between the decrease of exercise during COVID-19 pandemic and risk of exercise addiction only if there was not control on passion and perfectionism factors; otherwise, the relation was not significant ($r = -0.024$, $p > 0.05$). The negative relation between risk of exercise addiction and variation of exercise during COVID-19 pandemic was supported only until passion and perfectionism were not under control. Eventually, a positive and statistically significant correlation was found between exercise addiction and passion and perfectionism (Table 2).

Table 2. Individual and situational factors and possible predictors of exercise addiction development.

EXERCISE ADDICTION: INDIVIDUAL AND SITUATIONAL FACTORS AND POSSIBLE PREDICTORS
High time spent exercising weekly
Physical activity occurred in childhood
Low level of education
High levels of anxiety
High levels of hostility
Loneliness
Low self-esteem
Gender (higher incidence among women)
High levels of character aspects such as: persistence, avoidance of harm, self-direction and intolerance of uncertainty
Prolonged periods of inability to train (for example, COVID-19 pandemic) when associated with high levels of passion and perfectionism
Dysfunctional eating patterns and eating disorders
Body and muscle dysmorphisms

4. Discussion and Conclusions

Regarding the benefits of physical exercise on cognitive functions, we can say that most of the considered sample have greater precision and speed of response in information processing tasks; children have an improvement in executive functions, selective attention, linguistic understanding, and a wider lexical network, syntactic and spelling skills, working memory, cognitive flexibility, inhibition control and school performance.

Furthermore, a particular interest of our review was to explore the variable of the presence of ADHD in a sample of children, in which we found that short-term aerobic exercise, based on different formats of aerobic intervention, appears to be effective in mitigating symptoms such as attention, hyperactivity, impulsivity, anxiety, and may induce an improvement in executive functions and behavioral disorders at the socio-relational level.

Regarding another part of the sample, adults over 50 years old, physical exercise is inversely correlated to the risk of cognitive decline and the onset of dementia, while it would also favor a notable improvement in executive functions, visuospatial functions, episodic memory, fluidity of words, processing speed and global cognitive functions.

Finally, we investigated the importance of exercise in patients with schizophrenic spectrum disorder or bipolar disorder, where it was found that exercise dosage appears to be an important factor in achieving cognitive improvement, as previous studies demonstrated that the amount of exercise achieved by participants during an intervention is a significant predictor of cognitive improvements in overall functions, general intellectual skills, verbal memory, and working memory.

The second purpose of our review concerns exercise addiction and any individual and situational factors that have been considered as possible predictors for the onset of a sport addiction. Results showed that what may predict the occurrence of physical activity addiction may be high weekly time spent running, physical activity occurring during childhood, low education, high levels of anxiety and hostility, loneliness, low self-esteem, and gender (since we found greater incidence in the female gender). In addition, high levels of character aspects such as persistence and tenacity, a self-directed personality, avoidance of harm and intolerance of uncertainties.

Other risk elements for the onset of sport addiction are having developed dysfunctional eating patterns or eating disorders or expressing concerns resulting from body and muscle dysmorphisms.

A further prodrome is the impossibility of training, a factor contextualized in the current historical period, the advent of the COVID-19 Pandemic, even more so if associated with high levels of passion and perfectionism.

It is important to highlight the absence of specific studies concerning the cognitive consequences of exercise addiction. In fact, most of the literature currently available focuses on risk factors and other consequences, such as physical damage because of excessive and prolonged exertion and worsening of interpersonal or work relationships. We hypothesize that, since exercise addiction is considered a behavioral addiction, it may produce the following cognitive effects: constructs such as impulsivity, compulsivity, and attention regulation, which may also be relevant, applicable, and successful for understanding and subsequent treatment of behavioral addictions [38]. This, however, is only a hypothesis that should be explored in the future, and which can be a starting point for new research.

This review has some limitations to consider. First of all, presenting both healthy populations and clinical populations without any distinction may be a problem. In fact, in cognitive enhancement literature, it is sometimes shown that people with more performing cognitive functions at baseline show reduced enhancement as opposed to clinical populations. Besides, mechanisms of actions are not the same necessarily. For example, the neuroplasticity promoted by neurostimulation techniques among clinical populations can impact to a sufficient level to induce changes in behavior. However, among healthy populations with optimal homeostatic cortical activity, long-term alteration might be necessary to observe the effects of neuroplasticity on behavior [39]. Nevertheless, there are studies that claim the opposite, showing higher cognitive changes in non-clinical populations rather than in clinical populations at baseline [40]. This, therefore, requires further investigation in the future. Secondarily, we do not discuss the cognitive factors of sports addiction and about the risks ensuing from sports addiction. Eventually, a final limitation concerns the fact that the analysis of risk factors for developing exercise addiction during the COVID-19 pandemic refers to an event and a period still in progress, although, at the time of writing, lockdowns are no longer in effect.

In conclusion, these findings could lead to the dissemination of more informed policies on the use of PA to improve and shape cognitive functions throughout an individual's life. In accordance with the compared literature, a more than beneficial effect of physical activity can be affirmed in promoting a condition of mental health, an enhancement of cognitive function in healthy individuals but also in a preventive and curative key to the well-being of those who are affected by certain psychic disorders. In addition, about the other side of the review, the importance of an adequate psychological-clinical evaluation of psychological distress and personality characteristics associated with exercise addiction stands out. Therefore, the right balance of sports practice could thus become a real coping strategy useful for facing the problems of daily life and for reducing stress and negative emotions, but in a functional way to the psycho-physical health of the subject.

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The Validity of the World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition in Adolescence

Antonella Somma, PhD,[1] Lenard A. Adler, MD,[2] Giulia Gialdi, MSc,[1] Martina Arteconi, MSc,[1] Elisabetta Cotilli, MSc,[1] and Andrea Fossati, MD[1,*]

Abstract

Objectives: Short, self-report screening measures for adolescent and adult attention-deficit/hyperactivity disorder (ADHD) would greatly enhance the likelihood of ADHD subjects to be correctly diagnosed and treated. This study aimed at testing the reliability, factor structure, convergent validity, external validity, and diagnostic accuracy of the official Italian translation of the ADHD Self-Report Screening Scale for *DSM-5* (ASRS-5) in a sample of community-dwelling adolescents, extending previous data on adult participants to adolescent participants.

Methods: Five hundred sixty-four community-dwelling male adolescents (mean age ≅ 15) were administered the ASRS-5, the Adult ADHD Self-Report Scale 18-item and 6-item versions (ASRS-18 and ASRS-6), the Wender Utah Rating Scale (WURS), and the Structured Clinician Interview for *DSM-5*-Clinician Version ADHD Module (SCID-5-CV-ADHD). School performance variables were also collected.

Results: The item response theory (IRT) reliability of ASRS-5 was adequate. Dimensionality analyses strongly supported the unidimensional structure of ASRS-5 items; confirmatory factor analysis fit indices supported the adequacy of the one-factor model of ASRS-5. In terms of convergent validity, the ASRS-5 total score was significantly and positively associated with self-report and interview-based ADHD dimensional scores, as well as with school performance variables. Roughly 8.0% of our male adolescents met SCID-5-CV-ADHD criteria for categorical ADHD diagnosis. Ten-fold cross-validated receiver operating curve value was 0.843; precision-recall curve analysis suggests that an ASRS-5 total score >12 may be preferred for screening purposes in adolescence.

Conclusions: Our data showed that the ASRS-5 may represent a psychometrically sound self-report instrument to reliably screen for *DSM-5* ADHD, extending the range of application of ASRS-5 from adulthood to adolescence, suggesting that the ASRS-5 could be safely used for screening purposes also in community-dwelling adolescents, at least in its official Italian translation.

Keywords: ASRS-5, ADHD, adolescence, factor structure, reliability, validity

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder, defined by the presence of developmentally inappropriate and impairing levels of inattention, hyperactivity, and impulsivity (American Psychiatric Association 2013; Asherson and Agnew-Blais 2019). In childhood, ADHD is among the most common psychiatric disorders (Polanczyk et al. 2015), and it often persists into adulthood and old age. Sex differences in ADHD diagnosis are well documented (Kooji et al. 2019), with female-to-male ratios ranging between 1:5 and 1:9 (Rucklidge 2010). Indeed, ADHD has been recognized as a disorder affecting individuals across the lifespan (e.g., Faraone et al. 2006); about 80%–85% of preteens continue to experience symptoms into the adolescent years and 60% into adulthood (e.g., Barkley et al. 1990; Biederman et al. 1996). In the transition from childhood to adolescence, the burden associated with the disorder increases dramatically because adolescents are known to experience age-specific problems associated with ADHD (e.g., Brahmbhatt et al. 2016), and begin to experience impairments that characterize adults

[1]Faculty of Psychology, Vita-Salute San Raffaele University, Milan, Italy.
[2]Departments of Psychiatry and Child and Adolescent Psychiatry, New York University Grossman School of Medicine, New York, New York, USA.
*ORCID ID (https://orcid.org/0000-0001-9368-4058).
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suffering from this disorder, such as substance use (Molina et al. 2007). Accordingly, the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition; *DSM-5*) ADHD diagnostic criteria have been adapted by adding some examples describing how ADHD symptoms are expressed across the lifespan, and the symptom threshold required has been reduced to five symptoms instead of six for older adolescents and adults in either the inattention or hyperactive/impulsive domain.

Diagnosing ADHD requires a careful and systematic assessment of a lifetime history of symptoms and impairment (Kooji et al. 2019); nonetheless, screening for ADHD symptoms may be particularly important, and should be part of routine mental health assessment (Brahmbhatt et al. 2016). For instance, Murray et al. (2019) carried out a longitudinal study on ADHD symptoms from age 7 to age 15 in a community-ascertained cohort ($n = 1571$) and suggested that more attention may need to be focused on adolescence in terms of detection of ADHD symptoms. Indeed, their findings showed that adolescence is a potential period of vulnerability for symptom onset and escalation (Murray et al. 2019). Moreover, although perceptions of ADHD as a childhood disorder have been changing, many ADHD diagnostic indicators refer to childhood-specific behaviors and settings, and the inclusion of developmentally appropriate indicators across the lifespan will be beneficial for identifying and monitoring ADHD symptoms (Murray et al. 2019). From this perspective, although ADHD adolescent and adults are known to underreport their symptoms (Asherson et al. 2016), the availability of short, self-report screening measures would greatly enhance the likelihood of adolescent and adult ADHD subjects to be correctly diagnosed and treated.

Recently, Ustun et al. (2017) presented a new version of the widely used Adult ADHD Self-Report Screening Scale (ASRS; Kessler et al. 2005; Kessler et al. 2007) updated for *DSM-5* criteria (ASRS-5). The ASRS-5 is a 6-item, easily scored self-report measure developed and tested in national household, managed care subscribers, and specialty clinical samples (Ustun et al. 2017); it has been shown to detect the vast majority of general population cases at a threshold that also has high sensitivity (91.4%), specificity (96.0%), and positive predictive value (PPV = 67.3%). Despite these positive findings, the psychometric properties of ASRS-5 as a screening tool have been tested exclusively among adult participants (Ustun et al. 2017). Of course, ADHD may (and should) be easily diagnosed in childhood; however, detecting ADHD in adolescence may be relevant to reduce the burden that is associated with adult ADHD, as well as to identify late-onset ADHD subjects (Murray et al. 2019; Asherson and Agnew-Blais 2019). Thus, extending Ustun et al.'s (2017) findings to community-dwelling adolescents may be relevant.

Notably, screening campaigns usually involve subjects living in the community. In light of what was known about Berkson's bias (Berkson 1946) in the epidemiology literature, it should be observed that clinic/hospital patients may be unrepresentative of the ADHD population (e.g., showing more severe ADHD impairment, higher rates of psychiatric/medical comorbidity, etc.); thus, community-based studies may be particularly helpful for screening and identifying ADHD in adolescence (e.g., Buitelaar 2017; Murray et al. 2019). Finally, Ustun et al. (2017) provided excellent data on the diagnostic accuracy of ASRS-5 with respect to interview-based adult ADHD diagnoses. Nevertheless, providing data on the ASRS-5 reliability and factor structure may represent a useful addition to the existing literature on the ASRS-5.

Starting from these considerations, we aimed at testing the internal consistency reliability, factor structure, convergent validity, external validity, and diagnostic accuracy of the official Italian translation of ASRS-5 in a sample of community-dwelling Italian adolescents. Indeed, researchers and clinicians who work adolescents would benefit from a short rating scale for assessing ADHD symptoms (e.g., Keeley et al. 2018). Male adolescents with ADHD showed increased levels of real-life risk-taking behavior like substance abuse and reckless behavior (Dekkers et al. 2020). Adolescent participants were attending public professional schools in the Northern Italy, and were personally interviewed with a validated semistructured interview for diagnosing *DSM-5* ADHD, namely the Structured Clinician Interview for *DSM-5*-Clinician Version ADHD Module (SCID-5-CV-ADHD). Notably, 95.8% of the Italian general population adolescents are high school students (ISTAT 2017). In this study, we relied only on male adolescents who were attending schools, which does not require adolescents to be attentive and remain seated for a long time period. Consistent data documented that ADHD should be conceived as a dimension of psychopathology (Coghill and Sonuga-Barke 2012; Demontis et al. 2019); however, practitioners are used to consider categorical ADHD diagnoses for their clinical decision making. Thus, in this study, we computed both dimensional (i.e., number of symptoms met) and categorical (i.e., absence vs. presence) interview-based ADHD assessment.

Methods

Participants

The sample was composed of 564 community-dwelling male adolescents (mean [M] age = 15.5 and standard deviation [SD] = 1.6 years), who were receiving professional education at public professional schools in the North of Italy. After obtaining Institutional Review Board approval from the university and the principals of the schools, researchers recruited adolescents from classrooms (data were collected in Winter 2018–Spring 2019). Written informed parent consent and adolescent assent were obtained before study participation. To participate in this study, participants were required to speak Italian as their first language to avoid cultural and lexical bias in questionnaire responses; to maximize the likelihood of including adolescents potentially expressing the ADHD phenotype in our sample, only male adolescents were allowed to participate in this study. In our sample, 184 adolescents (32.6%) reported at least one school failure in the preceding years.

Measures

World Health Organization adult ASRS-5. The ASRS-5 was developed as a screening scale for adult ADHD with the same form as its *DSM-IV* counterpart: that is, a simple additive scale with a limited number of variables and integer scoring for quick calculation (Ustun et al. 2017). Using Risk-Calibrated Super-sparse Linear Integer Model (RiskSLIM) and 10-Fold Cross-Validated Receiver Operating Characteristic Curve (10-F ROC) analyses, Ustun et al. (2017) derived the six items that best discriminated adults with an interview-based *DSM-5* ADHD diagnosis from adults who were not diagnosed as suffering from ADHD from an original pool of 29 items. The six items in the final scale included (1) *DSM-5* symptom of inattention (Criterion A1c: does not listen when spoken to directly), (2) non–*DSM-5* symptoms of executive dysfunction (puts things off to last minute, depends on others to keep life in order), and (3) *DSM-5* symptoms of hyperactivity and impulsivity (CriterionA2b, leaves seat inappropriately; Criterion A2e, acts as if ''driven by a motor''; and Criterion A2g, blurts out answers). The ASRS-5 may be scored either using a fixed 0–5 range

for all items or relying on the RiskSLIM algorithm; for the latter, a 0 score is assigned to all ''never'' responses, but scores for higher responses vary, with the possible range of 0 to 24 (Ustun et al. 2017). Using the RiskSLIM scoring, Ustun et al. 2017 reported excellent diagnostic efficiency data for the ASRS-5 in two samples of adult subjects. After obtaining the permission to use the ASRS-5 proprietary scoring rules developed by the New York University and Harvard University, we relied on the RiskSLIM algorithm for assessing the diagnostic accuracy of ASRS-5 items.

Consistent with the translation procedure for the previous version of the scale, the ASRS-5 has been translated into Italian using the standard World Health Organization (WHO) translation and back-translation protocol (Somma et al. 2019). The reliability data of ASRS-5 in this sample are reported in the Results.

Adult ADHD Self-Report Scale 18-item and 6-item versions. The Adult ADHD Self-Report Screening Scale-18 item version (ASRS-18) includes 18 items, which were explicitly designed to assess ADHD in adults based on the *DSM-IV* criteria. Consistent with the other existing translations of ASRS-18, the scale has been translated into Italian using the standard WHO translation and back-translation protocol (National Comorbidity Survey 2005). The response options of the 18 items are arranged on a 5-point Likert scale. Kessler et al. (2007) showed that 5-point scores rather than dichotomous scores should be used in rating ASRS-18 items. The ASRS-18 items are summed to yield a total score; the higher the ASRS-18 score, the higher the likelihood of adult ADHD diagnosis. The first six items of the scale, which are thought to best predict the presence or absence of ADHD, compose the Adult ADHD Self-Report Screening Scale-6 item version (ASRS-6). Both the ASRS-18 and ASRS-6 were recently validated in Italian community-dwelling adolescents (Somma et al. 2019). In this study, the Cronbach's α values were 0.82 (average inter-item $r = 0.21$) and 0.54 (average inter-item $r = 0.21$) for the ASRS-18 and ASRS-6, respectively.

Wender Utah Rating Scale. The Wender Utah Rating Scale (WURS) is a self-report questionnaire designed to retrospectively assess the severity of ADHD symptoms during childhood (Ward et al. 1993). Adequate reliability and validity were reported for the WURS (Taylor et al. 2011). The Italian translation of the WURS showed adequate reliability and validity (Fossati et al. 2001). In this study, the Cronbach's α value of the WURS was 0.89 (average inter-item $r = 0.24$).

Structured Clinician Interview for DSM-5-Clinician Version ADHD Module. The SCID-5-CV-ADHD is a semistructured interview for assessing *DSM-5* ADHD criteria. It provides at least one question for each *DSM-5* ADHD criterion and impairment and exclusion criteria are explicitly tested. The assessment for ADHD begins with two screening questions that are designed to determine whether or not to proceed with the full assessment of the 18 ADHD items; then, questions concerning the nine inattention symptoms and the nine hyperactive/impulsive symptoms are asked (First et al. 2016). The psychometric properties of the Italian translation of the SCID-5-CV-ADHD in Italian adolescents have been recently reported (Somma et al. 2019).

In this study, the inter-rater reliability of both SCID-5-CV-ADHD dimensional and categorial assessment was assessed using a pairwise interview design in the first 35 adolescents. Four raters were included in the inter-rater reliability assessment; raters were randomly paired, and each rater acted roughly the same number of times as interviewer and as independent observer. The SCID-5-CV-ADHD interview was independently scored by the interviewer and the independent observer. In our study, the intraclass r coefficient for absolute agreement based on one-way random-effect ANOVA for the SCID-5-CV-ADHD dimensional score (i.e., total number of symptoms) was 0.94, $p < 0.001$. Rather, in our sample, the Cohen's κ value for the categorial SCID-5-CV ADHD diagnosis was 0.77, $p < 0.001$.

School performance variables. The current year school grade averaged across literature subjects (i.e., literature, history, etc.), the current year school grade averaged across scientific subjects (i.e., mathematics, biology, chemistry, etc.), current year behavior grade, and current year number of disciplinary notes were used as adolescent's school performance variables. Schools in Italy use a 10-point scale that can be divided into failing (0 to 5) and passing (6 to 10) grades. A behavior grade lower than 8 indicates severe problem behavior at school and in the case of 6 grade, or even 7 grade in behavior, failure may occur. School performance variables were evaluated directly by the adolescents' teachers.

Procedures

All participants were assessed anonymously by trained clinical psychologists during school time; an alphanumeric code was used to allow matching adolescent's, graded with his/her corresponding test scores and school performance variable values. All measures were administered individually in random order. The SCID-5-CV-ADHD was administered blind to self-reports and school performance variable scores by clinical psychologist who were extensively trained (i.e., 40 hours or more) in the SCID-5-CV-ADHD assessment. In this study, time considerations allowed for testing only SCID-5-CV ADHD module. All participants were personally interview at school during school time at lesson break; consistent with previous studies (Kumar et al. 2011), our adolescents were administered only the SCID-5-CV ADHD module to obtain *DSM-5* dimensional (i.e., total number of symptoms) and categorical diagnoses of ADHD.

Data analyses

Considering that Cronbach's α may yield suboptimal results in the case of short scales like the ASRS-5, in this study, we relied on item response theory (IRT) to obtain an estimate of ASRS-5 internal consistency reliability. The convergent validity of ASRS-5 total score was assessed by computing the Pearson r coefficients with both self-report and interview measures of ADHD. To provide further evidence of ASRS-5 validity, we computed Spearman r coefficients between the ASRS-5 total score and the school performance variable ordinal/non-normal scores. Quasi-inferential parallel analysis (PA; Buja and Eyuboglu 1992) was used to assess the dimensionality of ASRS-5 item polychoric correlation matrix (Zwick and Velicer 1986).

Since the factor analysis of ordinal data is still a controversial topic (Wirth and Edwards 2007), in this study, we relied both on weighted least square mean and variance adjusted (WLSMV) confirmatory factor analysis (CFA), and on IRT CFA based on graded response model (Samejima 1969). Based on the unidimensional nature of ASRS-5 and on the PA results, in this study we tested only a one-factor model of ASRS-5 item polychoric correlation matrix. In WLSMV CFA, we used several measures to identify model fit, including the χ^2 goodness-of-fit statistic, the root mean square error of approximation (RMSEA), the Tucker–Lewis index (TLI), the comparative fit index (CFI), and the standardized root mean square

residual (SRMSR). Following Hu and Bentler's (1999) (Maydeu-Olivares 2013) suggestions, TLI and CFI values ≥0.95, RMSEA values close to 0.06, and SRSMR <0.08 were considered indicating good model fit, whereas TLI and CFI values of 0.90 and higher, and an RMSEA of 0.08 and lower are indications of an adequate fit. M_2* statistic and its associated $RMSEA_2$, and SRMSR were used to assess model fit in IRT CFA (Maydeu-Olivares 2013).

In this study, Student's *t*-test was computed to compare the mean ASRS total score that was computed according to the optimal RiskSLIM response scoring (Coghill and Sonuga-Barke 2012) between ADHD adolescents and non-ADHD adolescents; Cohen's *d* was used as an effect size measure.

In this study, the area under the curve (AUC; i.e., the probability that a randomly selected clinical case would score higher on the ASRS-5 than a randomly selected noncase; Kessler et al. 2005) was used as a measure of the overall ability of ASRS-5 total score computed according to the RiskSLIM algorithm to predict the presence or absence of ADHD diagnosis. Specifically, we relied on AUC based on 10-F ROC analysis (LeDell et al. 2015); the AUC of a perfect measure is expected to be 1.0, whereas it is expected to be 0.5 for a useless instrument. Precision-recall curve analysis (i.e., a curve showing the relationship between precision and recall for every possible cutoff score) was used to identify the ASRS-5 total score cutoff value with respect to SCID-5-CV ADHD diagnosis. For all possible cutoff scores provided by precision-recall curve analysis, ASRS-5 cutoff scores providing the minimum positive predictive value (PPV) to justify more in-depth assessment of ADHD and adequate specificity were selected for detection purposes. In this study, sensitivity (i.e., recall), specificity, positive predictive value (PPV; i.e., precision), negative predictive value (NPV), and likelihood ratio values were computed (e.g., Grimes and Schulz 2005). Finally, decision curve analysis (Vickers and Elkin 2006) was used to identify the proportion of adolescents meeting criteria for *DSM-5* ADHD, which could be cost effectively treated relying on the ASRS-5 as the basis for selection based on various cost-benefit ratios (which were expressed as net benefits).

Results

The descriptive statistics, and results of the WLSMV CFA one-factor model and IRT CFA unidimensional model of ASRS items, as well as the quasi-inferential PA results, are summarized in Table 1. Based on IRT analyses of ASRS-5 items, the total amount of information in the ASRS-5 was 12.21, whereas the information in the in (−3, 3) range was 7.06 (i.e., 57.8% of the total information). This yielded an internal consistency reliability estimate of 0.714 (i.e., $1 - 1/12.21$) for the ASRS-5 total score, whereas the average inter-item polychoric *r* value for the ASRS-5 items was 0.18 (median polychoric $r = 0.19$, SD = 0.07). The ASRS-5 test information curve is displayed in Figure 1.

The correlations (i.e., Pearson *r* values) between the ASRS-5 total score and the ASRS-6, ASRS-18, and SCID-5-CV-ADHD total number of symptoms are listed in Table 2, as well as the Spearman *r* values for the associations between the ASRS-5 total score and the adolescent's school performance variables.

Based on SCID-5-CV-ADHD assessment, 46 adolescents (8.2%) received a *DSM-5* ADHD diagnosis. When we scored the ASRS-5 using the optimal RiskSLIM response scoring (Coghill and Sonuga-Barke 2012), participants who received a SCID-5-CV ADHD diagnosis ($n = 46$; M = 17.00, SD = 3.32) scored significantly higher than participants who did not receive a SCID-5-CV ADHD diagnosis ($n = 518$; M = 11.50, SD = 4.22), $t(562) = 8.61$, $p < 0.001$, $d = 1.32$. In ROC analyses, the AUC was 0.843, 95% confidence interval = 0.744–0.941. Based on the optimal scoring of ASRS-5, precision-recall curve analysis suggested that when the cutoff score was set at 14, sensitivity was 0.75, with a PPV of 0.16, and specificity value was 0.65, whereas NPV value was 0.97. Finally, LR+ and LR− values were 2.14 and 0.38, respectively. Setting the threshold at 16 resulted in a worse PPV (0.28) with the same sensitivity (75.0%), whereas considering an ASRS-5 threshold of 12 led to a PPV value of 0.13, with an increase in sensitivity (0.94); specificity value was 0.45, whereas NPV value was 0.99. Finally, LR+ and LR− values were 1.71 and 0.14, respectively. These results seemed to suggest that the 12 or higher operating threshold would most likely be preferred for screening purposes.

The decision curve plotting net benefit against threshold probability is depicted in Figure 2. As it can be observed in Figure 2, we showed the decision curve for a range of threshold probability ranging from 0 through 0.50.

Discussion

Extending Ustun et al.'s (2017) findings, our data seemed to show that ASRS-5 is likely to represent a psychometrically sound self-report instrument to reliably screen for *DSM-5* ADHD in community-dwelling adolescents, at least in its Italian translation. The relevance of this cross-cultural finding should not be underscored, since WHO measures are intended to be used worldwide.

According to our findings, the limited length (i.e., six items) of ASRS-5 did not prevent its total score to yield a reliable self-report assessment of the ADHD dimension. Dimensionality analyses strongly supported the unidimensional structure of ASRS-5 items; indeed, in our study, both WLSMV and IRT CFA fit indices supported the adequacy of the one-factor model of ASRS-5. Although previous symptom-level exploratory factor analysis studies (e.g., Adler et al. 2017) showed that adult ADHD symptoms may be organized across four factors representing executive dysfunction/inattention, hyperactivity, impulsivity, and emotional dyscontrol, it should be observed that the unidimensional factor structure of ASRS-5 was expected and desired. Indeed, the factor analysis of ASRS-5 items was not intended to assess the factor structure of ADHD symptoms *per se*. Rather, its purpose was to empirically test the hypothesis that six indicators (i.e., items) could be safely used to identify a latent ADHD dimension for screening purposes. This result supported previous indications (Ustun et al. 2017), suggesting that the ASRS-5 represented an improved version of the original ASRS (see also Somma et al. 2019). Our WLSMV CFA findings showed that all ASRS-5 item standardized factor loadings were positive, significant, and of non-negligible size; IRT CFA results showed that the ASRS-5 item 1, item 2, and item 6 showed discrimination parameter values that suggested strong relation with the latent dimension (Samejima 1969), although the remaining ASRS-5 items showed significant and moderate discrimination parameter estimates.

In terms of convergent validity, in our study, the ASRS-5 total score showed *r* coefficient values with both self-report and interview-based ADHD dimensional scores, which were all positive, significant, and suggesting a large effect size by conventional standards (Cohen 1988). Interestingly, the ASRS-5 total score showed positive, significant, although modest rank-order correlations with school performance variables. Notwithstanding the relatively small size of the correlation coefficients, the relevance of this finding should not be underscored, because it seemed to suggest

Table 1. Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 Items: Descriptive Statistics, Dimensionality Analysis (i.e., Quasi-Inferential Parallel Analysis Based on 1000 Random Permutations of the Original Data), Weighted Least Square Mean and Variance Adjusted Confirmatory Factor Analysis, and Item Response Theory Confirmatory Factor Analysis Results ($N=564$)

			Parallel analysis		*WLSMV CFA*	*IRT factor analysis parameters*				
ASRS-5 items	*M*	*SD*	*Eigen.*	*95* p	λ	a *(SE)*	d1 *(SE)*	d2 *(SE)*	d3 *(SE)*	d4 *(SE)*
(1) How often do you have difficulty concentrating…	1.23	0.93	**1.93**	1.23	0.47***	0.95 (0.15)	1.62 (0.13)	−0.89 (0.11)	−2.59 (0.18)	−4.21 (0.32)
(2) How often do you leave your seat…	0.73	1.01	1.03	1.28	0.55***	1.11 (0.18)	−0.23 (0.11)	−1.97 (0.16)	−2.75 (0.21)	−4.53 (0.37)
(3) How often do you have difficulty unwinding…	1.32	1.27	0.84	1.06	0.29***	0.52 (0.12)	0.72 (0.09	−0.54 (0.09)	−1.40 (0.11)	−2.60 (0.17)
(4) When you're in a conversation, how often…	1.33	1.02	0.80	1.01	0.40***	0.77 (0.13)	1.46 (0.12)	−0.55 (0.10)	−2.02 (0.14)	−3.82 (0.27)
(5) How often do you put things…	2.25	1.21	0.76	0.96	0.36***	0.68 (0.13)	2.57 (0.17)	0.93 (0.10)	−0.13 (0.09)	−1.73 (0.13)
(6) How often do you depend on others…	1.26	1.05	0.64	0.89	0.50***	1.01 (0.16)	1.30 (0.13)	−0.68 (0.11)	−2.36 (0.17)	−3.60 (0.26)

WLSMV CFA goodness-of-fit statistics

	χ^2	*df*	RMSEA	90% CI for RMSEA		TLI	CFI	SRMSR
One-factor model	20.64*	9	0.048	0.020	0.075	0.92	0.95	0.026

IRT factor analysis goodness-of-fit statistics

	M2	*df*	RMSEA	90% CI for RMSEA		SRMSR
Unidimensional model	7.65	9	0.000	0.000	0.045	0.045

Eigen., real data eigenvalues; 95 *p*, 95th percentile of random eigenvalues; λ, standardized factor loadings; *a*, Item discrimination parameter; *d1–d4*, item threshold parameters; bold highlights the correct number of factors to be extracted according to quasi-inferential parallel analysis results; χ^2, goodness-of-fit chi-square test.

90% CI, 90% confidence interval; ASRS-5, Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for *DSM-5*; CFI, comparative fit index; df, degrees of freedom; IRT, item response theory; M, mean; RMSEA, root mean square error of approximation; SD, standard deviation; SE, standard error; SRMSR, standardized root mean square residual; TLI, Tucker-Lewis index; WLSMV CFA, weighted least square mean and variance adjusted confirmatory factor analysis.

*$p<0.05$; ***$p<0.001$.

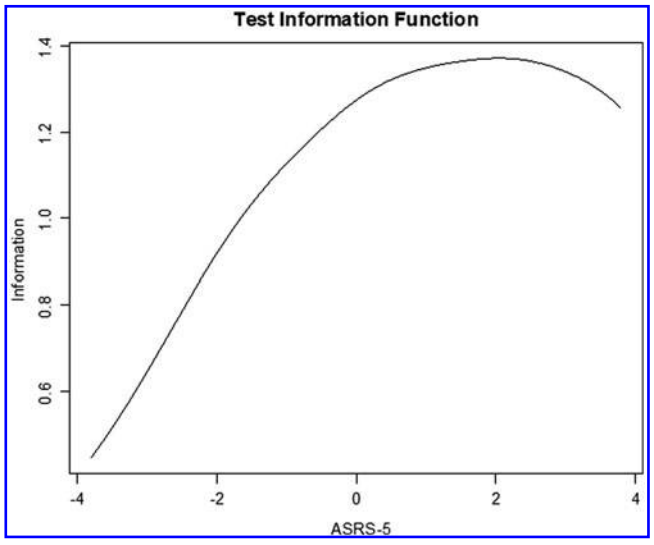

FIG. 1. Test information function of the adult ASRS-5. ADHD, attention-deficit/hyperactivity disorder; ASRS-5, ADHD Self-Report Screening Scale for *DSM-5*.

that the adolescent's ASRS-5 self-reports were significantly associated with teacher's ratings of school performance, particularly with the current year behavior grade and number of disciplinary notes. It should be observed that although ADHD is usually associated with poor school performance, poor school performance does not necessarily require the presence of ADHD to occur (Daley and Birchwood 2010).

Relatively, in line with previous SCID-5-CV-ADHD-based estimates of the ADHD base rate among Italian adolescents (Somma et al. 2019), in this study, roughly 8.0% of our male adolescent sample met SCID-5-CV-ADHD criteria for categorical ADHD diagnosis. As a whole, our SCID-5-CV-ADHD data suggested that ADHD is not likely to represent a rare condition in male adolescent students attending professional schools, and it may be reliably assessed using a semistructured interview based on the *DSM-5* criteria. Consistent with previous data (Ustun et al. 2017), in our study, adolescents who received a *DSM-5* ADHD categorical diagnosis based on the SCID-5-CV-ADHD interview scored significantly and substantially larger on the ASRS-5 than adolescents who did not receive a *DSM-5* ADHD categorical diagnosis. It should be observed that a Cohen's *d* value of 1.32 suggests that

Table 2. Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 Total Score: Pearson *r* Coefficients for the Associations with the Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale-6 Item Total Score, Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale-18 Item Total Score, Wender Utah Rating Scale Total Score, and Structured Clinical Interview for DSM-5-Clinician Version Adult Attention-Deficit/Hyperactivity Disorder Total Number of Symptoms, and Spearman *r* Coefficients for the Associations with the Adolescents' School Performance Indicators ($N = 564$)

	ASRS-5 Total score		
ADHD measures	r	*M*	*SD*
ASRS-6 total score	0.58***	8.94	3.82
ASRS-18 total score	0.68***	26.80	9.79
WURS total score	0.62***	29.40	15.09
SCID-5-CV-ADHD total number of symptoms	0.51***	7.61	3.90
School performance variables			
Literature subject average grade (current year)	−0.19***	6.81	0.96
Scientific subject average grade (current year)	−0.22***	6.79	1.19
Behavior grade (current year)	−0.26***	7.76	1.28
Number of disciplinary notes (current year)	0.26***	2.50	7.09
Number of previous school failures	0.13*	0.63	0.78
M	8.12		
SD	3.56		

ADHD, attention-deficit/hyperactivity disorder; ASRS-5, Adult ADHD Self-Report Screening Scale for *DSM-5*; ASRS-6, Adult ADHD Self-Report Screening Scale-6 item version; ASRS-18, Adult ADHD Self-Report Screening Scale-18 item version; M, mean; SCID-5-CV-ADHD: Structured Clinical Interview for *DSM-5*-Clinician Version Adult ADHD Module; SD, standard deviation; WURS, Wender Utah Rating Scale.
*$p < 0.05$; ***$p < 0.001$.

90.7% of our ADHD adolescent group will be above the mean of our non-ADHD adolescent group, and there is a 82.5% chance that a male adolescent picked at random from the ADHD group has a higher score on the ASRS-5 than a male adolescent picked at random from the non-ADHD group.

In our sample, 10-fold cross-validated ROC analysis results showed that an adolescent picked up at random from the ADHD group had 84.3% the probability of scoring higher on the ASRS-5 than an adolescent picked up at random from the non-ADHD group (i.e., AUC = 0.843). Using the ASRS-5 optimal RiskSLIM response scoring to compute the scale total score, precision-recall curve suggested that an ASRS-5 total score >12 yielded an acceptable PPV (i.e., 0.13) with a sensitivity of 0.94, which may be considered adequate for screening purposes. In our sample of community-dwelling male adolescents who were attending professional schools, the probability that an adolescent did not have ADHD, given a negative test result (NPV) was 0.99, suggesting a negative ASRS-5 result (i.e., an ASRS-5 total score of 16 or lower), may be effective in actually excluding ADHD in male adolescents, at least when ADHD was assessed using the SCID-5-CV-ADHD. However, it should be observed that adopting the consistently validated ASRS-5 > 14 cut score for adults (Ustun et al. 2017) in our adolescent sample yielded values of 75.0% for sensitivity and 0.16 for PPV. In other terms, we feel that both cutoff scores may work adequately for identifying adolescents who received a SCID-5-CV ADHD diagnosis, although the ASRS-5 > 12 cut score seemed to work better than the ASRS-5 > 14 cut score in identifying subjects who received an ADHD diagnosis among community-dwelling male adolescents. Although we have no definitive explanations for this difference in the ASRS-5 cut score values between adult and adolescent subjects, we feel that differences in ADHD base rate in our community-dwelling sample and in the US ASRS-5 standardization adult samples (Ustun et al. 2017) may have influenced our findings.

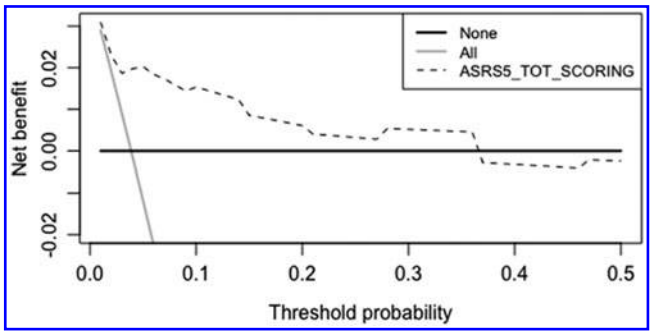

FIG. 2. Decision curve plotting net benefit against threshold probability for the adult ASRS-5 optimal RiskSLIM response scoring. ADHD, attention-deficit/hyperactivity disorder; ASRS-5, ADHD Self-Report Screening Scale for *DSM-5*; RiskSLIM, Risk-Calibrated Super-sparse Linear Integer Model.

Although, in this study, we do not know what the net benefit of any given intervention would be, we think that the results of decision curve analysis provided useful preliminary information. The ASRS-5 added value with threshold probabilities ranging from 0.00 to 0.40. In our study, the net benefit curve showed that at the 10% risk threshold, the net benefit was 0.02, which is equivalent to detecting two ADHD adolescents and suggesting zero unnecessary treatment (i.e., three true positives and zero false positives) per 100 patients. Of course, future studies focused on identifying risk models that can help making better clinical decisions are needed.

As a whole, extending previous findings (Ustun et al. 2017), our data showed that the ASRS-5 may be used as a screening instrument also among community-dwelling adolescents. Although ASRS-5 predictive values were somewhat lower than in the original validation study (Ustun et al. 2017), it should be observed that our data were collected among younger participants (i.e., male adolescents) who were not asking for treatment at the time the study was carried out. Thus, our results seemed to suggest that ASRS-5 may be helpful to detect ADHD in adolescence.

Limitations

Of course, our finding should be considered in light of several limitations. Our sample was composed of male adolescents who volunteered to participate in the study, rather than of adolescents who were randomly selected from the Italian adolescent population. Thus, our sample was more akin to a convenience study group than to a random sample representative of the adolescents in the Italian general population. Clinical assessment of ADHD requires careful consideration of multiple sources of information and indicators. Although we tried to increase the validity of our SCID-5-CVADHD diagnoses by testing their associations with objective indicators of school performance, our ADHD diagnoses were far from clinically

sound ADHD assessment. Although the SCID-5-CV-ADHD was validated in Italian community-dwelling adolescents (Somma et al. 2018), other interviews exist to diagnose ADHD in adolescents, and their use might lead to different findings. Diagnostic agreement statistics may be influenced by the disorder base rate estimates; thus, the ASRS-5 may yield different diagnostic accuracy estimates in samples that are characterized by different ADHD base rates. These considerations inherently limit the generalizability of our finding and stress the need for further studies before accepting our conclusions.

It should be observed that, in our sample of male adolescent participants, a cutoff score of 16 on the ASRS-5 seemed to be appropriate for adolescents, whereas a cutoff score of 14 has been validated for adult participants (Ustun et al. 2017). Of course, future studies on the use of ASRS-5 in adolescents across different languages (e.g., English) and cultures are badly needed before accepting our findings. Indeed, the differing cutoff score might be due to age (i.e., adolescence vs. adult participants), sample (pure community-dwelling adolescence), language (Italian vs. English), or potentially cultural differences (Italian vs. US).

Conclusions

Even keeping these limitations in mind, our findings suggested that the ASRS-5 could be safely used in adolescent participants, with scores higher than 16 suggesting the need for accurate assessment of ADHD. These findings may be relevant in extending the range of application of ASRS-5 from adulthood to adolescence, suggesting that the ASRS-5 could be safely used for screening purposes also in community-dwelling adolescents.

Clinical Significance

ADHD is a well-studied condition in children; however, far less is known about ADHD in adolescence. The generalization of results from research using children or adult samples to adolescent samples may be inherently problematic because there are many differences between ADHD in children and adolescents, and adolescents and adults (e.g., Nichols et al. 2017). From this perspective, the availability of data on the reliability and construct validity of ASRS-5 in a sample of adolescents is crucial to make this self-report instrument available for clinicians and researchers working with adolescents. Indeed, the persistence of ADHD over adolescence into adulthood is not matched by continuity of care in this important phase of life (Buitelaar 2017). Identifying adolescents who need a throughout assessment of ADHD characteristics through the administration of an easy-to-use short self-report screening measure for ADHD may represent the first step in preventing the negative sequelae of ADHD (e.g., Pollak et al. 2016), particularly when undiagnosed in childhood.

Disclosures

A.S., G.G., M.A., E.C., and A.F. have nothing to disclose. In the past 3 years, L.A.A. has received grant/research support from Sunovion Pharmaceuticals, Enzymotec, Shire Pharmaceuticals, Otsuka and Lundbeck; has served as a consultant to Bracket, Sunovion Pharmaceuticals, Shire Pharmaceuticals, Otsuka Pharmaceuticals, SUNY, the National Football League, and Major League Baseball; and has received royalty payments (as inventor) since 2004 from NYU for license of adult ADHD scales and training materials. He has no conflicts in regard to stock ownership or speakers bureaus.

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Address correspondence to:
Andrea Fossati, MD
School of Psychology
Vita-Salute San Raffaele University
Via Stamira d'Ancona 20
Milan 20127
Italy

E-mail: fossati.andrea@hsr.it

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ORIGINAL ARTICLE

Serum cytokines in pediatric neuropsychiatric syndromes: focus on Attention Deficit Hyperactivity Disorder

Renato DONFRANCESCO [1], Paola NATIVIO [2], Edoardo BORRELLI [3], Eleonora GIUA [4], Elda ANDRIOLA [3], Maria P. VILLA [5], Michela DI TRANI [6] *

[1]Roma Tre University, Rome, Italy; [2]Department of Molecular Medicine, Sapienza University, Rome, Italy; [3]LUMSA University, Rome, Italy; [4]Faculty of Medicine and Psychology, Sapienza University, Rome, Italy; [5]NESMOS Department, Sapienza University, S. Andrea Hospital, Rome, Italy; [6]Department of Dynamic and Clinical Psychology, and Health Studies, Sapienza University, Rome, Italy

*Corresponding author: Michela Di Trani, Department of Dynamic and Clinical Psychology, and Health Studies, Sapienza University, Via degli Apuli 1, 00185, Rome, Italy. E-mail: michela.ditrani@uniroma1.it

ABSTRACT

BACKGROUND: Inflammation may represent a common underlying mechanism in a wide range of diseases, including neuropsychiatric disorders. Cytokine involvement has been investigated in some studies on patients with childhood neuropsychiatric diseases. The aim of this study was to determine whether cytokines are involved in ADHD to provide a rationale for immune-based therapeutic strategies in this disorder.

METHODS: Sixty children were studied: 34 consecutive drug-naïve children with ADHD (30 males and 4 females; mean age of 10.10 years, SD=2.43 age) and 26 healthy control children (22 males and 4 females; mean age of 10.70 years, SD=1.81). All cytokines but IL-2 (IL4-IL6-IL10- IL17-TNFA and IFNG) were studied by ELISAs; IL-2 was instead studied by means of paired anti-cytokine Abs and cytokine standards obtained from PharMingen.

RESULTS: Data reveal higher IL-6 and IL-10 levels in ADHD patients than in the control group (P=0.03). No differences emerged between the two groups for the other cytokines.

CONCLUSIONS: Our study showed an imbalance between pro- and anti-inflammatory cytokines that may play a pivotal role in the pathogenesis of ADHD.

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KEY WORDS: Attention deficit disorder with hyperactivity; Cytokines; Inflammation.

There has recently been growing recognition of an involvement of the immune system in the pathogenesis of developmental, emotional and learning disabilities.[1] So the brain is not only immunologically active of its own accord, but also has complex peripheral immune interactions. Given the central role of cytokines in neuroimmmunoendocrine processes, it is hypothesized that these molecules influence cognition via diverse mechanisms.

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin: peripheral cytokines penetrate the blood-brain barrier directly via active transport mechanisms or indirectly via vagal nerve stimulation. Cytokines me-

diate cellular mechanisms subserving cognition (dopaminergic and cholinergic systems) and can modulate neuronal regeneration or neurodegeneration. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action (Table I).[2]

There is growing body of literature on inflammation and neuropsychiatric disorders in children and adolescents.[3] Proinflammatory markers are high in youths with major depressive disorder,[4] bipolar disorder,[5] obsessive-compulsive disorder,[6] Tourette's disorder[7, 8] and schizophrenia.[9, 10] Moreover, narrative reviews of immune system abnormalities and cytokine alterations in Autism Spectrum Disorder (ASD) have increased in recent years.[3, 11, 12] Several studies have reported that cytokine profiles in ASD differ from those in healthy controls.[13-15] Furthermore, associations have emerged between the severity of diagnostic features and high cytokine values in ASD.[16, 17]

Inflammation may thus represent a common underlying mechanism in a wide range of diseases, including Attention Deficit Hyperactivity Disorder (ADHD), a neurobehavioral childhood disorder that is characterized by persistent and maladaptive symptoms of hyperactivity/impulsivity and inattention. People with ADHD often have serious impairments in academic, social and interpersonal functioning. ADHD is also associated with several comorbid conditions and disorders, such as mood disorders, disruptive behavior disorders and learning disabilities.[18, 19] Despite considerable research efforts, the etiology and pathophysiology of ADHD remain unclear.[20]

Cytokine involvement has been investigated in some studies on childhood with ADHD diagnosis.[21] Mittleman *et al.*[22] found that the cytokine profiles from the cerebrospinal fluid of ADHD patients fall between those of patients with obsessive-compulsive disorder (OCD) and

TABLE I.—*Cytokine function table: interleukin.*

Cytokine	Cytokine receptor	Cytokine main function	Cytokine disease association
IL-1α; IL-1b	IL1RI and IL1R-AcP	Inflammatory; promotes activation, costimulation, and secretion of cytokines and other acute-phase proteins; pyrogenic	↑ = inflammatory bone resorption; gout; promotes Th17 response
IL-2	IL2Rα, IL2Rb, and IL2Rγ	Proliferation; enhancement of cytotoxicity, IFNγ secretion, and antibody production	↓ = lymphoproliferative disease and susceptibility to autoimmune disease; reduced Treg development. ↑ = reduced Th17 development.
IL-4	IL4Rα and IL2Rγ or IL4Rα and IL13Ra1, IL13Ra2	Proliferation; differentiation of Th2; promotes IgG and IgE production; inhibits cell-mediated immunity and Th17 development	↓ = susceptibility to extracellular pathogens and decreased response to allergens. ↑ = allergic asthma.
IL-6	IL6Rα and gp130	Inflammatory and costimulatory action; induces proliferation and differentiation; synergizes with TGFb to drive Th17	↓ = deficient innate immunity and acute- phase responses, lymphopenia
IL-10	IL10R1 and IL10R2	Immune suppression; decreases antigen presentation and MHC class II expression of dendritic cells; down- regulates pathogenic Th1, Th2, and Th17 responses	↓ = immune pathology due to uncon- trolled inflammation. ↑ = inhibits sterile immunity to some pathogens.
IL-13	IL13Ra1, IL13Ra2 and IL4Rα	Goblet cell activation in lung and gut; proliferation and promotion of IgE production; regulation of cell-mediated immunity	↓ = impaired Th2 responses to extracel- lular pathogens and allergens. ↑ = exacerbates airway diseases.
IL-16	Not defined	Recruitment of CD4+ T cells	
IL-17A	IL17RA or IL17RC	Proinflammatory; protective immunity in lung; tight junction integrity; promotes mobilization of neutrophils and cytokine production by epithelial cells; promotes angiogenesis	↓ = susceptibility to extracellular pathogens ↑ = exacerbates organ- specific autoimmune inflammation
IL-17F	IL17RA or IL17RC	Similar function as IL-17A but with 2 logs lower receptor affinity	Not well defined. ↑ = increases neutrophil recruit- ment at high concentration.

those with schizophrenia. A modest increase in some cytokines has been reported in patients with ADHD (*e.g.* interferon-c, IFN-c), though values returned to normal in a group treated with drugs.[23] Several studies have investigated whether metabolites of the tryptophan/kynurenine pathway and cytokine activity are associated with attention-related symptoms in ADHD children.[24] Autoimmune involvement in ADHD has been suggested by a previous study by our group in which the presence of the neuronal anti-Yo antibody in the Purkinje cells was demonstrated in patients with this disorder.[25]

Furthermore, some cytokines (*e.g.* interleukin 6 and 10, interleukin 1 beta, tumor necrosis factor) are known to play a critical role in physiological brain processes, such as cognitive function, under immunologically and clinically accepted conditions.[26] Interleukin 6 (IL-6) is a cytokine that displays neurodegenerative properties.[27] As mentioned above, IL-6 serum levels are reported to be increased in several neuropsychiatric conditions, including depression[28] and Alzheimer's disease.[29] In this regard, Haeri *et al*.[30] demonstrated the presence of high proinflammatory cytokine levels in otherwise healthy women with a prepregnancy diagnosis of depression. IL6 has also been found to be associated with neuroprotective mechanisms, displaying both anti-inflammatory and immunosuppressive features.[31] Moreover, it has been suggested that IL-6 may play a protective role by regulating histone deacetylase-dependent neuronal survival.[32]

IL-10 has broad anti-inflammatory properties resulting from its ability to inhibit antigen-presenting cell function and suppress production of proinflammatory cytokines and chemokines.[33] Several animal studies and clinical observations point to the anticonvulsant effects of IL-10. One report showed that IL-10 confers a protective effect against the development of epileptic activity evoked by transient episodes of hypoxia in rat hippocampal slices.[34] In hyperthermia-induced seizures of immature rats, the seizure threshold temperature in IL-10-treated rats was significantly higher than in saline-treated controls.[35] Moreover, the frequencies of the IL-10 592C allele and 1082A/-819C/-592C haplotype, which are reported to be associated with increased IL-10 production,[36, 37] are significantly lower in patients suffering from febrile seizures than in healthy controls. Inflammatory cytokines are also known to modify the metabolism of central neurotransmitters, such as norepinephrine and dopamine,[25] that are critically implicated in ADHD pathology. For instance, the administration of IL-1, IL-2, IL-6 or IFN-γ in animal studies increased norepinephrine levels and reduced dopamine levels.[38, 39] Comparable changes in these neurotransmitters have been described in ADHD patients.[40] Oades *et al*.[23, 24] explored systematically associations of 8 cytokines (indicators of pro/anti-inflammatory function) and 5 tryptophan metabolites with symptom ratings (*e.g.* anxiety, opposition, inattention) and continuous performance test (CPT) measures (*e.g.* movement, response time) in 35 ADHD (14 on medication) and 21 control children.

The authors found that total symptom ratings were associated with increases of the interleukins IL-16 and IL-13, and in particular IL-16 with hyperactivity, and IL-13 with inattention. Toto *et al*.[41] also found that antibasal ganglia antibody (ABGA) positivity was significantly higher in patients affected by ADHD than in controls, and that serum antistreptolysin O (ASO) was also significantly more frequent in the ADHD group. Similar results were found by Giana *et al*.[42] studying DAT Antibodies in a group of ADHD children.

In view of the growing body of evidence pointing to a link between a generalized proinflammatory state and many psychiatric conditions, we hypothesize that an imbalance between pro- and anti-inflammatory cytokines may play a pivotal role in the pathogenesis of ADHD.

The main aim of this study was to investigate the presence of cytokines in the serum of children affected by Attention Deficit Hyperactivity Disorders so as to provide a rationale for immune-based therapeutic strategies in this disorder.

Materials and methods

Participants

We studied 34 consecutive drug-naïve Caucasian outpatients (30 males and 4 females; mean age of 10.10 years, SD=2.43 age), diagnosed as suffer-

ing from ADHD at the Clinic for Developmental Neurology and Psychiatry of the S. Pertini Hospital in Rome between the January 1, 2015 and the June 1, 2015. As regards the distribution of the ADHD subtypes, 18 children were diagnosed with the combined subtype, 12 with the inattentive subtype and 4 with the hyperactive subtype.

The control group included 26 healthy Caucasian children (22 males and 4 females; mean age of 10.70 years, SD=1.81), who were randomly recruited in the same period from a community-based survey and were attending two elementary and junior high schools from the same urban area of Rome.

The two groups were matched for sex (χ^2=0.17, P=0.68) and age (t=1.09, P=0.13) and they were recruited in the same city district (same postal code). All the children in both groups were negative to the most common antibody searches designed to detect coeliac disease and Hashimoto thyroiditis. None of the subjects had diagnosis of eczema or other allergic or rheumatic diseases. The most common markers (ESR, RCP) for infections were negative and no subclinical inflammatory status were detected by the blood examination.

Clinical assessment

ADHD was diagnosed according to DSM 5 criteria. The children in the clinical sample of ADHD patients as well as their parents separately underwent a semi-structured psychiatric interview, *i.e.* the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[43] administered by an experienced child psychiatrist (RD). All the children (in both the ADHD and control groups) underwent an additional routine diagnostic assessment, including the ADHD-Rating Scale (ADHD-RS) adapted for the Italian population,[44] which was filled out by parents and schoolteachers; this additional assessment was designed to confirm the ADHD diagnosis, made according to DSM-5 criteria, in children with ADHD and ruled out the presence ADHD in the children in the control group. According to the Wechsler Intelligence Scale for Children-Revised (WISC- III), any child with an Intelligence Quotient (IQ) <70 was excluded. We have excluded in clinical sample the comorbidity of other diagnosis, as Oppositional Defiant Disorder (ODD) and Mood Disorders, using K-SADS. The subjects' medical history, neurological and physical examinations and electroencephalogram ruled out co-morbid medical and neurological conditions. Written informed consent was obtained from the parents of all the subjects included in the study.

Cytokines

All the cytokines but IL-2 (IL4-IL6-IL10- IL17-TNFA and IFNG) were studied by means of ELISAs; IL-2 was analyzed by means of paired anticytokine Abs and cytokine standards obtained from PharMingen (San Diego, CA). Anti-IL-2 reagents were obtained from Genzyme (Cambridge, MA). All the samples and standards were assayed in duplicate at a 1:2 dilution. Standard curves were generated on each plate. In brief, plates were coated with purified anticytokine Ab at 2 pg/mL, washed, and then blocked with 5% FCS in PBS. CSFL and standards were plated, incubated overnight at 4°C, washed, and biotinylated anticytokine Ab was plated at 1 pg/mL. Following washing, strepavidin-horseradish peroxidase was applied, and color was developed with ABTS (2.2' azino-di[3-ethylhenzthiazoline sulfonate]) and detected at 405 nm. Cytokine concentrations were calculated according to standard curves, using SOFTMAX PRO software.

Statistical analysis

Differences between the two groups (ADHD group and non-ADHD group) in demographic characteristics (age, gender and body mass index) were assessed by means of Chi-square Analysis on the gender variable and t-test on age variable.

In order to compare the serum cytokine concentrations in the ADHD and control groups, U-Mann Whitney tests were performed using cytokine levels (IL2-IL4-IL6-IL10-IL17-TNFA and IFNG) as dependent variables. A nonparametric analysis was performed because the continuous dependent variables did not follow a normal distribution (tested with the Kolmogorov-Smirnov test and the Shapiro-Wilk test).

Results

Data show no differences in gender distribution or mean age between the two groups. In the present study we compared the serum levels of several cytokines in ADHD children and a control group. Data on cytokine levels did not follow a normal distribution (IL2: Kolmogorov-Smirnov test=0.53, P=0.00, Shapiro-Wilk tes*t*=0.20, P=0.00; IL4: Kolmogorov-Smirnov test=0.50, P=0.00, Shapiro-Wilk test=0.24, P=0.00; IL6: Kolmogorov-Smirnov test=0.34, P=0.00, Shapiro-Wilk test=0.70, P=0.00; IL10: Kolmogorov-Smirnov test=0.45, P=0.00, Shapiro-Wilk test=0.58, P=0.00; IL17: Kolmogorov-Smirnov test=0.51, P=0.00, Shapiro-Wilk test=0.27, P=0.00; TNFA: Kolmogorov-Smirnov test=0.56, P=0.00, Shapiro-Wilk test=0.28, P=0.00; IFNG: Kolmogorov-Smirnov test=0.49, P=0.00, Shapiro-Wilk test=0.27, P=0.00). Therefore, a non-parametric test was used. Table I illustrates the characteristics of the two patient groups studied. Data show that IL-6 and IL-10 levels increased in ADHD patients (Table II). No differences were found between the two groups for the other cytokines.

Discussion

Serum cytokine levels in the first paper by Oades *et al*.[23] were not significantly higher in ADHD children than in the control group. By contrast, our results show that IL6 levels are significantly higher in ADHD children than in the control group. This finding supports the hypothesis that immune processes and mediators may play a role in the pathogenesis of ADHD and confirms the results of the second paper by Oades *et al*.[24] It should however be borne in mind that the high cytokine levels in the study by Oades *et al*. were detected in IL13 and IL16, which we did not instead include in our study. Moreover, the contemporary increase in IL10 levels designed to act as a protective factor in the ADHD children may explain the absence of marked inflammatory damage in the brain of these children and suggest that subtle cellular alterations may be involved. Another possible effect of IL6 on the brain of ADHD children may be of an endocrine nature owing to the passage of these molecules in the cerebrospinal fluid.[22] This passage may cause damage in the brain structures, as has been documented by means of fMRI in patients with allergic attacks.[45]

TABLE II.—*Differences between ADHD and control children in serum cytokine levels.*

	ADHD group	Control group	Mann Whitney U	P
	Mean rank	Mean rank		
IL-2	30.50	30.50	442.00	n.s.
IL-4	30.50	30.50	442.00	n.s.
IL-6	34.06*	25.85*	321.00*	0.03*
IL-10	33.34*	26.79*	345.50*	0.03*
IL-17	30.37	30.67	437.50	n.s.
TNFA	30.50	30.50	442.00	n.s.
INFG	30.74	30.19	434.00	n.s.

IL-2, IL-4, IL-6, IL-10 IL-17: cytokines; TNFA: tumor necrosis factor; INFG: interferon.
*Significant IL-6 and IL-10 differences.

Strengths and limitations of the study

The small number of subjects is the first major limitation of this pilot study. This prevented us from using statistical analyses to investigate any differences in cytokine levels between the ADHD subtypes (18 combined, 12 inattentive and only 4 hyperactive). The fact that we did not study the IL1, IL13 and IL16 serum levels may be considered another limitation. These results warrant confirmation in a larger group of probands, in whom the study could be extended to include more cytokines. In addition, with a larger sample we could analyze the studied variables in different groups of ADHDs with different symptoms presentations. Moreover, the possibility that our results are due to a marked prevalence of obesity in the ADHD group cannot be ruled out because anti-inflammatory cytokine production from adipose tissue tends to occur in such children.[46] Indeed, some studies have suggested that ADHD is associated with an increased presence of obesity.[47]

The strength of this paper is the potential new therapeutic options it affords. Indeed, if these results are confirmed, an anti-IL6 drug may be recommended as an add-on to traditional stimulant therapy in ADHD children. Some noteworthy results have recently published in this regard, with Celecoxib used as an anti-IL6 add-on drug in patients with Major Depressive Disorder prov-

ing effective in a double-blind trial.[48] However, several issues related to the cost-benefit ratio of an anti-IL6 drug during childhood are debatable given the current state of technology of biological drugs. This study, and other future studies on the same topic, are likely to encourage the use of an immune therapy against IL-6 only when the side effects of this type of medication are reduced.

Conclusions

In conclusion, proinflammatory cytokine interleukin-6 (IL-6) and the anti-inflammatory interleukin-10 (IL-10) are the key mediators of neuroimmune interactions, and they are the pathogenic factor shared by a range of perinatal pathologies that lead to severe neurological and mental diseases.

Our study highlights an imbalance between pro- and anti-inflammatory cytokines, which may be one of the pathogenetic mechanism of a subset of ADHD children. Bearing in mind the growing body of evidence pointing to a link between a generalized proinflammatory state and psychiatric conditions, we believe that further investigation of this association in ADHD children may help to fill a gap in our knowledge regarding the pathogenesis of ADHD. If our results are confirmed, they could suggest the use of anti IL6 drugs as add-therapy in a subset of ADHD children.

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Author for correspondence:
Maurizio Bonati,
E-mail: maurizio.bonati@marionegri.it

CAMBRIDGE UNIVERSITY PRESS

Still too much delay in recognition of autism spectrum disorder

Bonati Maurizio, Massimo Cartabia and Antonio Clavenna

Department of Public Health, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Cohort studies have consistently reported trends in autism spectrum disorder (ASD) diagnosis with a considerable increase in prevalence and incidence over the last two decades (Lyall *et al.*, 2016). Although the descriptive epidemiological studies of ASD, mainly focused on children and in high-income countries (Chiarotti and Venerosi, 2020), are affected by numerous methodological limitations all are in agreement with the increase. The rising incidence rates have been attributed differently from one country to another to different factors such as increased awareness of ASD, changes in diagnostic tools and criteria, lowered stigma and improved health service organisation (Hodges *et al.*, 2020). To define the size and slope of the increase is useful to determine whether the prevalence has stabilised. Thus, we examined the time trends of cumulative incidence of ASD over the last 20 years in a large Italian population.

Methods

This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. No statistical tests were conducted in this study. Data on children born in 2000–2017, resident in Lombardy Region until 31/12/2020, and diagnosed with ASD (International Statistical Classification of Diseases, Ninth Revision [ICD-9] code 2990*) were retrieved from the administrative health databases of Italy's Lombardy Region. The Lombardy Region is one of the largest Italian regions; it is situated in the north and is one of the most prominent from the socioeconomic point of view. In Lombardy Region, healthcare is provided free up to the age of 14. The used databases have been previously validated and extensively used for epidemiological studies.

For each child included in the study, we defined an observational period starting from the first birthday and ending on the day before the birthday of 2020. Then, ASD case status (incidence case) was determined using the first time that for a child was reported ASD condition in one of the health administrative regional databases (hospitalisations or specialist visits) during the observational period.

Extracted information included date of birth, gender and day of the first diagnosis. Thus, for each birth cohort from 2000 to 2017, we calculated cumulative ASD incidence as the cumulative sum of the number of new cases of ASD for each age divided by the total number of children born in the same cohort. Lifetime cumulative incidence refers to individuals with a reported ASD condition in a period of years of life considered.

Results

We included in this study 1 323 792 children (681 048 boys and 642 744 girls) born between 2000 and 2017 and resident in Lombardy Region until 31/12/2020. The number of children diagnosed with ASD between 1 and 19 years of age was 8105 (0.61%), 6627 (0.97%) boys and 1478 (0.23%) girls. Table 1 shows the cumulative incidence values for the 18 birth cohorts. The maximum value was 1.06% (95% CI 0.98–1.13%) at age 4 years for persons born in 2015. This class of age showed the major increase in the cumulative incidence (+0.97%) going from 0.09% (95% CI 0.07–0.11%) for the 2001 cohort to 1.06% (95% CI 0.98–1.13%) for the 2015 cohort.

The 2-year lifetime cumulative incidence ranges between 0.02% (95% CI 0.01–0.04%) for the 2001 cohort and 0.42% (95% CI 0.37–0.46%) for the 2015 cohort (Fig. 1). The 2-year lifetime cumulative incidence value achieved since the 2013 birth cohort is similar to that of 2000 at 18 years of age. These trends are particularly marked in all cohorts with a boys/girls cumulative incidence ratio ranging from 3.35 in 2000 birth cohort to 6.00 in that of 2010 (see online Supplementary Table S1). A continuous increase in the slope of cumulative incidence is observable for all the studied cohorts but it is starting from those of the last decade that the shift is more marked (Fig. 1).

Discussion

In recent years, cases of autism have risen everywhere in the world (Baxter *et al.*, 2015). About one in 105 children born in 2015 in the Italian Lombardy Region was identified with ASD by

Table 1. Cumulative incidence of autism spectrum disorder through 2020 by age per 100 persons (%) born between 2000 and 2017 (95% CI) in Lombardy Region, Italy

Birth year	Age 2	Age 4	Age 6	Age 8	Age 10	Age 18
2000	0.04 (0.03–0.06)	0.13 (0.10–0.16)	0.16 (0.13–0.19)	0.18 (0.15–0.21)	0.21 (0.18–0.25)	0.33 (0.29–0.37)
2001	0.02 (0.01–0.04)	0.09 (0.07–0.11)	0.13 (0.10–0.15)	0.17 (0.14–0.20)	0.20 (0.17–0.23)	0.34 (0.30–0.39)
2002	0.04 (0.02–0.05)	0.13 (0.10–0.15)	0.19 (0.16–0.22)	0.23 (0.20–0.27)	0.28 (0.24–0.31)	
2003	0.06 (0.04–0.07)	0.13 (0.11–0.16)	0.19 (0.16–0.23)	0.24 (0.21–0.28)	0.29 (0.25–0.33)	
2004	0.05 (0.03–0.06)	0.16 (0.13–0.19)	0.22 (0.18–0.25)	0.29 (0.25–0.33)	0.34 (0.30–0.38)	
2005	0.05 (0.04–0.07)	0.17 (0.14–0.20)	0.26 (0.22–0.30)	0.32 (0.28–0.36)	0.37 (0.33–0.41)	
2006	0.06 (0.05–0.08)	0.19 (0.16–0.22)	0.30 (0.27–0.34)	0.37 (0.33–0.41)	0.44 (0.40–0.49)	
2007	0.07 (0.05–0.09)	0.23 (0.19–0.26)	0.30 (0.26–0.34)	0.38 (0.34–0.43)	0.47 (0.42–0.52)	
2008	0.07 (0.05–0.09)	0.23 (0.20–0.27)	0.33 (0.29–0.36)	0.42 (0.38–0.46)	0.51 (0.46–0.56)	
2009	0.07 (0.05–0.09)	0.24 (0.21–0.27)	0.37 (0.32–0.41)	0.47 (0.43–0.52)	0.55 (0.50–0.60)	
2010	0.10 (0.08–0.13)	0.30 (0.25–0.34)	0.42 (0.37–0.47)	0.54 (0.49–0.60)		
2011	0.15 (0.12–0.18)	0.43 (0.38–0.47)	0.64 (0.58–0.70)	0.77 (0.71–0.84)		
2012	0.22 (0.18–0.25)	0.66 (0.60–0.72)	0.90 (0.83–0.97)			
2013	0.32 (0.28–0.36)	0.81 (0.74–0.88)	1.04 (0.96–1.11)			
2014	0.35 (0.31–0.39)	0.97 (0.90–1.05)				
2015	0.42 (0.37–0.46)	1.06 (0.98–1.13)				
2016	0.37 (0.33–0.42)					
2017	0.28 (0.24–0.32)					

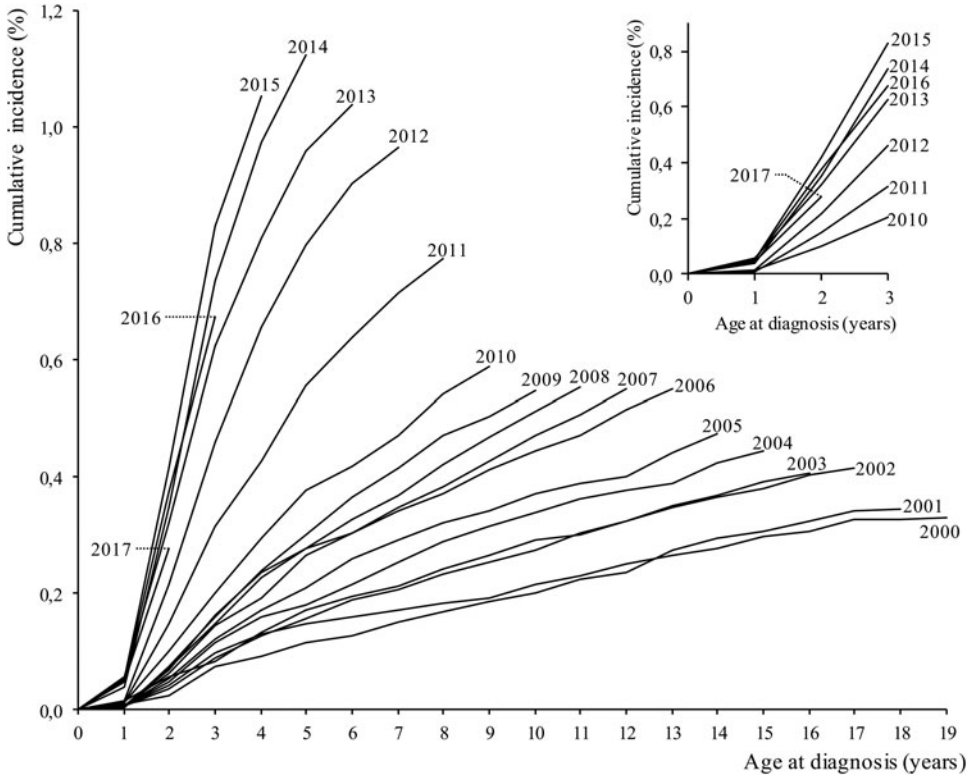

Fig. 1. Each curve in the main body of the figure corresponds to the autism spectrum disorder cumulative incidence through 2020 among person in each birth cohort (beginning 2000, bottom curve). The inset is a close-up view of the ASD cumulative incidence through age 3 years for each birth cohort.

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age 4. This is a 75% increase from children born in 2009. These trends are consistent with other reported birth cohort analyses, although the national slope and profile of the cumulative incidence curve show different trajectories (Schendel and Thorsteinsson, 2018; Segev *et al.*, 2019; Rah *et al.*, 2020; Cybulski *et al.*, 2021; Sasayama *et al.*, 2021). However, also these findings suggest that ASD cumulative incidence has not stabilised, and the appearance of ASD condition in the administrative health databases with increasing age indicates a delay in the interception of ASD status. That ASD is more than four times common among boys than among girls is generalisable, not so much the effective rate of ASD as long as the curve of incidence will reach a plateau, and the value of the rate will be stable between the new births cohorts. The increasing rate of the young cohorts and with the age in older ones suggests the improvement in making an early diagnosis than in the past. Although it is difficult to make accurate predictive estimates, early cumulative incidence could exceed 1.1% (one in 91 new births). Expanding public awareness may have contributed to the increased nationwide incidence of ASD, as well as non-etiological factors (e.g. accessibility to services, diagnostic criteria). However, the results highlight the need for quickly improving effective initiatives tracking appropriately trends in prevalence and incidence of ASD (e.g. national registries, surveillance programmes) (Fombonne *et al.*, 2021), and covering the whole ASD care, throughout the life span, for a growing target population. A public challenge for everyone and not just healthcare.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796021000822.

Data. The dataset supporting the conclusions of this study is available from the corresponding author upon request.

Author contributions. MB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors conceived and designed the study. MC acquired and analysed the data. All authors contributed to the interpretation of data. MB drafted the text.

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Conflict of interest. None.

Ethical standards. Ethical approval and informed consent were not required because this study retrieved and synthesised anonymous data.

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AGENZIA ITALIANA DEL FARMACO

DETERMINA 22 dicembre 2021

Modifica della determina AIFA n. 488 del 27 aprile 2015, cosi' come rettificata dalla determina AIFA n. 860 del 13 luglio 2015, relativa all'inserimento del Metilfenidato nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento del disturbo da deficit dell'attenzione e iperattivita' (ADHD) negli adulti gia' in trattamento farmacologico prima del compimento del diciottesimo anno di eta'. (Determina n. 149900/2021). (22A00071)

(GU n.6 del 10-1-2022)

IL DIRIGENTE
dell'area pre-autorizzazione

Visti gli articoli 8 e 9 del decreto legislativo 30 luglio 1999, n. 300;

Visto l'art. 48 del decreto-legge n. 30 settembre 2003, n. 269, convertito con modificazioni dalla legge 24 novembre 2003, n. 326, che istituisce l'Agenzia italiana del farmaco (AIFA);

Visto il decreto del Ministro della salute, di concerto con il Ministro della funzione pubblica e il Ministro dell'economia e delle finanze, 20 settembre 2004, n. 245, e successive modificazioni, recante norme sull'organizzazione e il funzionamento AIFA;

Visto il regolamento di organizzazione, del funzionamento e dell'ordinamento del personale dell'AIFA, adottato dal consiglio di amministrazione con deliberazione 8 aprile 2016, n. 12;

Visto il decreto del Ministro della salute del 15 gennaio 2020, con cui il dott. Nicola Magrini e' stato nominato direttore generale dell'Agenzia italiana del farmaco e il relativo contratto individuale di lavoro sottoscritto in data 2 marzo 2020 e con decorrenza in pari data;

Vista la determina direttoriale n. 257 del 13 marzo 2020 di conferma della determina direttoriale di delega n. 1792 del 13 novembre 2018, con cui la dott.ssa Sandra Petraglia, dirigente dell'Area pre-autorizzazione, e' stata delegata dal direttore generale all'adozione dei provvedimenti di autorizzazione della spesa di farmaci orfani per malattie rare e di farmaci che rappresentano una speranza di cura, in attesa della commercializzazione, per particolari e gravi patologie, nei limiti della disponibilita' del «Fondo del 5%», di cui all'art. 48, commi 18 e 19, lettera a) del decreto-legge 269/2003, convertito con modificazioni dalla legge n. 326/2003 e dei provvedimenti per l'aggiornamento dell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge n. 648/1996;

Visto il decreto del Ministro della salute 28 settembre 2004 che ha costituito la Commissione consultiva tecnico-scientifica (CTS) dell'AIFA;

Visto il decreto del Ministro della salute 20 settembre 2018 che ha ricostituito la Commissione consultiva tecnico-scientifica (CTS) dell'AIFA;

Visto il decreto-legge 21 ottobre 1996, n. 536, convertito, con modificazioni, dalla legge 23 dicembre 1996, n. 648, relativo alle misure per il contenimento della spesa farmaceutica e la determina del tetto di spesa per l'anno 1996 e, in particolare, l'art. 1, comma 4, che dispone l'erogazione a totale carico del Servizio sanitario nazionale per i medicinali innovativi la cui commercializzazione e' autorizzata in altri Stati ma non sul territorio nazionale, dei

medicinali non ancora autorizzati ma sottoposti a sperimentazione clinica e dei medicinali da impiegare per un'indicazione terapeutica diversa da quella autorizzata;

Visto il provvedimento della Commissione unica del farmaco (CUF), del 20 luglio 2000, pubblicato nella Gazzetta Ufficiale n. 219 del 19 settembre 2000 con errata-corrige nella Gazzetta Ufficiale n. 232 del 4 ottobre 2000, concernente l'istituzione dell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale ai sensi della legge 23 dicembre 1996, n. 648;

Visto il provvedimento CUF del 31 gennaio 2001, concernente il monitoraggio clinico dei medicinali inseriti nel succitato elenco, pubblicato nella Gazzetta Ufficiale del 24 marzo 2001, n. 70;

Vista la determina AIFA n. 488 del 27 aprile 2015, pubblicata nella Gazzetta Ufficiale n. 107 dell'11 maggio 2015, relativa all'inserimento nel suddetto elenco del medicinale METILFENIDATO per il trattamento del disturbo da deficit dell'attenzione e iperattivita' (ADHD) negli adulti gia' in trattamento farmacologico prima del compimento del diciottesimo anno di eta';

Vista la determina AIFA n. 860 del 13 luglio 2015, pubblicata nella Gazzetta Ufficiale n. 168 del 22 luglio 2015, relativa alla rettifica della determina AIFA n. 488 del 27 aprile 2015 sopra citata in cui la dicitura «metilfenidato (Ritalin)» e' stata sostituita con quella relativa al solo principio attivo metilfenidato;

Vista la determina AIFA n. 50247 del 6 maggio 2019, pubblicata nella Gazzetta Ufficiale n. 113 del 16 maggio 2019, relativa alla prescrivibilita' del metilfenidato per la suddetta indicazione nel rispetto delle condizioni presenti nella scheda di registro di monitoraggio AIFA;

Vista la determina AIFA n. 1264 del 20 ottobre 2021, pubblicata per estratto nella Gazzetta Ufficiale n. 263 del 4 novembre 2021, relativa all'autorizzazione all'immissione in commercio di Medikinet, medicinale a base di metilfenidato a rilascio modificato, per la seguente indicazione: «Adulti. Negli adolescenti i cui sintomi persistono nell'eta' adulta e che hanno mostrato evidenti benefici dal trattamento, puo' essere opportuno continuare il trattamento con «Medikinet» alla stessa dose giornaliera (mg/die) nell'eta' adulta»;

Ritenuto, pertanto, di escludere dal suddetto elenco i medicinali a base di metilfenidato a rilascio modificato e di mantenere il medicinale a base di metilfenidato a rilascio immediato (Ritalin) per le condizioni in cui sia necessario impiegare tale formulazione;

Ritenuto percio' opportuno consentire la prescrizione di detto medicinale a totale carico del Servizio sanitario nazionale nella sola formulazione a rilascio immediato (Ritalin) per il trattamento del disturbo da deficit dell'attenzione e iperattivita' (ADHD) negli adulti gia' in trattamento farmacologico prima del compimento del diciottesimo anno di eta';

Tenuto conto della decisione assunta dalla CTS dell'AIFA nella riunione del 1, 2 e 3 dicembre 2021 - stralcio verbale n. 57;

Vista la delibera di approvazione del consiglio d'amministrazione di AIFA del 20 dicembre 2021, n. 68 - punto n. 6;

Ritenuto, pertanto, di provvedere alla modifica della determina AIFA n. 488 del 27 aprile 2015, cosi' come rettificata dalla determina AIFA n. 860 del 13 luglio 2015, includendo soltanto la formulazione del medicinale Ritalin, a rilascio immediato;

Determina:

Art. 1

Il medicinale «Metilfenidato» e' mantenuto nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, per le indicazioni di cui al successivo art. 2, nella sola formulazione a

rilascio immediato (Ritalin).

Art. 2

Il medicinale metilfenidato (Ritalin) e' erogabile a totale carico del Servizio sanitario nazionale per il trattamento del disturbo da deficit dell'attenzione e iperattivita' (ADHD) negli adulti gia' in trattamento farmacologico prima del compimento del diciottesimo anno di eta', che necessitano di trattamento con formulazione a rilascio immediato, nel rispetto delle condizioni presenti nella scheda di registro di monitoraggio AIFA all'indirizzo: https://servizionline.aifa.gov.it che costituisce parte integrante della presente determina.

Art. 3

La presente determina ha effetto dal giorno successivo alla sua pubblicazione nella Gazzetta Ufficiale della Repubblica italiana.

Roma, 22 dicembre 2021

Il dirigente: Petraglia

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter

link per potersi cancellare dalla mailing list:
http://adhd.marionegri.it/index.php/newsletter/cancellazione-newsletter

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014, N. 778 del 05/02/2015, n. 5954 del 05/12/2016, N. 1077 del 02/02/2017, N. 1938 del 15/02/2019, N. 3885 del 30/03/2020)
Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Percorsi diagnostico-terapeutici per l'ADHD*".

IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI
DIPARTIMENTO DI SALUTE PUBBLICA
Laboratorio per la Salute Materno Infantile
Via Mario Negri, 2 - 20156 Milano MI - Italia - www.marionegri.it
tel +39 02 39014.511 - mother_child@marionegri.i