NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD LUGLIO 2021

Acad Pediatr. 2021.

ASSOCIATION OF PRIMARY AND BEHAVIORAL HEALTH INTEGRATED CARE UPON PEDIATRIC MENTAL DISORDER TREATMENT.

Chen H, Upadhyay N, Lyu N, et al.

OBJECTIVE: The objective of this study was to examine whether linkage with mental health (MH) treatment differed across 3 different integrated care arrangements (ICAs), following incident attention deficit hyperactive disorder (ADHD) and major depressive disorder (MDD) diagnoses given by primary care providers (PCPs) in the pediatric setting.

METHODS: Using claims linking with multiple public data sources, we examined the treatment initiation among children receiving an incident diagnosis of ADHD or MDD from PCPs working in practices with various ICAs. ICAs were categorized as PCP practiced alone (non-co-located), PCP practiced with specialist outside the practice but co-located at the practice site (co-located), and employed specialists who were co-located (co-located and co-affiliated).

RESULTS: A total of 4203 incident ADHD and 298 incident MDD cases diagnosed by PCPs were identified, of which 3123 (74%) with ADHD and 200 (67%) with MDD received treatment within 90 days since the diagnosis. Children diagnosed with ADHD by co-located and co-affiliated PCPs were twice as likely to receive treatment as those diagnosed by non-co-located PCPs (odds ratio [OR] = 1.93; 95% confidence interval [CI], 1.24-2.78). Of those treated, children diagnosed by co-located and co-affiliated PCPs were 2 times more likely to receive guideline recommended psychotherapy (OR = 2.15; 95% CI, 1.35-3.44). These patients were also more likely to be treated at the diagnosing site versus elsewhere. Similar beneficial effects were not observed in those first diagnosed by co-located but non-affiliated PCPs.

CONCLUSIONS: Service co-location between co-affiliated PCPs and MH specialists was associated with significant higher ADHD treatment rate and the receipt of guideline-recommended psychotherapy

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

Acta Pediatr Esp. 2020;78:14-18.

PSYCHOEDUCATIONAL GROUPS FOR PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

de Valmaseda MCHM.

In the treatment of the child with attention deficit hyperactivity disorder (ADHD) we have to include the family from the beginning, mainly the parents, since it is going to be through them how our interventions can have a greater repercussion and benefit for the minor. We propose as a pillar of any intervention, the psychoeducational groups of parents, in which they are given the information and the necessary tools to begin to understand the problem of the child, how to help him, the different alternatives of treatments and from there improve the alliance with the therapists who will intervene. A psychoeducational program of 4 sessions of two hours each for parents with children with ADHD is established at the mental health center, directed by the psychologist and the psychiatrist of the children and youth program. At the end of each group an anonymous evaluation is done to have a feedback about how the parents had received the information transmitted with 4 questions, assessment of the sessions and the possibility of suggestions. An analysis of the questionnaires collected during a school year is made, obtaining a very positive assessment in all the suggested aspects and suggesting to expand them or include more topics in new sessions. These results encourage us to improve this alternative and include it as a basis in all treatments for children with ADHD, proposing to parents that before this diagnosis start this group and from there each case is raised individually

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Alcohol Clin Exp Res. 2021.

PERSISTENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PREDICTS SOCIALLY ORIENTED, BUT NOT PHYSICAL/PHYSIOLOGICALLY ORIENTED, ALCOHOL PROBLEMS IN EARLY ADULTHOOD.

Wang FL, Pedersen SL, Kennedy TM, et al.

Background: Although individuals with histories of childhood attention-deficit/hyperactivity disorder (ADHD) report more alcohol-related problems in adulthood than those without ADHD, it is unknown whether there are group differences in certain types of alcohol problems. We tested whether the nature of alcohol problems differed for individuals with and without childhood ADHD, as well as adulthood-persistent ADHD, to facilitate a personalized medicine approach for alcohol problems in this high-risk group.

Methods: Data were drawn from a prospective, observational study. Children diagnosed with ADHD and demographically similar individuals without childhood ADHD were followed prospectively through young adulthood (N=453; 87.6% male). ADHD symptom persistence was assessed using self-reports and parent reports. Alcohol problems and heavy drinking were assessed repeatedly from 18ΓÇô30-áyears old to construct lifetime measures.

Results: Full-sample confirmatory factor analyses identified 5 alcohol problem types: interpersonal problems/risky behaviors, occupational/academic impairment, impaired control/treatment seeking, tolerance/withdrawal, and drinking to blackout. Latent class analyses of items within each type yielded the best fit for 3-class solutions for all sets of items except blackout drinking, for which 2-áclasses emerged. Children with ADHD were more likely than those without ADHD to belong to high-risk latent classes for interpersonal problems/risky behaviors, occupational/academic problems, and impaired control (the high-risk class that indexed treatment-seeking behavior). These effects were driven by individuals whose ADHD symptoms persisted into adulthood. Few group differences emerged for tolerance/withdrawal and blackout drinking, except that individuals with only childhood ADHD (no persistence) were more likely to belong to the low-risk groups than those with adulthood-persistent ADHD and without ADHD.

Conclusions: Individuals with ADHD histories whose symptoms persist into adulthood may be more likely to experience socially oriented alcohol problems and impaired control/treatment seeking than individuals without an ADHD history and those with childhood ADHD only. Tailored alcohol prevention and treatment programs may benefit this high-risk population

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Am J Drug Alcohol Abuse. 2021.

CURRENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND NONMEDICAL PRESCRIPTION OPIOID USE ATTRIBUTED TO TRAMADOL AMONG MALE ADOLESCENTS WITHOUT CONDUCT DISORDER IN EGYPT.

Bassiony MM, Mahdy RS, Haggag N, et al.

Background: Evidence for the association between attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) is common. However, little research has investigated this relationship among adolescents using nonmedical prescription opioids, particularly tramadol.

Objective: To estimate the prevalence and correlates of ADHD among adolescents with tramadol misuse and without conduct disorder (CD).

Methods: This study included 122 Egyptian adolescents (100% male) with opioid use disorders attributed to tramadol. The diagnosis of SUDs, ADHD, and CD (to exclude) was based on the SCID-I criteria of the DSM-IV-TR. Drug-related problems were assessed using the Drug Use Disorders Identification Test (DUDIT). All adolescents were screened for drugs by urinalysis.

Results: Thirty-eight percent of adolescents with tramadol misuse had ADHD. Adolescents with tramadol misuse and ADHD were more likely to have a younger age of onset of smoking, substance use, and tramadol misuse than adolescents without ADHD.

Conclusions: ADHD is common among adolescents with tramadol misuse. There is an association between ADHD and young age of onset of tramadol misuse and drug-related problems

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Annals of Clinical and Analytical Medicine. 2021;12:S72-S76.

EMOTIONAL DYSREGULATION IN MOTHERS OF CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Luş MG, Eroğlu MZ.

Aim: Emotion dysregulation (ED) is frequently observed in attention deficit and hyperactivity disorder (ADHD). People suffering from ADHD have difficulty with ED, and the nature of the relationship between the two is an important area of research. In this study, we aimed to investigate ED in mothers of children with ADHD.

Material and Methods: Seventy-two children (n = 49 male, n = 23 female) with a diagnosis of ADHD and their mothers participated in the study Clinical Interview was used for the the Diagnostic and Statistical Manual of Mental Disorders (fourth edition (DSM-IV) (SCID-II), Child Anxiety Sensitivity Index (CASI)). Mothers completed the McMaster Family Assessment Device (FAD) and ConnersΓÇÖ Parent Rating Scale (CPRS-48) as applied to individuals.

Results: The distribution of SCID-II diagnoses in mothers was as follows: without diagnosis 73.6 %, avoidant 8.3%, histrionic 5.6%, obsessive-compulsive 5.6%, passive-aggressive 2.8%, dependent 1.4%, self-defeating 2.8%. CASI scale points were higher in children with SCID II (-¦31.73, -¦6.98 vs 27.84, -¦7.19, p =.037). There was no difference in the subscales of Conners and McMaster scales according to the presence or absence of SCID-II diagnoses.

Discussion: The relationship of ED with ADHD and personality disorders has been frequently noted. However, a number of questions remain unaddressed about the association between ADHD and ED

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Asian J Psychiatry. 2021.

DEVELOPMENT AND EFFECTIVENESS OF PARENT SKILLS TRAINING INTERVENTION FOR INDIAN FAMILIES HAVING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Shah R, Sharma A, Grover S, et al.

Objective: Parent skills training interventions (PSTIs) are considered first-line treatment for ADHD. We describe development and effectiveness of a culturally-contextualised PSTI for Indian families.

Method: Forty-one families divided into 5 groups, each group with 6-10 families received group PSTI comprising of 10 weekly sessions using multi-point videoconferencing as an adjunct to routine care in the non-randomized pre-post intervention study.

Results: Thirty-six families attended more than 3 sessions. RM ANOVA revealed significant improvements in parent-rated measures of inattention ($p < 0.001$), hyperactivity/ impulsivity ($p = 0.007$), conduct problems ($p = 0.002$), academic performance ($p = 0.001$) and classroom behavior ($p = 0.001$). Mixed ANOVA analysis

did not reveal significant differences between those who received PSTI with medication and those who received PSTI on any VADPRS domains except depression/ anxiety scores, wherein former group performed better (p = 0.008). More than 60 % parents perceived that PSTI was helpful in increasing awareness, reducing guilt/ blame, improving parent-child relation and decreasing stress. Difficulty in sustaining with the strategies was reported by 50 % of parents.
Conclusion: Findings suggest that PSTI is effective and helpful for Indian families dealing with ADHD

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Autism. 2021.

ADDING THE MISSING VOICE: HOW SELF-REPORT OF AUTISTIC YOUTH SELF-REPORT ON AN EXECUTIVE FUNCTIONING RATING SCALE COMPARES TO PARENT REPORT AND THAT OF YOUTH WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER OR NEUROTYPICAL DEVELOPMENT.

Kenworthy L, Verbalis A, Bascom J, et al.

Executive functions are related to key outcomes. Studies of autistic youth self-report of other nonsocial traits indicate that their insights into their own functioning and internal experiences provide important information that is not captured by their parents report, but youth self-report of executive function has not been researched in autism. We investigate self- and parent-report on the Behavior Rating Inventory of Executive Function-2 in 197 autistic youth without intellectual disability, including the magnitude and profile of problems reported across subdomains of executive function. We also compare autistic self-report to that of 114 youth with attention deficit hyperactivity disorder and 197 neurotypical youth. We find that autistic youth report significant executive function challenges in comparison to neurotypical youth and a distinctive profile of challenges in comparison to attention deficit hyperactivity disorder youth. Parents and their autistic children diverge regarding the severity of the youth's executive function difficulties, but both emphasize flexibility problems within their profile of executive function challenges. Intraclass correlation coefficients between parent and youth ratings were moderate to poor in the autistic group, indicating that autistic youth report adds important information beyond that captured by their parents report. These data elevate the importance of asking autistic youth directly about their own executive function. Lay abstract: Executive functions are often impaired in autistic people and relate to important outcomes such as mental health, success in school and work, and quality of life. Evaluating executive functions helps autistic people, clinicians, and families identify targets for external supports and skill building. Youth self-report of executive function has not been studied, yet we know that self-report from autistic youth is key to understanding other cognitive/behavioral phenomena in autism such as anxiety, obsessions/compulsions, sensory sensitivities, and repetitive behaviors. We investigated self- and parent-report of executive function problems in 197 autistic youth without intellectual disability (ages 11-18 years), including the magnitude and profiles of executive function problems autistic youth report across subdomains of executive function. We compared autistic self-report with that of 114 youth with attention deficit hyperactivity disorder without intellectual disability and 197 neurotypical youth. We found that autistic youth report significant executive function problems compared to neurotypical youth and a distinctive profile of challenges in comparison to attention deficit hyperactivity disorder youth. Parents and their autistic children diverged regarding the magnitude of the youth's executive function difficulties, but both identify inflexibility as the most impaired executive function subdomain. Autistic youth and their parents were somewhat more concordant in their report of executive function problems than youth with attention deficit hyperactivity disorder and their parents, but only showed moderate concordance at best. These findings elevate the importance of asking autistic youth directly about their executive functioning when engaging them in assessment and intervention, or researching executive functions in autism

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Autism. 2021.

THE UTILITY OF PARENT-REPORT SCREENING TOOLS IN DIFFERENTIATING AUTISM VERSUS ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOL-AGE CHILDREN.

Guttentag S, Bishop S, Doggett R, et al.

Symptoms of autism spectrum disorder and attention-deficit/hyperactivity disorder often co-occur, challenging timely, and accurate diagnosis. We assessed the performance of three parent-report measures in discriminating autism spectrum disorder from attention-deficit/hyperactivity disorder without autism

spectrum disorder (ADHDw/oASD) in school-age verbally fluent children. We examined the Autism Symptom Interview School-Age and two widely used parent questionnaires: Social Responsiveness Scale 2nd Edition and Social Communication Questionnaire Lifetime. Receiver operating characteristic curves assessed each instrument's performance against the best-estimate clinician Diagnostic and Statistical Manual of Mental Disorders, 5th Edition diagnosis of autism spectrum disorder or of ADHDw/oASD (n = 74, n = 102, respectively; 6-11 years). These yielded moderate accuracies: area under the curve = 0.85, 0.79, and 0.78 for Social Communication Questionnaire Lifetime, Autism Symptom Interview, and Social Responsiveness Scale 2nd Edition, respectively. Area under the curve pairwise comparisons reached our statistical significance ($p < 0.01$) for the Social Communication Questionnaire Lifetime versus the Social Responsiveness Scale 2nd Edition. Within instruments, sensitivity and specificity varied across autism spectrum disorder cutoffs. Along with the between-instrument variability, this indicates that clinicians and researchers have valid options, depending on the settings and their goals. Comparing children correctly and incorrectly classified as autism spectrum disorder showed no differences in demographics, intellectual abilities, or in any specific clinical profile(s), except for the degree of parent concerns across autism spectrum disorder and comorbid psychopathology-related symptoms. Together, results suggest that complementing parent screeners with multiple sources may be needed to best differentiate school-age verbally fluent children with autism spectrum disorder versus ADHDw/oASD. Lay abstract: We tested the ability of a short, recently developed parent interview and two widely used parent-report questionnaires to discriminate school-age verbal children with autism spectrum disorder from those with attention-deficit/hyperactivity disorder without autism spectrum disorder (ADHDw/oASD). These measures included the Autism Symptom Interview School-Age, the Social Responsiveness Scale 2nd Edition, and the Social Communication Questionnaire Lifetime. The classification accuracy of all three parent screeners fell in the moderate range. Accuracy varied by instrument, and the Social Communication Questionnaire Lifetime questionniare showed the highest accuracy. Children with autism spectrum disorder who were incorrectly classified by all parent screeners did not differ from those correctly classified in regard to demographics, intellectual abilities, nor in any specific clinical area beyond general parent concerns. These findings showed that there are valid screening options for assessing school-age verbal children with autism spectrum disorder versus ADHDw/oASD. They also underscore the need to assess multiple sources of information for increased accuracy

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Autism Res. 2021.

MATERNAL ANTIBODIES TO GLIADIN AND AUTISM SPECTRUM DISORDERS IN OFFSPRING A POPULATION-BASED CASE-CONTROL STUDY IN SWEDEN.

Gardner RM, Samuelsson I, Severance EG, et al.

While individuals diagnosed with autism spectrum disorders (ASD) have higher levels of antibodies directed towards gliadin, a component of wheat gluten, no study has examined anti-gliadin antibodies (AGA) in etiologically relevant periods before diagnosis. The objective of this study was to investigate if maternal levels of AGA, during pregnancy and at the time of birth, are associated with ASD in offspring. We analyzed AGA in archived neonatal dried blood spots (NDBS) for 921 ASD cases and 1090 controls, and in paired maternal sera collected earlier in pregnancy for a subset of 547 cases and 428 controls. We examined associations with ASD diagnoses as a group and considering common comorbidities (intellectual disability [ID] and attention-deficit/hyperactivity disorder). We compared 206 cases to their unaffected siblings to examine the potential for confounding by shared familial factors. Odds of ASD tended to be lower among those with the highest levels (90th percentile) of AGA compared to those with low levels (<80th percentile; OR 0.78, 95% CI 0.56ΓÇô1.09, measured in NDBS). This pattern was more apparent for ASD with comorbid ID when measured in NDBS (0.51, 0.30-0.87), with a similar trend in maternal sera (0.55, 0.24-1.29). High levels of AGA were similarly associated with lower odds of ASD in the sibling comparison. In summary, we found little association between maternal antibodies raised against components of gluten and risk of ASD in general. Exposure to high levels of AGA in the pre- and perinatal periods may be protective in terms of risk for ASD with ID. Lay Summary: There is a debate among both scientists and community members as to whether an immune reaction to gluten exposure could be considered a cause of autism. We examined antibodies that are directed against gliadin, a part of gluten, in samples collected from pregnant mothers and their newborn babies. We did not see any major differences in the antibody level among those children diagnosed with ASD or their mothers compared to children who were not diagnosed with ASD. High levels of the antibodies were

in fact associated with a somewhat lower risk of ASD with co-occurring intellectual disabilities, though we cannot tell from this study why that might be the case

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Behav Ther. 2021 Jul;52:847-60.

COMMUNITY IMPLEMENTATION OF MI-ENHANCED BEHAVIOR THERAPY FOR ADOLESCENT ADHD: LINKING FIDELITY TO EFFECTIVENESS.

Sibley MH, Bickman L, Coxe SJ, et al.

Evidence-based behavior therapy for adolescent ADHD faces implementation challenges in real-world settings. The purpose of this trial was to investigate the relationship between implementation fidelity and outcomes among adolescents receiving services in the active treatment arm (N = 114; Motivational Interviewing [MI]-enhanced parent-teen behavior therapy) of a community-based randomized trial of adolescent ADHD treatment. Participants received therapy from community clinicians (N = 44) at four agencies in a large, ethnically diverse metropolitan setting. Therapists provided self-report of session-by-session adherence to content fidelity checklists and audio recordings of sample sessions that were coded for MI integrity. Parents provided report of ADHD symptoms and family impairment at baseline, posttreatment, and follow-up, while academic records were obtained directly from the local school district. Results indicated that content fidelity significantly waned across the 10 manualized sessions (d = -1.23); these trends were steepest when therapy was delivered outside the office-setting and parent attendance was low. Community therapist self-report of content fidelity predicted significantly greater improvements in academic impairment from baseline to follow-up. MI delivery quality was not associated with improved outcomes; contrary to hypotheses, lower MI relational scores predicted significantly greater improvements in family impairment over time. Findings indicate that community-based outcomes for evidence-based ADHD treatment are enhanced when treatment is implemented with fidelity. Future work should revise community-based implementation strategies for adolescent ADHD treatment to prevent declines in fidelity over time, thereby improving outcomes

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2021.

ATYPICAL AROUSAL REGULATION IN CHILDREN WITH AUTISM BUT NOT WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AS INDICATED BY PUPILLOMETRIC MEASURES OF LOCUS COERULEUS ACTIVITY.

Bast N, Boxhoorn S, et al.

Background: Atypical arousal regulation may explain slower mean reaction time (MRT) in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder compared with typical development. The locus coeruleus-norepinephrine system (LC-NE) underlies arousal regulation and adapts its activity to the utility of a task. LC-NE tonic and phasic activity are indexed by baseline pupil size (BPS) and stimulus-evoked pupillary response (SEPR).

Methods: The study assessed pupillometry in ASD (n = 31, 3 female/28 male), attention-deficit/hyperactivity disorder (n = 28, 3 female/25 male), and typically developing control subjects (n = 31, 16 female/15 male) during a visuospatial reaction-time task that manipulates arousal by conditions with low and high task utility. We estimated linear mixed models of BPS, SEPR, and MRT in a per-trial analysis to investigate arousal regulation of task performance.

Results: Slower MRT occurred in the ASD group compared with the typically developing control group during low-utility conditions while controlling for dimensional ASD and attention-deficit/hyperactivity disorder symptoms. In low-utility conditions, BPS and SEPR were inversely related and both were associated with faster MRT. Increased ASD symptoms across groups were associated with higher BPS during low-utility conditions. Changes in BPS and SEPR between task-utility conditions were smaller in the ASD group.

Conclusions: Slower visuospatial task performance in ASD is specific to low task utility. Arousal was associated with task performance and showed altered activity in ASD. Increased BPS during low-utility conditions suggested increased LC-NE tonic activity as an ASD symptom marker in children. Smaller changes in BPS and SEPR in ASD indicated attenuated LC-NE activity adaptation in response to high-utility

conditions. Slower performance and atypical arousal regulation are probably associated with attenuated LC-NE activity adaptation

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Biomedical and Pharmacology Journal. 2021;14:541-48.

MMP-2, MMP-9, TNF-A LEVELS IN RELATION TO SUB TYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hamed RA, Elmalt HA, Salama AAA, et al.

Many authors have suggested the association between Attention Deficit Hyperactivity Disorder (ADHD) and inflammation through various mechanisms among which increased serum cytokines. 30 newly diagnosed ADHD children, aged 6-12 and of both sexes were collected from outpatient clinic, Psychiatry Department, Al Zahraa University Hospital and a matched control group of 30 children. They were subjected to Clinical assessment, Whechsler Intelligence Scale for children (WISC), Conners' Parent Rating Scale-Revised & serum MMP-2, MMP-9, TNF-a levels were determined. There was statistical significant difference between patient and control groups regarding MMP-2 level (648.50 -¦ 81.94 vs 344.13 -¦ 32.02), MMP-9 level (143.00-¦16.98 vs 102.90 -¦ 4.13) & TNF-a level (345 -¦ 7.1.vs 202 -¦ 22.3). Hyperactive/ impulsive subtype represented 16(53.3%), Inattentive subtype represented 6(20%), Combined subtype represented 8(26.7%) of the ADHD group. MMP-2, MMP-9, TNF-a levels were all higher among the Hyperactive/impulsive subtype, followed by the combined subtype then the Inattentive subtype with high statistical significant difference. A high statistical significant difference was found in all subscales of Conners' scale among the 3 subtypes of ADHD. A positive correlation was found between TNF-a level and age, whereas, a negative correlation exists between MMP-2, MMP-9, TNF-a level and IQ. In addition, correlation was found between MMP-2, MMP-9 levels and cognitive problems, TNF-a level and inattention. Our study illustrates the co-occurrence of inflammatory process and ADHD, but further studies on larger sample are needed

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Biomedical Signal Processing and Control. 2021.

EOG BIOFEEDBACK PROTOCOL BASED ON SELECTING DISTINCTIVE FEATURES TO TREAT OR REDUCE ADHD SYMPTOMS.

Sho'ouri N.

There are various evidences about existence of a difference between the electrooculography (EOG) signals of healthy individuals and that of people with attention deficit hyperactivity disorder (ADHD). Therefore, the use of EOG biofeedback might be effective in the decrease in ADHD symptoms. Therefore, the present study aimed to propose an EOG biofeedback protocol to treat ADHD. To this end, a set of diverse features of EOG signals was extracted in two groups of healthy children and subjects with ADHD during a focused attention task. Afterwards, the most effective features in distinguishing the EOG signals of the two groups were determined using the genetic algorithm. According to the results of the study, the values of low-frequency (0.5-4.125 Hz) band power, entropy, and fractal dimension were significantly lower in the EOG signals of the ADHD group, compared to the healthy children (P <.001). In addition, the scaling exponent was significantly higher in this regard (P <.001). Furthermore, entropy and fractal dimension were selected as the most effective features in distinguishing the two groups. It is recommended that entropy and fractal dimensions of EOG signals be increased as a protocol to treat or reduce ADHD symptoms

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Bipolar Disord. 2021;23:51.

CLINICAL PHENOTYPE AND TREATMENT OUTCOMES OF BIPOLAR PATIENTS WITH COMORBID ATTENTION DEFICIT SYMPTOMS.

Nunez N, Coombes B, Romo-Nava F, et al.

Introduction: Co-occurrence of bipolar disorder (BD) and attention deficit-hyperactivity disorder (ADHD) is associated with an unfavorable course of illness. Our aim in this study was to evaluate clinical features between BD with or without ADHD comorbidity (BD+ADHD or BD+ noADHD, respectively) and to examine differences by time of ADHD symptom onset: either childhood ADHD (cADHD)] or adult attention deficit (aAD).

Method: Clinical data of BD patients were extracted from the Mayo Clinic Bipolar Disorder Biobank (N = 2198). Demographic and illness related variables were compared among the two groups and by time of attention deficit symptom onset using chi-square tests or analysis of variance.
Results: BD +ADHD (N = 604) compared to BD+noADHD (N=1594) was associated with male sex ($p < 0.001$). BD+ADHD, in comparison to BD+noADHD, exhibited greater severity in course of illness including: greater number of lifetime diagnosed anxiety disorders ($p < 0.001$), lifetime mood instability symptoms ($p < 0.001$), higher rates of drug use [alcohol ($p < 0.001$), nicotine ($p < 0.001$), and cocaine-methamphetamine ($p = 0.014$)], higher rates of family history of psychiatric disorders [bipolar disorder ($p < 0.001$), depression ($p < 0.001$) and alcoholism ($p < 0.001$)], and less adherence to treatment ($p = 0.013$). Finally, cADHD in comparison to aAD were more likely to be male ($p < 0.001$), older ($p < 0.001$), and had lower prevalence of OCD ($p = 0.018$).
Conclusion: BD+ADHD was associated with a more severe clinical presentation underscoring worse clinical outcomes. Overall, those with cADHD onset did not differ greatly with respect to clinical presentation. Further studies examining genetic associations and clinical variables may emphasize a relevant different genetic and clinical structures between phenotypes

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Bipolar Disord. 2021;23:81.

PEDIATRIC BIPOLAR DISORDER AND COMORBIDITY WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE CHALLENGES OF CHRONIC IRRITABILITY AND EMOTIONAL DYSREGULATION.

Marques P, Queirs O.

Introduction: To assess the challenges of irritability and emotional dysregulation in pediatric Bipolar Disorder (BD) and its comorbidity with Attention-Deficit/ Hyperactivity Disorder (ADHD).
Method: A review of recent literature was performed.
Results: BD often begins in late adolescence or early adulthood, and more than 50% of patients report mood symptoms since prepubertal or adolescent years. Presentation in adolescence differs from adulthood classic symptomatology: a chronic, non-episodic course marked by chronic irritability, often without the characteristic symptoms of mania and with more mood fluctuations, mixed episodes and longer manic or depressive episodes. Chronic irritability and emotional dysregulation in adolescents with BD imposes a challenging differential diagnosis with ADHD. Restlessness and impulsivity are other overlapping symptoms. In BD patients with symptom onset before 18 years old, 13% fulfill ADHD criteria. When the two disorders are comorbid, (hypo)manic symptoms usually have a 3-5 years earlier onset, more severe course of the mood disorder, shorter periods of euthymia and higher rates of anxiety, substance abuse, suicidal behaviors, treatment non-compliance and psychosocial impairments. Emotional dysregulation and impulsivity in both disorders emerge from related cerebral circuits dysfunction and researchers suggest that BD and ADHD comorbidity may be a distinct clinical identity with its own phenotype and common genetic background.
Conclusion: When evaluating a young patient with irritability and emotional dysregulation, clinicians should be aware of the symptom overlap between ADHD and BD and its potential comorbidity. The phenomenology of pediatric mania is still a subject of controversy and long-term outcomes of pediatric BD still need to be thoroughly assessed

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BMC Psychiatry. 2021 Jun;21.

ADHD SYMPTOMATOLOGY OF CHILDREN WITH CONGENITAL HEART DISEASE 10 YEARS AFTER CARDIAC SURGERY: THE ROLE OF AGE AT OPERATION.

Czobor NR, Ocsovszky Z, Roth G, et al.

Background: The aim of the present study was to investigate the differences in ADHD symptomatology between healthy controls and children who underwent cardiac surgery at different ages.
Methods: Altogether, 133 children (54 patients with congenital heart disease undergoing first cardiac surgery under 3 years of age, 26 operated at the age of 3 or later, and 53 healthy controls) were examined. Patients completed the Youth Self Report (YSR), while their parents completed the Child Behaviour Checklist (CBCL) and the ADHD Rating Scale-IV.

Results: Children receiving surgery for the first time under the age of 3 years were more likely diagnosed with cyanotic type malformation and have undergone to a greater number of operations. However, ADHD symptoms of those treated surgically at or above 3 years of age were more severe than that of the control group or those who were treated surgically at a younger age. The control group and those treated surgically below the age of three did not differ across any of the ADHD symptom severity indicators.
Conclusions: The age at the time of cardiac surgery might be associated with later ADHD symptom severity—with lower age at operation associated with better outcomes. Further, adequately powered studies are needed to confirm these exploratory findings and investigate the moderators of this relationship

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BMJ Case Rep. 2021 Jul;14.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RARE CLINICAL PRESENTATION OF L-2-HYDROXYGLUTARIC ACIDURIA.

George J, Sandhya P, Sajitha KV, et al.

L-2-hydroxyglutaric aciduria (L2HGA) is a rare autosomal recessive neurometabolic disorder caused by the deficiency of L-2-hydroxyglutarate dehydrogenase (L2HGDH) enzyme. Dystonia, ataxia, pyramidal involvement and seizures are the common clinical manifestations. Coexisting behavioural problems and intellectual disability are also seen, however attention deficit hyperactivity disorder (ADHD) as the presenting clinical feature in L2HGA is rarely described. Here, we report a 5-year-old boy with behavioural problems and mild language delay. On clinical assessment, he fulfilled the diagnostic criteria for ADHD. His MR brain sequences showed classical finding of L2HGA-bilateral symmetrical T2-weighted hyperintensity involving subcortical white matter, basal ganglia and dentate nucleus. Urine analysis showed increased levels of 2-hydroxyglutaric acid and exome sequencing (targeted leukodystrophy panel) revealed homozygous likely pathogenic mutation in L2HGDH He was started on high dose of riboflavin and levocarnitine and rehabilitative measures with which he had improvement in behavioural symptoms. This case illustrates the pivotol role of MR brain imaging in the diagnosis of inborn errors of metabolism

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BMJ Open. 2021 Apr;11:e044667.

COCO20 PROTOCOL: A PILOT LONGITUDINAL FOLLOW-UP STUDY ABOUT THE PSYCHIATRIC OUTCOMES IN A PAEDIATRIC POPULATION AND THEIR FAMILIES DURING AND AFTER THE STAY-AT-HOME RELATED TO CORONAVIRUS PANDEMIC (COVID-19).

Gindt M, Fernandez A, Richez A, et al.

INTRODUCTION: In the context of a viral outbreak and the stay-at-home measures, a significant increase in psychological distress, such as stress or fear behaviours, has previously been reported in adult and paediatric population. Children and adolescents seem to be particularly at risk of developing psychiatric disorders during and after the stay-at-home but evidences are lacking. The main objective of this article is to present the methodology of Coronavirus Confinement 2020 (CoCo20) Study, which aims to assess the impact of the coronavirus pandemic (COVID-19) and stay-at-home on the development of psychiatric disorders, including post-traumatic stress disorder (PTSD), in children and adolescents.
METHODS AND ANALYSIS: We describe a longitudinal and multicentre study in the paediatric population during and after stay-at-home related to COVID-19 pandemic. Inclusions started on 30 March 2020 for 6 months. This study is proposed to all consecutive paediatric outpatients consulting during and after stay-at-home related to COVID-19 pandemic in medical-psychological centres and in a paediatric psychotrauma centre and/or calling the emergency COVID-19 hotline. We perform standardised and internationally validated psychiatric assessments (Diagnosis Infant and Preschool Assessment, Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version) together with anxiety, attention deficit hyperactivity disorder, PTSD, parenting stress and somatic symptoms scales during five visits (baseline, 1week after baseline, 1month after baseline, 1week after the end of the containment and 1month after the end of the containment) in patients and their families enrolled during the containment and during three visits in case of enrolment after the containment. The inclusion period will end in 30 November 2020.
ETHICS AND DISSEMINATION: The protocol has been approved by the Ethics Committee of Cote d'Azur University CERNI (number 2020-59). All patients and their legal caregivers provide a written informed

consent on enrolment in the study. We will submit the results of the study to relevant journals and offer national and international presentations. This study will enable better characterisation of the impact of the stay-at-home (related to COVID-19 pandemic) on the mental health of children and adolescents.
TRIAL REGISTRATION NUMBER: NCT04498416

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Brain Sciences. 2021;11.

DISRUPTED FUNCTIONAL RICH-CLUB ORGANIZATION OF THE BRAIN NETWORKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, A RESTING-STATE EEG STUDY.

Ahmadi M, Kazemi K, Kuc K, et al.

Growing evidence indicates that disruptions in the brainΓÇÖs functional connectivity play an important role in the pathophysiology of ADHD. The present study investigates alterations in resting-state EEG source connectivity and rich-club organization in children with inattentive (ADHDI) and combined (ADHDC) ADHD compared with typically developing children (TD) under the eyes-closed condition. EEG source analysis was performed by eLORETA in different frequency bands. The lagged phase synchronization (LPS) and graph theoretical metrics were then used to examine group differences in the topological properties and rich-club organization of functional networks. Compared with the TD children, the ADHDI children were characterized by a widespread significant decrease in delta and beta LPS, as well as increased theta and alpha LPS in the left frontal and right occipital regions. The ADHDC children displayed significant increases in LPS in the central, temporal and posterior areas. Both ADHD groups showed small-worldness properties with significant increases and decreases in the network degree in the +© and +¦ bands, respectively. Both subtypes also displayed reduced levels of network segregation. Group differences in rich-club distribution were found in the central and posterior areas. Our findings suggest that resting-state EEG source connectivity analysis can better characterize alterations in the rich-club organization of functional brain networks in ADHD patients

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Brain Sciences. 2021;11.

THE EFFECT OF COMORBID ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS ON FACE MEMORY IN CHILDREN WITH AUTISM SPECTRUM DISORDER: INSIGHTS FROM TRANSDIAGNOSTIC PROFILES.

Chen Q, Wang Z, Wan B, et al.

Face memory impairments are common but heterogeneous in autism spectrum disorder (ASD), which may be influenced by co-occurrence with attention-deficit/hyperactivity disorder (ADHD). Here, we aimed to investigate the phenotype change of face memory in children with ASD comorbid ADHD symptoms, and discuss the potential role of executive function (EF). Ninety-eight children were analyzed in the present study, including ASDΓêÆ (ASD-only, n = 24), ADHD (n = 23), ASD+ (with ADHD symptoms, n = 23) and neurotypical controls (NTC, n = 28). All participants completed two tests: face encoding and retrieving task and Wisconsin Card Sorting Test (WCST) for measuring face memory and EF, respectively. Results revealed that: compared with the NTC group, children with ASDΓêÆ exhibited lower accuracy in both face encoding and retrieving, and participants with ASD+ showed lower accuracy only in the retrieving, whereas no differences were found among participants with ADHD. Moreover, in the ASD+ group, face encoding performance was correlated with response perseverative errors (RPE) and failure to maintain sets (FMS) of WCST; significantly, there were no group differences between ASD+ and NTC in these two indices. The transdiagnostic profiles indicated that comorbid ADHD symptoms could modulate the face encoding deficiency of ASD, which may be partially compensated by EF. Shared and distinct intervention strategies to improve social cognition are recommended for children undergoing treatment for each condition

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Brazilian Journal of Psychiatry. 2021;43:153-59.

SLUGGISH COGNITIVE TEMPO IS ASSOCIATED WITH AUTISTIC TRAITS AND ANXIETY DISORDER SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ekinci O, et al.

Objective: To investigate the association of sluggish cognitive tempo (SCT) with autistic traits (ATs) and anxiety disorder symptoms among children with attention-deficit/hyperactivity disorder (ADHD).

Methods: A total of 195 children with a DSM-5 diagnosis of ADHD were included. The Barkley Sluggish Cognitive Tempo Scale (BSCTS) was used to measure SCT symptoms. Other study measures included the Autism Spectrum Quotient (AQ), Screen for Child Anxiety and Related Disorders (SCARED), Turgay DSM-IV Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S), and Conners Teacher Rating Scale (CTRS-R).
Results: The frequency of SCT was 30.3% (n=59) in the whole group. Those with SCT had higher total AQ and SCARED scores. Significant associations and correlations were also found between SCT and certain subscores of AQ and SCARED. According to the linear regression model, the total score and social skills, attention switching, and imagination scores of AQ, as well as generalized anxiety and panic/somatic scores of SCARED and the total and inattention scores of parent T-DSM-IV, were predictive of SCT total score ($p < 0.05$).
Conclusions: SCT is associated with ATs and anxiety disorders. Children with ADHD and SCT symptoms should be screened for such conditions

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Child's Nerv Syst. 2021;37:1797-802.

DISCONNECTING SURGERY AT ALVEUS AND CORNU AMMONIS OF HIPPOCAMPUS, AMYGDALA SUPERFICIALIS, AND AMYGDALA MEDIAL NUCLEI FOR EPILEPSY ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Idris Z, Zakaria Z, Halim SA, et al.

The neural basis for epilepsy and attention deficit hyperactivity disorder (ADHD) is currently incompletely known. We reported a young girl with both epilepsy and ADHD, who had a calcified lesion in the right basolateral amygdalo-hippocampal region extending to the ventral striatum. The child underwent disconnecting surgery and biopsy of the lesion. Fascinatingly, the childΓÇÖs behavior changed immediately after the surgery from inattentive and impulsive to nearly normal behavior experiencing no more breakthrough seizures since after 3-áyears of surgery. The Schaltenbrand Wahren Brain Atlas revealed alveus, cornu ammonis, amygdala superficialis, and medium as the disconnected region in this surgery

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Child Adolesc Psychiatr Clin North Am. 2021 Jul;30:537-60.

PSYCHOPHARMACOLOGY OF TREATING EXPLOSIVE BEHAVIOR .

Vaudreuil C, Farrell A, Wozniak J.

Explosive and aggressive behavior in children can pose safety risks, disturb family functioning, and lead to significant impairments. Pharmacologic management should be based on the first-line treatment of the primary psychiatric diagnoses of the patient and initiated in combination with appropriate psychosocial interventions. Review of the literature suggests that risperidone has the most supporting evidence in the treatment of explosive behavior. Stimulants have been shown to be helpful in the treatment of explosive behavior in attention-deficit/hyperactivity disorder. Medication treatment can be associated with significant side effects and therefore the risks and benefits of medication management must be weighed carefully

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Child Adolesc Psychiatry Ment Health. 2021;15.

THE IMPACT OF CHILDHOOD DIAGNOSED ADHD VERSUS CONTROLS WITHOUT ADHD DIAGNOSES ON LATER LABOUR MARKET ATTACHMENTΓÇÖA SYSTEMATIC REVIEW OF LONGITUDINAL STUDIES.

Christiansen MS, Labriola M, Kirkeskov L, et al.

Previous studies have suggested that Attention Deficit Hyperactive Disorder (ADHD) affect individuals across their lifespan, especially in relation to employment. The purpose of this review was to synthesize the results from studies examining the prospective association of ADHD diagnosis in childhood and later education, earnings and employment, compared to children without an ADHD diagnosis. A review protocol was prospectively registered with PROSPERO (ID = CRD42019131634). The findings were reported according to the PRISMA guidelines. The systematic review is based on a structured and preplanned analysis of original prospective longitudinal studies. A total of 2505 potential records were identified, two through backward search. Six papers met the inclusion criteria. One paper was assessed as good, four as fair and one as poor quality. The studies indicated that ADHD diagnosis affected the nature of the individualΓÇÖs attachment to

the labour market across different labour market attachment outcomes. Adults with persisting symptoms, had significantly more problems at work. Even if ADHD symptoms desist in adulthood, the negative impact of earlier ADHD symptoms can still be seen on occupational outcomes. Significantly fewer probands had a BachelorΓÇÖs degree compared to controls. Based on one good quality study and four fair quality studies, it is indicated that patients with childhood diagnosed ADHD, generally experience employment of lower quality compared with peers, in relation to income, education and occupational attainment. The overall level of evidence is rated as poor

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Child Adolesc Psychiatry Ment Health. 2021;15.

CALLOUS-UNEMOTIONAL TRAITS IN CHINESE PRESCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Zhang J, Li W, Zhang H, et al.

Background: Children with early onset of Callous-Unemotional (CU) traits are at a higher risk for long-term, persistent psychosocial problems. The current study aimed to explore the characteristics of CU in preschool children with Attention Deficit Hyperactivity Disorder (ADHD) and the diagnostic significance of CU traits in ADHD.

Methods: A total of 176 preschool children (89 with ADHD and 87 Typically Developing Children [TDC]) aged 4years old were recruited to the study. The participants were assessed for CU traits, emotional and behavioral problems, and how their executive functioning was associated with ADHD using multiple assessment scales. Multiple linear regression analysis was performed to assess the incremental validity of the Inventory of Callous-Unemotional Traits (ICU), adjusting for possible covariates by child's sex, conduct problems, and oppositional defiant symptoms.

Results: The results showed that there was a significant difference of ICU scores between the ADHD and TDC groups (F = 30.12, P < 0.001). In terms of callousness, ADHD + Oppositional Defiant Disorder (ODD) group showed a significant high score, and the ADHD only group scored significantly higher than the TDC group (F = 20.42, P < 0.001). The ICU was negatively associated with the prosocial behaviour subscale (+¦ = 0.57, P < 0.01) and showed low to moderate positive correlations with emotional and behavioural problems, as well as executive function (+¦ = 0.24-0.67, P < 0.05). The ICU scores explained 6% of the incremental validity in ADHD symptoms. The diagnostic value of the ICU for ADHD was medium and acceptable.

Conclusions: The current study indicated that early identification of CU traits may help clinicians better understand symptoms and behavioural problems in children with ADHD. CU traits therefore could be considered as a useful assessment tool for ADHD

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Clin Neurophysiol. 2021;132:1937-46.

ELECTROPHYSIOLOGICAL CORRELATES OF IMPROVED EXECUTIVE FUNCTION FOLLOWING EEG NEUROFEEDBACK IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Deiber MP, Ammann C, Hasler R, et al.

Objective: Event-related potentials (ERPs) are reported to be altered in relation to cognitive processing deficits in attention deficit hyperactivity disorder (ADHD). However, this evidence is mostly limited to cross-sectional data. The current study utilized neurofeedback (NFB) as a neuromodulatory tool to examine the ERP correlates of attentional and inhibitory processes in adult ADHD using a single-session, within-subject design.

Methods: We recorded high-density EEG in 25 adult ADHD patients and 22 neurotypical controls during a Go/NoGo task, before and after a 30-minute NFB session designed to down-regulate the alpha (8ΓÇô12 Hz) rhythm.

Results: At baseline, ADHD patients demonstrated impaired Go/NoGo performance compared to controls, while Go-P3 amplitude inversely correlated with ADHD-associated symptomatology in childhood. Post NFB, task performance improved in both groups, significantly enhancing stimulus detectability (d-prime) and reducing reaction time variability, while increasing N1 and P3 ERP component amplitudes. Specifically for ADHD patients, the pre-to-post enhancement in Go-P3 amplitude correlated with measures of improved executive function, i.e., enhanced d-prime, reduced omission errors and reduced reaction time variability.

Conclusions: A single-session of alpha down-regulation NFB was able to reverse the abnormal neurocognitive signatures of adult ADHD during a Go/NoGo task. Significance: The study demonstrates for the first time the beneficial neurobehavioral effect of a single NFB session in adult ADHD, and reinforces the notion that ERPs could serve as useful diagnostic/prognostic markers of executive dysfunction

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Clin Psychopharmacol Neurosci. 2021;19:145-54.

A DIFFERENT VIEW ON THE ETIOPATHOGENESIS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER FROM AN INFLAMMATION PERSPECTIVE.

Dursun S, Demirci E, Kilic E, et al.

Objective: Attention-deficit hyperactivity disorder (ADHD) has a complex etiology and genetic, environmental and biological factors are considered to play a role in the etiology of ADHD by mutually interacting. Recent studies have emphasized that inflammation may be present in the etiology of ADHD. This study aims to investigate the possible role of visfatin, IL-6, IL-1+¦ and TNF-+¦ molecules in the etiology of ADHD.

Methods: The study included 60 patients and 20 healthy controls between the ages of 6-18. Serum visfatin, IL-6, IL-1+¦ and TNF-+¦ levels were evaluated with enzyme-linked immunosorbent assay (ELISA) kits at a biochemistry laboratory.

Results: The study showed no statistically significant difference between children with ADHD and healthy controls in terms of visfatin, IL-6, IL-1? and TNF-? levels. When ADHD subgroups (combined and predominantly inattentive types) and the control group were compared in terms of visfatin, IL-6, IL-1? and TNF-? levels, no statistically significant difference was recorded.

Conclusion: Data on the relationship between ADHD and IL-6, IL-1? and TNF-? in this study are in compliance with the literature. However, no study was found on visfatin in ADHD. This study is the first one evaluating the ADHD-Visfatin relationship

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CNS Drugs. 2021;35:769-79.

TREATMENT WITH METHYLPHENIDATE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND THE RISK OF ALL-CAUSE POISONING IN CHILDREN AND ADOLESCENTS: A SELF-CONTROLLED CASE SERIES STUDY.

Gao L, Man KKC, Chan EW, et al .

Background: Children and adolescents with attention deficit hyperactivity disorder (ADHD) are at higher risk of all-cause poisoning by drugs and chemicals (intentional or accidental). Currently, there is limited data on whether medication treatment for ADHD can reduce the risk of all-cause poisoning.

Methods: Patients aged 5ΓÇô18 years with a methylphenidate (MPH) prescription and an incident poisoning diagnosis between January 2001 and June 2020 were identified from the Hong Kong Clinical Data Analysis and Reporting System. A self-controlled case series study design was used to compare the incidence rate ratios (IRRs) of all-cause poisoning during different risk windows (30 days before the first MPH prescription, exposure periods within 30 days of the first prescription, and periods of subsequent exposure) compared with the reference window (other non-exposure periods).

Results: 42,203 patients were prescribed ADHD medication in Hong Kong during the study period. Of these, 417 patients who had both an MPH prescription and poisoning incident recorded were included in the main analysis. Compared with other non-exposed periods, a higher risk of poisoning was found in the 30 days before the first prescription (IRR 2.64, 95% confidence interval [CI] 1.33ΓÇô5.22) and exposure periods within 30 days of the first prescription (IRR 2.18, 95% CI 1.06ΓÇô4.48), but not during prolonged exposure. However, compared with 30 days before the first prescription as well as exposure periods within 30 days of the first prescription, there was a lower risk during the subsequent exposure (IRRs 0.49 and 0.60, respectively). Similar results to the main analysis were also found in the subgroup analysis of intentional poisoning and females, but not in that of accidental poisoning and males.

Conclusions: The risk of all-cause poisoning was higher shortly before and after the first MPH prescription and became lower during the subsequent prescription period. Our results do not support an association between the use of MPH and an increased risk of all-cause poisoning in children and adolescents and, in

fact, suggest that longer-term use of MPH may be associated with a lower risk of all-cause poisoning, although this latter finding requires further study

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CNS Drugs. 2021.

IMPACT OF CNS STIMULANTS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON GROWTH: EPIDEMIOLOGY AND APPROACHES TO MANAGEMENT IN CHILDREN AND ADOLESCENTS.

Baweja R, Hale DE, Waxmonsky JG.

Central nervous system stimulants are established treatments for pediatric attention-deficit/hyperactivity disorder with robust efficacy data. Reductions in appetite, weight, and growth velocity are some of the most common concerns regarding the long-term use of central nervous system stimulants in developing children. They are associated with suppression of weight and body mass index in childhood. However, both weight and body mass index often progressively increase over adolescence at rates faster than those seen in non-attention-deficit/hyperactivity disorder youth to the degree that attention-deficit/hyperactivity disorder is associated with elevated body mass index by the end of adolescence regardless of medication use. The capacity of central nervous system stimulants to slow growth was identified 50 years ago. Recent work has established that the growth deficits accumulate during the first 2 years of use and may persist provided medication is used. Early initiation coupled with persistent use through adolescence is most likely to be associated with clinical impactful growth suppression. There has been limited formal investigation of treatments for stimulant-associated reductions in weight and height. The most robust evidence exists for drug holidays improving weight gain. Observational studies suggest that limiting lifetime exposure or discontinuing medication is associated with greater adult height. Additional research is needed to identify the causal mechanisms driving the observed slowing in growth as well as the identification of predictors of clinically impactful growth suppression

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Cognitive Neurodynamics. 2021.

FUNCTIONAL NEURONAL NETWORKS REVEAL EMOTIONAL PROCESSING DIFFERENCES IN CHILDREN WITH ADHD.

Ansari Nasab S, Panahi S, Ghassemi F, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that, in addition to inattention, excessive activity, or impulsivity, makes it difficult for children to process facial emotions and thus to interact with their peers. Here we analyze neuronal networks of children with this disorder by means of the phase-locking value (PLV) method. In particular, we determine the level of phase synchronization between 62 EEG channels of 22 healthy boys and 22 boys with ADHD, recorder whilst observing facial emotions of anger, happiness, neutrality, and sadness. We construct neuronal networks based on the gamma sub-band, which according to previous studies, shows the highest response to emotional stimuli. We find that the functional connectivity of the frontal and occipital lobes in the ADHD group is significantly (P-value < 0.01) higher than in the healthy group. More functional connectivity in these lobes shows more phase synchronization between the neurons of these brain regions, representing some problems in the brain emotional processing center in the ADHD group. The shortest path lengths in these lobes are also significantly (P-value < 0.01) higher in the ADHD group than in the healthy group. This result indicates less efficiency of information transmission and segregation in occipital and frontal lobes of ADHD neuronal networks, responsible for visual and emotional processing in the brain, respectively. We hope that our approach will help obtain further insights into ADHD with methods of network science

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Complement Ther Med. 2021;60.

BALANCE-BASED ATTENTIVE REHABILITATION OF ATTENTION NETWORKS (BARAN) IMPROVES EXECUTIVE FUNCTIONS AND AMELIORATES BEHAVIORAL SYMPTOMS IN CHILDREN WITH ADHD.

Nejati V.

Introduction: Balance as a motor activity requires integrating different sensory information to maintain the center of gravity above the base of support through proper motor strategies in the light of cognitive processing.

Methods: In the present study, twenty-nine children with attention deficit- hyperactivity disorder (ADHD) were recruited in a random clinical trial design in two intervention and active control groups. The N-Back, Wisconsin Card Sorting, Go/No-Go tasks, and ConnersΓÇÖ Teacher and Parent Rating Scales were performed in baseline, post-intervention, and follow-up sessions. The intervention group received balance-based attentive rehabilitation of attention (BARAN), and the active control group received aerobic exercise and running in 12-15 sessions.
Results: BARAN improves working memory (P < .05), cognitive flexibility (P < .01), and inhibitory control (P < .05) and ameliorates ADHD symptoms at home (P < .01) and school (P < .05).
Conclusion: Dual-balance and cognitive tasks improve executive functions and ameliorate symptoms in children with ADHD

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Dtsch Z Akupunkt. 2021.
AURICULOTHERAPY IN CHILDREN WITH ADHD.
Eisenhardt S.

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Dev Cognitive Neurosci. 2021;50.
INCREASED INTEGRATION BETWEEN DEFAULT MODE AND TASK-RELEVANT NETWORKS IN CHILDREN WITH ADHD IS ASSOCIATED WITH IMPAIRED RESPONSE CONTROL.
Duffy KA, Rosch KS, Nebel MB, et al.
Default mode network (DMN) dysfunction is theorized to play a role in attention lapses and task errors in children with attention-deficit/hyperactivity disorder (ADHD). In ADHD, the DMN is hyperconnected to task-relevant networks, and both increased functional connectivity and reduced activation are related to poor task performance. The current study extends existing literature by considering interactions between the DMN and task-relevant networks from a brain network perspective and by assessing how these interactions relate to response control. We characterized both static and time-varying functional brain network organization during the resting state in 43 children with ADHD and 43 age-matched typically developing (TD) children. We then related aspects of network integration to go/no-go performance. We calculated participation coefficient (PC), a measure of a region's inter-network connections, for regions of the DMN, canonical cognitive control networks (fronto-parietal, salience/cingulo-opercular), and motor-related networks (somatomotor, subcortical). Mean PC was higher in children with ADHD as compared to TD children, indicating greater integration across networks. Further, higher and less variable PC was related to greater commission error rate in children with ADHD. Together, these results inform our understanding of the role of the DMN and its interactions with task-relevant networks in response control deficits in ADHD

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Educ Treat Children. 2021 Jun;44:55-69.
INCORPORATING CURRICULAR REVISION TO TREAT ESCAPE-MAINTAINED BEHAVIOR FOR CHILDREN WITH ADHD.
Romano LM, St.Peter CC, Milyko KL, et al.
Functional communication training (FCT) reduces escape-maintained challenging behavior but can result in time away from instruction. Instructional time could be maintained if interventions incorporated academic interventions like curricular revision. We compared FCT with extinction to a curricular-revision treatment package involving antecedent modifications of task difficulty and differential reinforcement for compliance for three children with attention deficit/hyperactivity disorder whose behavior was maintained by escape from academic tasks. During sessions with FCT, we taught the child to request a mastered task and did not permit escape following challenging behavior. During sessions with the curricular-revision package, we modified the instruction to a simpler component of the task and initially reinforced both compliance and challenging behavior. The curricular-revision package (without extinction) was more effective than FCT for one participant. Once we added escape extinction to the curricular-revision package, that intervention suppressed challenging behavior as well as FCT, resulted in more time engaged with the academic task than did FCT, and did not increase the likelihood of relapse when the interventions were abruptly discontinued. Practitioners attempting to treat escape-maintained behavior for children with ADHD should consider a

multifaceted approach that addresses both antecedents (like curricular revision) and consequences of behavior

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eNeurologicalSci. 2021;24.

EFFECTIVENESS OF STRUCTURED EXERCISES ON MOTOR SKILLS, PHYSICAL FITNESS AND ATTENTION IN CHILDREN WITH ADHD COMPARED TO TYPICALLY DEVELOPING CHILDREN-A PILOT STUDY.

Jeyanthi S, Arumugam N, Parasher RK.

Purpose: Children with ADHD exhibit decrements in fitness levels, motor skill ability and attention. The purpose was to evaluate the benefits of a structured, school-based exercise program on motor skill, physical fitness and attention in children with ADHD.

Method: Ten 8-12 year old school boys with ADHD and ten typically developing (TD) were recruited. They underwent a six week structured exercise program which included aerobics, resistance exercises, motor skills and attention training.

Results: Following the 6 week, school -based exercise program significant improvements in physical fitness, motor skills and attention were observed in ADHD children compared to the TD children. Additionally, the exercise sessions were acceptable and enjoyable to all children.

Conclusion: It is proposed that an exercise program be incorporated in school physical education curriculum. Exercises should be considered, in addition to other forms of intervention, as an essential treatment for improving problems associated with ADHD in school children

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Eur Arch Psychiatry Clin Neurosci. 2021.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY IN DEVELOPMENTAL PSYCHIATRY: A REVIEW OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Goss LK, Bell SW, Hosseini SMH.

Research has linked executive function (EF) deficits to many of the behavioral symptoms of attention deficit hyperactivity disorder (ADHD). Evidence of the involvement of EF impairment in ADHD is corroborated by accumulating neuroimaging studies, specifically functional magnetic resonance imaging (fMRI) studies. However, in recent years, functional near-infrared spectroscopy (fNIRS) has become increasingly popular in ADHD research due to its portability, high ecological validity, resistance to motion artifacts, and cost-effectiveness. While numerous studies throughout the past decade have used fNIRS to examine alterations in neural correlates of EF in ADHD, a qualitative review of the reliability of these findings compared with those reported using gold-standard fMRI measurements does not yet exist. The current review aims to fill this gap in the literature by comparing the results generated from a qualitative review of fNIRS studies (children and adolescents ages 6-16 years old) to a meta-analysis of comparable fMRI studies and examining the extent to which the results of these studies align in the context of EF impairment in ADHD. The qualitative analysis of fNIRS studies of ADHD shows a consistent hypoactivity in the right prefrontal cortex in multiple EF tasks. The meta-analysis of fMRI data corroborates altered activity in this region and surrounding areas during EF tasks in ADHD compared with typically developing controls. These findings indicate that fNIRS is a promising functional brain imaging technology for examining alterations in cortical activity in ADHD. We also address the disadvantages of fNIRS, including limited spatial resolution compared with fMRI

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Eur Child Adolesc Psychiatry. 2021.

PARENTAL REJECTION IN EARLY ADOLESCENCE PREDICTS A PERSISTENT ADHD SYMPTOM TRAJECTORY ACROSS ADOLESCENCE.

Brinksma DM, Hoekstra PJ, de Bildt A, et al.

Despite a general decrease of attention-deficit/hyperactivity disorder (ADHD) symptoms during adolescence, these may persist in some individuals but not in others. Prior cross-sectional studies have shown that parenting style and their interaction with candidate genes are associated with ADHD symptoms. However, there is a lack of longitudinal research examining the independent and interactive effects of parenting and plasticity genes in predicting the course of attention-deficit/hyperactivity disorder (ADHD) symptoms across

adolescence. Here, we investigated how children perceived their parentsΓÇÖ parenting style (i.e., rejection, overprotection, and emotional warmth) at the age of 11, and their interaction with DRD4,MAOA, and 5-HTTLPR genotypes on parent-reported ADHD symptoms at three time points (mean ages 11.1, 13.4, and 16.2 years) in 1730 adolescents from the TRacking Adolescents Individual Lives Survey (TRAILS). Growth Mixture Modeling in Mplus identified four ADHD symptom trajectories: low, moderate stable, high decreasing, and high persistent. Perceived parental rejection predicted class membership in the high persistent trajectory compared to the other classes ($p < 0.001$, odds ratios between 2.14 and 3.74). Gene-environment interactions were not significantly related to class membership. Our results indicate a role of perceived parental rejection in the persistence of ADHD symptoms. Perceived parental rejection should, therefore, be taken into consideration during prevention and treatment of ADHD in young adolescents

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Eur Child Adolesc Psychiatry. 2021.

A RANDOMIZED CONTROLLED TRIAL OF A NEW INTERVENTION IN EARLY SYMPTOMATIC SYNDROMES ELICITING NEURODEVELOPMENTAL CLINICAL EXAMINATIONS: PR-ESSENCE.

Johnson M, Gillberg C, Vinsa I, et al.

The need for effective intervention programs for youth with neurodevelopmental problems (ESSENCE) and challenging behaviour is great. This study examines Problem Resolution in ESSENCE (PR-ESSENCE), a newly developed model in which children and parents develop mutual problem resolution strategies. Ten-week randomized controlled trial of PR-ESSENCE for children and adolescents aged 5ΓÇô18-áyears, compared to treatment as usual. Outcomes were assessed at baseline and randomized period endpoint. Primary outcome was the Clinical Global ImpressionΓÇöImprovement scale (CGI-I) rated by blinded assessors. Secondary outcomes were rated by parentsΓÇöSNAP-IV, Eyberg Child Behavior Inventory (ECBI), Relationship Problems Questionnaire, Family Burden of Illness Module, and childrenΓÇöBeck Youth Inventories (BYI). ClinicalTrials.gov identifier: NCT03780413. The study enrolled 108 participants (active n = 72; controls n = 36, randomized 2:1), of whom 95 completed the randomized period. No clinically significant group differences were found in baseline characteristics. More than half had autism and 80% had ADD or ADHD. Large treatment effects were seen on CGI-I (ITT analysis, Effect Size 1.48). Treatment responders, much/very much improved on CGI-I, were 51.4% in active group and 5.6% of controls. Effect sizes were medium to large in parent ratings on SNAP-IV (ODD and ADHD symptoms), ECBI (behaviour problems), and in BYI child self-ratings of disruptive behaviour. PR-ESSENCE treatment improved global symptoms and functioning (CGI-I), behaviour problems, ADHD and ODD symptoms, and disruptive behaviour. Treatment effects were at least equivalent to those in previous studies of well-established Parent Management Training and Collaborative Problem Solving programs

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Experimental Biology and Medicine. 2021.

DEEP LEARNING PREDICTION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN AFRICAN AMERICANS BY COPY NUMBER VARIATION.

Liu Y, Qu HQ, Chang X, et al.

Current understanding of the underlying molecular network and mechanism for attention-deficit hyperactivity disorder (ADHD) is lacking and incomplete. Previous studies suggest that genomic structural variations play an important role in the pathogenesis of ADHD. For effective modeling, deep learning approaches have become a method of choice, with ability to predict the impact of genetic variations involving complicated mechanisms. In this study, we examined copy number variation in whole genome sequencing from 116 African Americans ADHD children and 408 African American controls. We divided the human genome into 150 regions, and the variation intensity in each region was applied as feature vectors for deep learning modeling to classify ADHD patients. The accuracy of deep learning for predicting ADHD diagnosis is consistently around 78% in a two-fold shuffle test, compared with Γê+50% by traditional k-mean clustering methods. Additional whole genome sequencing data from 351 European Americans children, including 89 ADHD cases and 262 controls, were applied as independent validation using feature vectors obtained from the African American ethnicity analysis. The accuracy of ADHD labeling was lower in this setting (70-75%) but still above the results from traditional methods. The regions with highest weight overlapped with the

previously reported ADHD-associated copy number variation regions, including genes such as GRM1 and GRM8, key drivers of metabotropic glutamate receptor signaling. A notable discovery is that structural variations in non-coding genomic (intronic/intergenic) regions show prediction weights that can be as high as prediction weight from variations in coding regions, results that were unexpected

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Frontiers in Computational Neuroscience. 2021;15.

ACCURATE PREDICTION OF CHILDREN'S ADHD SEVERITY USING FAMILY BURDEN INFORMATION: A NEURAL LASSO APPROACH.

Laria JC, Delgado-G+¦mez D, Pe+¦uelas-Calvo I, et al.

The deep lasso algorithm (dlasso) is introduced as a neural version of the statistical linear lasso algorithm that holds benefits from both methodologies: feature selection and automatic optimization of the parameters (including the regularization parameter). This last property makes dlasso particularly attractive for feature selection on small samples. In the two first conducted experiments, it was observed that dlasso is capable of obtaining better performance than its non-neuronal version (traditional lasso), in terms of predictive error and correct variable selection. Once that dlasso performance has been assessed, it is used to determine whether it is possible to predict the severity of symptoms in children with ADHD from four scales that measure family burden, family functioning, parental satisfaction, and parental mental health. Results show that dlasso is able to predict parents' assessment of the severity of their children's inattention from only seven items from the previous scales. These items are related to parents' satisfaction and degree of parental burden

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Front Human Neurosci. 2021;15.

DOSE-RESPONSE EFFECTS OF ACUTE AEROBIC EXERCISE INTENSITY ON INHIBITORY CONTROL IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Tsai YJ, Hsieh SS, Huang CJ, et al.

The present study aimed to examine whether the effect of acute aerobic exercise on inhibitory control of children with attention-deficit/hyperactivity disorder (ADHD) is moderated by exercise intensity. Using a within-subjects design, 25 children with ADHD completed a flanker task with concurrent collection of electroencephalography (EEG) data after three different intensities of treadmill running. The results showed that low- and moderate-intensity exercises resulted in shorter reaction times (RTs) relative to vigorous-intensity exercise during the incompatible condition of the flanker task regardless of task congruency. A P3 congruency effect was observed following low- and vigorous-intensity exercises but not after moderate-intensity exercise. The mean alpha power, a measure of cortical arousal, increased following low- and moderate-intensity exercises but decreased following vigorous-intensity exercise. In addition, the change in arousal level after moderate-intensity exercise was negatively correlated with RT during incompatible flanker tasks. The current findings suggest that children with ADHD have better inhibitory control following both low- and moderate-intensity exercises relative to vigorous aerobic exercise, which could be characterized by an optimal state of cortical arousal

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Frontiers in Neuroscience. 2021;15.

SHARED AND DISTINCT TOPOLOGICALLY STRUCTURAL CONNECTIVITY PATTERNS IN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Qian L, Li Y, Wang Y, et al.

Background: Previous neuroimaging studies have described shared and distinct neurobiological mechanisms between autism spectrum disorders (ASDs) and attention-deficit/hyperactivity disorder (ADHD). However, little is known about the similarities and differences in topologically structural connectivity patterns between the two disorders.

Methods: Diffusion tensor imaging (DTI) and deterministic tractography were used to construct the brain white matter (WM) structural networks of children and adolescents (age range, 6-16 years); 31 had ASD, 34 had ADHD, and 30 were age- and sex-matched typically developing (TD) individuals. Then, graph theoretical analysis was performed to investigate the alterations in the global and node-based properties of the WM

structural networks in these groups. Next, measures of ASD traits [Social Responsiveness Scale (SRS)] and ADHD traits (Swanson, Nolan, and Pelham, version IV scale, SNAP-IV) were correlated with the alterations to determine the functional significance of such changes.
Results: First, there were no significant differences in the global network properties among the three groups; moreover, compared with that of the TD group, nodal degree (Ki) of the right amygdala (AMYG.R) and right parahippocampal gyrus (PHG.R) were found in both the ASD and ADHD groups. Also, the ASD and ADHD groups shared four additional hubs, including the left middle temporal gyrus (MTG.L), left superior temporal gyrus (STG.L), left postcentral gyrus (PoCG.L), and right middle frontal gyrus (MFG.R) compared with the TD group. Moreover, the ASD and ADHD groups exhibited no significant differences regarding regional connectivity characteristics. Second, the ADHD group showed significantly increased nodal betweenness centrality (Bi) of the left hippocampus (HIP.L) compared with the ASD group; also, compared with the ADHD group, the ASD group lacked the left anterior cingulate gyrus (ACG.L) as a hub. Last, decreased nodal efficiency (Enodal) of the AMYG.R, Ki of the AMYG.R, and Ki of the PHG.R were associated with higher SRS scores in the ASD group. Decreased Ki of the PHG.R was associated with higher SRS scores in the full sample, whereas decreased Bi of the PHG.R was associated with lower oppositional defiance subscale scores of the SNAP-IV in the ADHD group, and decreased Bi of the HIP.L was associated with lower inattention subscale scores of the SNAP-IV in the full sample.
Conclusion: From the perspective of the topological properties of brain WM structural networks, ADHD and ASD have both shared and distinct features. More interestingly, some shared and distinct topological properties of WM structures are related to the core symptoms of these disorders

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Frontiers in Pediatrics. 2021;9.
BREASTFEEDING IN PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME: AN ITALIAN OBSERVATIONAL STUDY.
Murciano M, Biancone DM, De Luca F, et al.
Objective: Pediatric acute-onset neuropsychiatric syndrome (PANS) is a condition defined by sudden onset of obsessive-compulsive symptoms and/or severe eating restrictions, along with at least two other cognitive, behavioral, or neurological symptoms. Its pathogenesis is unknown but it seems triggered by infections, metabolic disturbances, and other inflammatory reactions. PANS represents a neurodevelopmental problem and infant feeding can play a role. Breast milk is the ideal food for infants and influences children's brain, cognitive, and socio-emotional development.
Methods: We enrolled 52 children diagnosed with PANS. We interviewed their parents in order to investigate perinatal history, infant feeding, neurologic development, and confounding factors like socio-economic status and region of origin. We subgrouped PANS patients into three subsets: those who only received human milk (HMO), those who only received infant formula, and those who received mixed feeding.
Results: The cohort is composed of 78.9% males, with a median age of 11 years (range 7-17). We found some neurodevelopmental problems (13.5%): walking disorders, ASD, ADHD, oppositional attitude, and delayed psychomotor development. We found scholar performance deficits (25%), including language problems like dysgraphia, dyslexia, and dyscalculia. The achievement of some milestones in the development of the infant is affected in 73.1% of cases. Breastfeeding is not homogeneously practiced in Italy because of social, economic, and cultural phenomena. The richest and the poorest families (100%) in the sample choose breastfeeding, probably with a different approach and for different reasons (awareness or need). In the group of PANS patients fed with HMO, compared to the rest of the patients, we registered fewer cases of growth problems (0 vs. 12.9%; $p = 0.14$), school performance problems or the need for school support (19.1% vs. 29%; $p = 0.42$), and a delay in the age of babbling/speaking (range 4-20 vs. 7-36 months; $p = 0.066$).
Conclusion: This is the first study that investigates the role of breastfeeding in the development of PANS. Promoting breastfeeding is important in the general population and also in PANS patients because it has an important social and global health impact, also during adult life. Further studies with a bigger population are needed to investigate the mechanisms underlying PANS and the role that breastfeeding may play in their short- and long-term neurodevelopment

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Front Psychiatry. 2021;12.

LINK BETWEEN TOPOGRAPHIC MEMORY AND THE COMBINED PRESENTATION OF ADHD (ADHD-C): A PILOT STUDY.

Faedda N, Guariglia C, Piccardi L, et al.

Background: Topographic memory is the ability to reach various places by recognizing spatial layouts and getting oriented in familiar environments. It involves several different cognitive abilities, in particular executive functions (EF), such as attention, working memory, and planning. Children with attention deficit hyperactivity disorder (ADHD) show impairments in inhibitory control, regulation of attention, planning, and working memory.

Aim: The aim of this study was to evaluate the topographic memory in children with ADHD-combined subtype (ADHD-C).

Method: Fifteen children (8ΓÇô10 years) with a diagnosis of ADHD-C (DSM-5) (ADHD-C group) were compared to 15 children with typical development (TD group) of the same age. All children performed Raven's colored progressive matrices (CPM) test to obtain a measure related with cognitive functioning. The walking Corsi test (WalCT), a large-scale version of the Corsi block-tapping test, was used to assess topographic memory in experimental environment.

Results: A higher impairment was observed in ADHD-C than TD with significant differences in the WalCT, in particular on the topographic short-term memory (TSTM) task, on the topographic learning (TL) task, and on the repetition number (RN) task during the TL task. Perseverative errors were reported in performing the square-sequence in the WalCT. Zero-order correlations showed a positive correlation between TSTM and auditory attention, and memory of design of NEPSY-II and digit span of WISC-IV. No statistically significant differences were found between the ADHD-C group and TD group in the TL task in the WalCT condition.

Conclusion: In ADHD-C, initial topographic learning was compromised whereas the long-term retention of learned topographical material seemed to not be impaired. In particular, these impairments seem to be linked with difficulties in sustained attention, in spatial memory for novel visual materials, in a poor working memory, and in perseverative behaviors

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IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2021.

NEURAL DYNAMICS FOR FACILITATING ADHD DIAGNOSIS IN PRESCHOOLERS: CENTRAL AND PARIETAL DELTA SYNCHRONIZATION IN THE KIDDIE CONTINUOUS PERFORMANCE TEST.

Chen I, Chang C, Chang Y, et al.

The present study aimed to characterize children at risk of attention-deficit/hyperactivity disorder (ADHD) during preschool age and provide early intervention. The continuous performance test (CPT) and electroencephalography (EEG) can contribute additional valuable information to facilitate diagnosis. This study measured brain dynamics at slow and fast task rates in the CPT using a wireless wearable EEG and identified correlations between the EEG and CPT data in preschool children with ADHD. Forty-nine preschool children participated in this study, of which 29 were diagnosed with ADHD and 20 exhibited typical development (TD). The Conners Kiddie Continuous Performance Test (K-CPT) and wireless wearable EEG recordings were employed simultaneously. Significant differences were observed between the groups with ADHD and TD in task-related EEG spectral powers (central as well as parietal delta, P 003C;0.01), which were distinct only in the slow-rate task condition. A shift from resting to the CPT task condition induced overall alpha powers decrease in the ADHD group. In the task condition, the delta powers were positively correlated with the CPT perseveration scores, whereas the alpha powers were negatively correlated with specific CPT scores mainly on perseveration and detectability (P 003C; 0.05). These results, which complement the findings of other sparse studies that have investigated within-task-related brain dynamics, particularly in preschool children, can assist specialists working in early intervention to plan training and educational programs for preschoolers with ADHD

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Innov Clin Neurosci. 2021;18:43-46.

TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT OF ADOLESCENT ATTENTION DEFICIT/ HYPERACTIVITY DISORDER: A NARRATIVE REVIEW OF LITERATURE.

Memon AM.

Attention deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders, affected 3.3 million adolescents in the United States (US) in 2016. Ten to 30 percent of these patients do not respond to standard pharmacotherapy and, as a result, suffer adverse physical/mental health and socioeconomic consequences. Despite being approved by the US Food and Drug Administration (FDA) for treatment of adult depression, with evidence suggesting positive outcomes in children and adults in treatment of ADHD and good safety and tolerability records, there is no existent literature reviewing the efficacy, safety, and feasibility of use of transcranial magnetic stimulation (TMS) in the treatment of adolescent ADHD. Thus, We have conducted this review for which a thorough literature search was conducted on PubMed and PsycInfo databases using a combination of MeSH terms that yielded 32 articles, five of which satisfied the inclusion criteria. We observed objective improvements in ADHD treatment outcomes in adolescent patients who participated in a randomized, sham-controlled, crossover pilot study that assessed the safety and efficacy of TMS. The study participants did not suffer any major adverse events, which was also supported by findings from other studies. However, since only one study out of five included in the review is an interventional study with limited number of study participants, there is a need to conduct large-scale clinical trials that recruit a greater number of study participants to explore the clinical efficacy and safety of TMS in the treatment of adolescent ADHD patients who do not respond to or tolerate standard pharmacotherapy based on the preliminary data extracted to this end

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

PERPETRATION OF AND VICTIMIZATION IN CYBERBULLYING AND TRADITIONAL BULLYING IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: ROLES OF IMPULSIVITY, FRUSTRATION INTOLERANCE, AND HOSTILITY.

Liu TL, Hsiao RC, Chou WJ, et al.

Victimization and perpetration of cyberbullying and traditional bullying are prevalent among adolescents with attention-deficit/hyperactivity disorder (ADHD). This study examined the associations of impulsivity, frustration discomfort, and hostility with victimization and with the perpetration of cyberbullying and traditional bullying in adolescents with ADHD. Self-reported involvement in cyberbullying and traditional bullying was assessed in 195 adolescents with a clinical diagnosis of ADHD. Adolescents also completed questionnaires for impulsivity, frustration discomfort, and hostility. Caregivers completed the Child Behavior Checklist for adolescents' ADHD, internalization, oppositional defiance, and problems with conduct. The associations of impulsivity, frustration discomfort, and hostility with victimization and perpetration of cyberbullying and traditional bullying were examined using logistic regression analysis. The results demonstrated that after the effects of demographic characteristics and behavioral problems were controlled for, frustration intolerance increased the risks of being cyberbullying victims and perpetrators whereas hostility increased the risks of being the victims and perpetrators of traditional bullying. Impulsivity was not significantly associated with any type of bullying involvement. Prevention and intervention programs should alleviate frustration intolerance and hostility among adolescents with ADHD

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

THE PERCEPTION OF PRIMARY SCHOOL TEACHERS REGARDING THE PHARMACOTHERAPY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gregario J, Ferreira R, Fernandes AS.

Attention Deficit Hyperactivity Disorder (ADHD) is raising concerns across health systems, affecting about 5% of the school-age population. Therapy usually involves psychostimulants, which are prone to adverse drug reactions (ADRs). Teachers have many contact hours with children and can easily detect behavioral changes upon the beginning of medication. However, few studies have focused on the role of teachers in the management of ADHD children and detection of ADRs. The present work aimed to characterize the

perception of primary school teachers regarding the impact of ADHD therapeutics. A questionnaire was constructed focused on teachers' training regarding ADHD and its therapy; experience with students with ADHD; changes upon beginning of medication; and observation of ADRs. A total of 107 completed questionnaires were obtained. The results indicate that more than 40% of the inquired teachers have received training in ADHD, but in most cases, the theme of therapeutics was absent from that training. The vast majority of teachers (91.6%) have had students with ADHD and observed mood alterations associated with medications. More than 60% of the teachers answered that they are aware of the ADRs and of these, 24% have already detected them in their students. The teachers reported the observed ADRs to parents in 93% of the cases and to doctors in 28% of the cases. In conclusion, the results show the need to reinforce teachers' training in ADHD and its therapeutics

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Int J Mol Sci. 2021 Jul;22.

CARDIOVASCULAR AND CEREBROVASCULAR IMPLICATIONS OF GROWTH RESTRICTION: MECHANISMS AND POTENTIAL TREATMENTS.

Rock CR, White TA, Piscopo BR, et al.

Fetal growth restriction (FGR) is a common complication of pregnancy, resulting in a fetus that fails to reach its genetically determined growth potential. Whilst the fetal cardiovascular response to acute hypoxia is well established, the fetal defence to chronic hypoxia is not well understood due to experiment constraints. Growth restriction results primarily from reduced oxygen and nutrient supply to the developing fetus, resulting in chronic hypoxia. The fetus adapts to chronic hypoxia by redistributing cardiac output via brain sparing in an attempt to preserve function in the developing brain. This review highlights the impact of brain sparing on the developing fetal cardiovascular and cerebrovascular systems, as well as emerging long-term effects in offspring that were growth restricted at birth. Here, we explore the pathogenesis associated with brain sparing within the cerebrovascular system. An increased understanding of the mechanistic pathways will be critical to preventing neuropathological outcomes, including motor dysfunction such as cerebral palsy, or behaviour dysfunctions including autism and attention-deficit/hyperactivity disorder (ADHD)

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Int J Environ Res Public Health. 2021;18.

DID AFFILIATE STIGMA PREDICT AFFECTIVE AND BEHAVIORAL OUTCOMES IN CAREGIVERS AND THEIR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Chang CC, Chen YM, Hsiao RC, et al.

The aim of this follow-up study was to examine the predictive values of caregivers affiliate stigma at baseline for depression in caregivers and internalizing and externalizing symptoms in children with attention-deficit/hyperactivity disorder (ADHD) 1 year later. The Study on Affiliate Stigma in Caregivers of Children with ADHD surveyed the levels of affiliate stigma and depression in 400 caregivers and the behavioral problems of their children with ADHD. The levels of the caregivers depression and childrenɔs behavioral problems were assessed 1 year later. The associations of care-givers affiliate stigma at baseline with depression in caregivers and internalizing and externalizing symptoms in children with ADHD at follow-up were examined using stepwise multiple regres-sion. The results indicated that before caregivers depression and childrenɔs behavioral problems at baseline were controlled, caregivers affiliate stigma at baseline positively predicted caregivers' depression and all children's behavioral problems. After caregivers depression and children's behavioral problems at baseline were controlled, caregivers affiliate stigma at baseline still positively predicted children's affective and somatic problems. Parenting training and cognitive behavioral therapy should be provided to caregivers with intense affiliate stigma to prevent emotional problems and difficulties in managing their children's behavioral problems

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Int J Environ Res Public Health. 2021;18.

SELF-REPORTED DEPRESSIVE SYMPTOMS AND SUICIDALITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: ROLES OF BULLYING INVOLVEMENT, FRUSTRATION INTOLERANCE, AND HOSTILITY.

Liu TL, Hsiao RC, Chou WJ, et al.

This study examined the relationships of cyberbullying and traditional bullying victimization and perpetration, perceived family function, frustration discomfort, and hostility with self-reported depressive symptoms and suicidality in adolescents diagnosed as having attention-deficit/hyperactivity disorder (ADHD). Both the self-reported severity of depressive symptoms on the Center for Epidemiological Studies Depression Scale and the occurrence of suicidal ideation or a suicide attempt on the suicidality module of the Kiddie Schedule for Affective Disorders and Schizophrenia were assessed in 195 adolescents with ADHD. The adolescents completed the Cyberbullying Experiences Questionnaire, Chinese version of the School Bullying Experience Questionnaire, Frustration-Discomfort Scale, BussΓÇôDurkee Hostility Inventory, and Family APGAR Index. Caregivers completed the ADHD problems component of the Child Behavior Checklist for Ages 6ΓÇô18. Multiple regression analyses were used to examine the correlates for each of self-reported depressive symptoms and suicidality. The results showed that after the effects of gender, age, ADHD symptoms, and family function were controlled, greater frustration discomfort and bullying perpetration significantly predicted self-reported depressive symptoms. Being cyberbullying victims and displaying hostility significantly predicted the risk of suicidality. Various types of bullying involvement, frustration intolerance, and hostility significantly predicted self-reported depressive symptoms and suicidality in adolescents with ADHD. By monitoring and intervening in these factors, we can reduce the risk of depression-related problems and suicidality in adolescents with ADHD

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Iran J Psychiatr Behav Sci. 2021;15.

EFFECTS OF PIRACETAM AS AN ADJUVANT THERAPY ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.

Alavi K, Shirazi E, Akbari M, et al.

Background: Stimulants are highly effective in controlling symptoms of Attention-deficit/hyperactivity disorder (ADHD), but 30% of individuals with ADHD do not respond to them or cannot tolerate their side effects; thus, alternative treatment approaches need to be considered.

Objectives: To evaluate the effect and safety of piracetam as an adjuvant therapy plus methylphenidate (MPH) in children with ADHD.

Methods: Thirty-six children with ADHD (6-16 years old), admitted to three academic outpatient child psychiatric clinics in the second half of 2015, were randomly assigned to the "methylphenidate plus piracetam group"and the "methylphenidate plus placebo"group, in a double-blind, placebo-controlled study, for 6 weeks. The "Conner's Parents' Rating Scale-Revised (CPRS-R), Children Symptom Inventory-4 (CSI-4), Clinical Global Impression-Improvement scale (CGI-I), and Children' Global Assessment Scale (CGAS) were completed at baseline and at the ends of the third and the sixth week, and the New York State Psychiatric Institute side effect forms were completed weekly, as outcome measures.

Results: The level of improvement in CPRS-R, CSI-4, and CGI-I scales were significantly higher in the "methylphenidate plus piracetam"group compared with the "methylphenidate plus placebo"group. Side effects were not remarkable in any group.

Conclusions: Piracetam as a short-term adjuvant treatment to methylphenidate can have considerable therapeutic effect and safety profile in children with ADHD and deserves further exploration to assess its potentialities in ADHD treatment

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J Affective Disord. 2021;293:484-91.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AMONG ELEMENTARY STUDENTS IN RURAL CHINA: PREVALENCE, CORRELATES, AND CONSEQUENCES.

Pang X, Wang H, Dill SE, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a widely recognized mental health problem in developed countries but remains under-investigated in developing settings. This study examines the prevalence, correlates, and consequences of ADHD symptoms among elementary school students in rural China.

Methods: Cross-sectional data were collected from 6,719 students across 120 rural primary schools in China on ADHD symptoms, demographic characteristics, and academic performance in reading and math. ADHD symptoms were evaluated using the caregiver-reported ADHD Rating Scale-IV.

Results: The prevalence of ADHD symptoms was 7.5% in our sample. Male students, students in lower grade levels, and students with lower cognitive ability showed a significantly higher prevalence of ADHD symptoms (ORs = 2.56, 2.06, and 1.84, respectively; $p<0.05$). Left-behind children showed a significantly lower prevalence of ADHD symptoms than did children who were living with their parents (OR = 0.74, $p < 0.05$). Adjusted regressions show that students with ADHD symptoms scored 0.12 standardized deviations lower in reading ($p < 0.05$) and 0.19 standardized deviations lower in math ($p < 0.01$). Limitations: The ADHD Rating Scale-IV is a screening scale rather than a diagnostic test. Caregiver self-report measures also may underestimate ADHD symptoms for our sample.

Conclusions: ADHD is a common disorder among rural students in China and appears to be contributing to poor academic outcomes. The higher prevalence of ADHD among students with low cognitive ability also suggests that many rural children in China face multifactorial learning challenges. Taken together, the findings indicate a need for educators and policymakers in rural China to develop programs to reduce risk and support students with ADHD symptoms

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J Affective Disord. 2021;293:186-96.

DEVELOPMENT OF BIPOLAR DISORDER IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE STUDIES.

Brancati GE, Perugi G, Milone A, et al.

Background: Increasing attention has been recently paid to precursors of bipolar disorder (BD). Symptoms of attention-deficit/hyperactivity disorder (ADHD) have been reported among the most common prodromes of BD. The aim of this study was to estimate the risk of BD in youths affected by ADHD based on prospective studies.

Methods: A systematic review was conducted according to the PRISMA guidelines. A meta-analysis of single proportions was performed to compute the overall occurrence of BD in ADHD individuals. Binary outcome data were used to calculate risk estimates of BD occurrence in ADHD subjects versus Healthy Controls (HC).

Results: An overall proportion of BD occurrence of 10.01% (95%-confidence interval [CI]: 6.47%-15.19%; I2 = 82.0%) was found among 1248 patients with ADHD over 10 prospective studies. A slightly higher proportion was found when excluding one study based on jack-knife sensitivity analysis (11.96%, 95%-CI: 9.15%-15.49%; I2 = 54.1%) and in three offspring studies (12.87%, 95%-CI: 8.91%-18.23%). BD occurrence was not significantly associated with mean follow-up duration (p-value = 0.2118). A greater risk of BD occurrence in ADHD versus HC from six studies was found (risk ratio: 8.97, 95%-CI: 4.26-18.87, p-value < 0.0001).

Limitations: Few prospective studies have been retrieved in our search and most were not specifically aimed at assessing BD in followed-up ADHD patients.

Conclusions: Greater clinical attention should be paid to ADHD as an early precursor of BD since a substantial proportion of ADHD patients is expected to be diagnosed with BD during the developmental age

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J Affective Disord. 2021;292:475-86.

THE EFFICACY OF MINDFULNESS-BASED INTERVENTIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BEYOND CORE SYMPTOMS: A SYSTEMATIC REVIEW, META-ANALYSIS, AND META-REGRESSION.

Oliva F, Malandrone F, di Girolamo G, et al.

Background: Mindfulness-Based Interventions (MBIs) have been increasingly proposed as treatment in patients with Attention-Deficit/Hyperactivity Disorder (ADHD), showing promising results on different proposed outcomes, in both children and adults.

Objectives: To systematically review and meta-analyse studies concerning the effects of MBIs on either ADHD and associated features, associated clinical conditions, neurocognitive impairments, mindfulness skills, global functioning and quality of life.

Methods: Searches were conducted on five databases, including controlled and observational studies on both adults and children populations. The review process was compliant to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Meta-analyses and meta-regression models were conducted.

Results: Thirty-one full-texts were included. In both adults and children, MBIs showed to be more effective than waiting lists in improving ADHD symptoms and some other outcomes. In adults, a medium pooled effect size was shown by meta-analysis for ADHD symptoms but in some cases a publication bias was detected. Subgroup analysis and meta-regression confirmed the gap detected by our systematic review between the medium/large effect size of inactive-controlled studies and the low/negligible one of active-controlled studies. In children, no active-controlled studies have been conducted. Mindfulness Awareness Practice (MAP) and Mindfulness Based Cognitive Therapy (MBCT) were the most used protocols in adult studies, whereas a combination of MBCT and Mindfulness Based Stress Reduction (MBSR) was more preferred for children and adolescent patients.

Conclusions: Even if further studies with a better methodology are needed, we can suggest the MBIs may be useful as complementation and not as replacement of other active interventions

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J Autism Dev Disord. 2021.

CONVERSATION DURING A VIRTUAL REALITY TASK REVEALS NEW STRUCTURAL LANGUAGE PROFILES OF CHILDREN WITH ASD, ADHD, AND COMORBID SYMPTOMS OF BOTH.

Boo C, Alpers-Leon N, McIntyre N, et al.

Many studies have utilized standardized measures and storybook narratives to characterize language profiles of children with Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD). They report that structural language of these children is on par with mental-age-matched typically developing (TD) peers. Few studies have looked at structural language profiles in conversational contexts. This study examines conversational speech produced in a virtual reality (VR) paradigm to investigate the strengths and weaknesses of structural language abilities of these children. The VR paradigm introduced varying social and cognitive demands across phases. Our results indicate that children from these diagnostic groups produced less complex structural language than TD children. Moreover, language complexity decreased in all groups across phases, suggesting a cross-etiology sensitivity to conversational contexts

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J Autism Dev Disord. 2021.

THE IMPACT OF THE COMORBIDITY OF ASD AND ADHD ON SOCIAL IMPAIRMENT.

Harkins CM, Handen BL, Mazurek MO.

Children with autism spectrum disorder (ASD) and children with attention deficit/hyperactivity disorder (ADHD) both experience behavioral and social difficulties. Prior research has shown that when these disorders co-occur, behavioral symptoms associated with both disorders may be more severe. There is only limited research on the impact of ASD + ADHD comorbidity on social functioning. The present study investigated social impairment in 282 children diagnosed with ASD, ADHD, or ASD + ADHD. No significant differences in social impairment were found between the ASD and ASD + ADHD groups. This study

contributes to extant literature indicating mixed findings in regard to social functioning amidst the ASD + ADHD comorbidity

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J Autism Dev Disord. 2021 Jul;51:2297-307.

RELATIVE FREQUENCY OF PSYCHIATRIC, NEURODEVELOPMENTAL, AND SOMATIC SYMPTOMS AS REPORTED BY MOTHERS OF CHILDREN WITH AUTISM COMPARED WITH ADHD AND TYPICAL SAMPLES.

Mayes SD, Calhoun SL, Baweja R, et al.

No study has analyzed the relative occurrence of a broad range of symptoms reported by mothers of children with autism, ADHD-Combined, and ADHD-Inattentive and typical controls. Mothers rated 1436 children with autism, 1056 with ADHD without autism, and 186 controls, 2–17 years, on 41 internalizing, externalizing, neurodevelopmental, and somatic problems. Most children with autism had symptoms of ADHD, oppositional defiant disorder, disruptive mood dysregulation disorder, and expressive language disorder and almost half had dysgraphia and receptive language disorder. Symptom overlap between autism and ADHD-Combined was high. Clinicians specializing in autism and ADHD must have expertise in evaluating and treating these comorbidities identified as most problematic by mothers in order to relieve family concerns and develop treatment plans relevant to families. (PsycInfo Database Record (c) 2021 APA, all rights reserved)

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J Autism Dev Disord. 2021.

THE IMPORTANCE OF UNDERSTANDING INDIVIDUAL DIFFERENCES OF EMOTION REGULATION ABILITIES IN 22Q11.2 DELETION SYNDROME.

Campbell LE, Swaab L, Freeman EE, et al.

Chromosome 22q11.2 deletion syndrome (22q11DS) is characterised by a complex behavioural phenotype including anxiety, attention-deficit/hyperactivity disorder and psychosis. In the current study, we aimed at improving our understanding of the heterogeneity of behavioural characteristics in a group of 129 young people (aged 4-22) with a confirmed 22q11.2 microdeletion and 116 age and gender matched typically developing controls. Half the participants with 22q11DS had behaviour characterised by emotion dysregulation. A cluster analyses, of the participants with 22q11DS, revealed four groups characterised by intact emotion regulation; predominantly internalizing problems; both internalizing and externalizing problems; and predominantly externalizing difficulties. Importantly, it was found that young people with 22q11DS whose emotion dysregulation was characterised by externalizing problems had the poorest levels of functioning. As our understanding of 22q11DS improves, it is becoming increasingly clear that we need a better understanding of how individual differences and psychosocial factors contribute to, and interact with one another, to result in the observable individual differences in the 22q11DS behavioural phenotype

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J Child Adolesc Psychopharmacol. 2021;31:332-41.

ATOMOXETINE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH AND WITHOUT COMORBID MOOD DISORDERS.

Shaker NM, Osama Y, Barakat DH, et al.

Objectives: Mood disorders are commonly associated with attention-deficit/hyperactivity disorder (ADHD), adding to the clinical complexity. Some symptoms associated with ADHD are often associated with an increase in emotional disorders and depression. Hence, the management of comorbid mood symptoms in the context of ADHD represents a particularly difficult clinical challenge. Few studies in literature, and probably none in the Arab world, have investigated the impact of individual common comorbid disorders on the efficacy of atomoxetine (a nonstimulant norepinephrine reuptake inhibitor) as a monotherapy for the treatment of these comorbid mood symptoms. Therefore, our aim was to investigate the effect of atomoxetine in a sample of drug-naive Egyptian children with ADHD, with and without comorbid mood disorders.

Methods: A prospective, naturalistic, open-label study.

Results: Atomoxetine is an effective treatment for the symptoms of ADHD in the presence of comorbid mood disorder, but with a slower rate of improvement than if applied in the absence of mood disorder; in addition, our study showed improvement regarding the depressive symptoms in the mood group after 1 month.

Conclusions: The study highlighted that atomoxetine is an effective treatment for ADHD in the presence of comorbid mood disorder, and improves depressive symptoms in the mood group. It also predicts mild resistance to the effects of atomoxetine on ADHD with slower improvement than those with ADHD only

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J Child Adolesc Psychopharmacol. 2021;31:342-49.

OPEN-LABEL DOSE OPTIMIZATION OF METHYLPHENIDATE EXTENDED-RELEASE ORALLY DISINTEGRATING TABLET IN A LABORATORY CLASSROOM STUDY OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Kollins SH, Cutler AJ, et al.

Objective: To examine the efficacy, safety, and tolerability of methylphenidate extended-release orally disintegrating tablets (MPH XR-ODT) for the treatment of attention-deficit/hyperactivity disorder (ADHD) during the open-label dose-optimization/stabilization period of a phase 3 laboratory classroom study.

Methods: Children (6-12 years) diagnosed with ADHD were enrolled. Treatment was initiated with MPH XR-ODT 20 mg daily. Doses were adjusted weekly by 10-20 mg during the 4-week dose-optimization period (visits 2-5) until an optimal dose was reached. The optimal dose was sustained during a 1-week stabilization period (visits 6-7). Efficacy was assessed using the ADHD Rating Scale-IV (ADHD-RS-IV) score and the Clinical Global Impression-Improvement (CGI-I) score. Adverse events (AEs) were recorded throughout the study. A secondary subgroup analysis by baseline ADHD-RS-IV score, sex, age, and weight was also performed.

Results: The mean (standard deviation [SD]) final optimized MPH XR-ODT daily dose was 41.8 (14.6) mg and ranged from 20 to 60 mg. Final optimized dose was higher for children with more severe baseline ADHD-RS-IV total scores. ADHD-RS-IV total scores decreased progressively during dose optimization, with a mean (SD) change from baseline at visit 7 of -21.4 (8.9). CGI-I scores shifted from "minimally improved"(mean [SD]: 3.1 [1.1]) at visit 3 to "much improved"(1.6 [0.6]) at visit 7. Baseline ADHD-RS-IV total score was highest for participants optimized to 40 mg (mean [standard error]: 40.0 [1.4]) and lowest for those optimized to 20 mg (34.8 [2.1]). By visit 6, mean ADHD-RS-IV score was comparable for all optimized dose groups. Common treatment-emergent AEs (5% of participants) included decreased appetite, upper abdominal pain, headaches, and insomnia.

Conclusions: Dose optimization of MPH XR-ODT led to a reduction in ADHD symptoms, indicated by a decrease in ADHD-RS-IV and CGI-I scores. AEs were consistent with those of other MPH products.

Clinical Trial Registry: NCT01835548 (ClinicalTrials.gov)

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J Child Psychol Psychiatry. 2021 Jul;62:868-75.

MATERNAL AND CORD PLASMA BRANCHED-CHAIN AMINO ACIDS AND CHILD RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A PROSPECTIVE BIRTH COHORT STUDY.

Anand NS, Ji Y, Wang G, et al.

Background: Branched-chain amino acids (BCAA: leucine, isoleucine, and valine) are essential amino acids involved in biological functions of brain development and recently linked with autism. However, their role in attention-deficit hyperactivity disorder (ADHD) is not well-studied. We investigated individual and combined relationships of maternal plasma and newborn cord plasma BCAAs with childhood development of ADHD.

Methods: We utilized the Boston Birth Cohort, a predominantly urban, low-income, US minority population. Child developmental outcomes were defined in three mutually exclusive groups – ADHD, neurotypical (NT), or other developmental disabilities based on physician diagnoses per ICD-9 or 10 in medical records. The final sample included 626 children (299 ADHD, 327 NT) excluding other developmental disabilities. BCAAs were measured by liquid chromatography–tandem mass spectrometry. We used factor analysis to create composite scores of maternal and cord BCAA, which we divided into tertiles. Logistic regressions analyzed relationships between maternal or cord BCAA tertiles with child ADHD risk, controlling for maternal race, age, parity, smoking, education, low birth weight, preterm birth, and child sex. Additionally, we analyzed maternal and cord plasma BCAAs jointly on child ADHD risk.

Results: Adjusted logistic regression found significantly increased odds of child ADHD diagnosis for the second (OR 1.63, 95% CI: 1.04, 2.54, p = .032) and third tertiles (OR 2.01, 95% CI: 1.28, 3.15, p = .002) of cord BCAA scores compared to the first tertile. This finding held for the third tertile when further adjusting for

maternal BCAA score. There was no significant association between maternal BCAA score and child ADHD risk, nor a significant interaction between maternal and cord BCAA scores.
Conclusions: In this prospective US birth cohort, higher cord BCAA levels were associated with a greater risk of developing ADHD in childhood. These results have implications for further research into mechanisms of ADHD development and possible early life screening and interventions

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Journal of Clinical Pharmacy and Therapeutics. 2021.

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

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

What is known and Objective: Attention-deficit hyperactivity disorder (ADHD) symptoms usually impairs academic achievement and can trigger the onset of medication. Methylphenidate is a drug widely prescribed to treat ADHD. However, systematic reviews of randomized clinical trials suggest that it does not lead to great improvements in academic performance. Thus, we aimed to evaluate the evidence on the ΓÇ£real-worldΓÇØ effectiveness of methylphenidate in improving the academic achievement of ADHD students. Methods: We conducted a systematic review of observational studies retrieved from five electronic databases, besides a manual search and search in grey literature. Studies evaluating treatment with methylphenidate compared to no treatment or other pharmacological/non-pharmacological alternatives used in ADHD were included. The risk of bias of the selected studies was assessed using adapted versions of the Newcastle-Ottawa Scale. Results and Discussion: Nine studies (from ten reports) were included in the review: four cohorts, two before-and-after designs and three cross-sectional studies. They involved 12,269 children and adolescents aged 6ΓÇô18-áyears. The doses of methylphenidate ranged from 10 to 72-ámg/day, and the duration of the treatment from 2.6-ámonths to 4.25-áyears. Five of these studies concluded that methylphenidate improves academic performance. However, three of the four lowest-bias risk studies concluded that the drug is ineffective. Five studies assessed the long-term use of methylphenidate, and four of them concluded that it does not result in better outcomes in the school setting. Most included studies had considerable limitations and significant heterogeneity regarding methodological design and academic performance measurement criteria. What is new and Conclusion: Although some studies indicate that the short-term use of methylphenidate may improve outcomes in the school environment, the available evidence does not support the establishment of adequate conclusions about the real benefits of methylphenidate in the academic improvement of ADHD students

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Journal of Clinical Psychology in Medical Settings. 2021.

CROSS-SECTIONAL AGE ANALYSIS OF SLEEP PROBLEMS IN 2 TO 17 YEAR OLDS WITH ADHD COMBINED, ADHD INATTENTIVE, OR AUTISM.

Mayes SD, Puzino K, DiGiovanni C, et al.

Sleep problems are common in autism and ADHD. No study has compared sleep problems by age in 2 to 17 year olds with autism versus ADHD-Combined versus ADHD-Inattentive type. Mothers rated 1415 youth with autism and 1041 with ADHD on 10 Pediatric Behavior Scale sleep items. Nighttime sleep problems were most severe in autism, followed by ADHD-Combined, and then ADHD-Inattentive. Difficulty falling asleep, restless during sleep, and waking during the night were the most common problems. Adolescents slept more at night than other age groups, and youth who slept more at night were sleepier during the day. Sleep problems declined with age, but correlations were small. In adolescence, 63% with autism, 53% with ADHD-Combined, and 57% with ADHD-Inattentive had difficulty falling asleep. Given that the majority of children in all age groups had one or more sleep problem, developmentally appropriate interventions are needed to address sleep difficulties and limit their adverse effects

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J Clin Psychopharmacol. 2021;41:490-92.
TREATING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SEVERE INTELLECTUAL DISABILITY WITH LISDEXAMFETAMINE: A CASE REPORT.
Arajo A, Madeira N, Ventura F, et al.

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J Clin Psychopharmacol. 2021;41:370-80.
A PHASE 3, PLACEBO-CONTROLLED TRIAL OF ONCE-DAILY VILOXAZINE EXTENDED-RELEASE CAPSULES IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Nasser A, Liranso T, Adewole T, et al.
Purpose This phase 3 clinical trial evaluated the efficacy and safety of viloxazine extended-release capsules (VLX-ER) as a monotherapy for attention-deficit/hyperactivity disorder (ADHD) in adolescents (12-17 years). Methods Eligible subjects (n = 310) were randomized to receive once-daily 200 and 400 mg VLX-ER, or placebo for 6 weeks. The primary efficacy end point was change from baseline (CFB) at the end of study (EOS) in ADHD Rating Scale-5 Total score. Key secondary end points were Clinical Global Impression - Improvement score at EOS, CFB at EOS in Conners 3 - Parent Short Form Composite T-score, and CFB at EOS in Weiss Functional Impairment Rating Scale - Parent Total average score. Results In the 200-mg/d and 400-mg/d VLX-ER treatment groups, a significant improvement was found in the CFB at EOS in ADHD Rating Scale-5 Total (P = 0.0232, P = 0.0091) and Inattention (P = 0.0424, P = 0.0390) and Hyperactivity/Impulsivity (P = 0.0069, P = 0.0005) subscale scores versus placebo. The Clinical Global Impression - Improvement score was significantly improved at EOS in the 200-mg/d and 400-mg/d VLX-ER groups versus placebo (P = 0.0042, P = 0.0003). The Conners 3 - Parent Short Form composite T-score and Weiss Functional Impairment Rating Scale - Parent Total average score exhibited improvement in both VLX-ER groups; however, the difference versus placebo was not statistically significant. The most common treatment-related adverse events were somnolence, headache, decreased appetite, nausea, and fatigue. The adverse event-related discontinuation rates were <5% in all groups. Conclusions Viloxazine extended-release demonstrated statistically significant and clinically meaningful improvement in ADHD symptoms in adolescents and was generally well tolerated

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J Indian Assoc Child Adolesc Ment Health. 2021;17:57-78.
PARENTING EXPERIENCES OF RAISING A CHILD WITH ATTENTION-DEFICIT / HYPERACTIVITY DISORDER: A PILOT STUDY FROM INDIA.
Shah R, Sharma A, Chauhan N, et al.
Background: Qualitative research that explores parenting experiences while raising a child with ADHD can help in developing and implementing interventions that are meaningful to the families. Contextual factors may influence the parenting experiences to a great extent, and hence, it is important to understand these experiences in our unique cultural context.
Objectives: This pilot qualitative study aimed to understand the experiences of Indian parents within the family, community and their interactions with the school while raising children with ADHD by applying thematic analysis.
Methods: In-depth interviews were conducted with 15 consenting parents (8 mothers and 7 fathers) of 12 children. Open-ended questions explored how the child's symptoms had affected them in different domains of life, namely, family life, social and community life and interaction with the school.
Results: Six themes were identified; Burden of care, Emotional burden with a ray of hope, Assigning responsibility, Stigma and discrimination, Parent in charge of the situation, and Family support systems. Despite being largely similar to existing literature, there were three important differences that can be understood in our context. First, there was a difference in the themes per se, in that family support systems emerged as an important theme; second, in the way the themes were experienced, for example, stigma was expressed as feelings of shame and embarrassment more often than discrimination and third in the context of experiences such as stigma and blame.

Conclusions: Findings may be helpful to mental health professionals for culturally therapeutic engagement and interventions for these families

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J Neural Transm. 2021.

THE IMPACT OF PRESCHOOL CHILD AND MATERNAL ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS ON MOTHERS' PERCEIVED CHRONIC STRESS AND HAIR CORTISOL.

Szop A, Skoluda N, et al.

Providing care for a child with attention-deficit/hyperactivity disorder (ADHD) is associated with parenting stress. Moreover, adults with elevated ADHD symptoms report increased perceived stress. Despite this, it has rarely been examined whether and how child and maternal ADHD symptoms may affect maternal perceived stress and the stress-sensitive hypothalamicΓÇôpituitaryΓÇôadrenal axis. This study therefore investigated the possible impact of child and maternal ADHD symptoms on mothers' perceived chronic stress and hair cortisol concentration (HCC), while simultaneously considering the effects of child oppositional defiant/conduct disorder (ODD/CD) and maternal depressive symptomatology. In total, 124 mothers (35.96 -¦ 5.21-áyears) of preschool children were included. Maternal perceived stress, ADHD and depressive symptoms were assessed using self-report measures. Child ADHD symptoms were assessed using an interview and questionnaires completed by mothers and teachers. Additionally, mothers provided information about their children's ODD/CD symptoms. Hair samples were taken from mothers to assess HCC. Child and maternal ADHD, child ODD/CD, and maternal depressive symptoms accounted for 50% of the variance in perceived chronic stress (F(4, 119) = 30.24; p < 0.01), with only maternal ADHD (+¦ = 0.52, p < 0.01) and depressive symptoms (+¦ = 0.49, p < 0.01) being uniquely significant. Maternal ADHD symptoms did not moderate the relationship between child ADHD symptoms and maternal perceived chronic stress (b = ΓêÆ 0.01; SE b = 0.17; t(5, 118) = 0.05; p = 0.96). Mother's age became the only significant predictor of maternal HCC (+¦ = 0.29; p < 0.01). Based on these findings, practitioners are advised to be aware of and take into account possible maternal ADHD and depressive symptomatology and perceived chronic stress when treating children diagnosed with ADHD

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J Neurosci. 2021;41.

CLOSED-LOOP NEUROFEEDBACK OF ALPHA SYNCHRONY DURING GOAL-DIRECTED ATTENTION.

Mishra J, Lowenstein M, Campusano R, et al.

Alpha oscillations in sensory cortex, under frontal control, desynchronize during attentive preparation. Here, in a selective attention study with simultaneous EEG in humans of either sex, we first demonstrate that diminished anticipatory alpha synchrony between the mid-frontal region of the dorsal attention network and ventral visual sensory cortex (frontal-sensory synchrony (FSS)) significantly correlates with greater task performance. Then, in a double-blind, randomized controlled study in healthy adults, we implement closed-loop neurofeedback of the anticipatory alpha FSS signal over ten days of training. We refer to this closed-loop experimental approach of rapid neurofeedback (NF) integrated within a cognitive task as cognitive neurofeedback (cNF). We show that cNF results in significant trial-by-trial modulation of the anticipatory alpha FSS measure during training, concomitant plasticity of stimulus-evoked alpha/theta responses, as well as transfer of benefits to response time improvements on a standard test of sustained attention. In a third study, we implement cNF training in children with ADHD, replicating trial-by-trial modulation of the anticipatory alpha FSS signal as well as significant improvement of sustained attention response times. These first findings demonstrate the basic mechanisms and translational utility of rapid cognitive-task-integrated neurofeedback

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Journal of Personalized Medicine. 2021;11.

GENOMICS AS A CLINICAL DECISION SUPPORT TOOL: SUCCESSFUL PROOF OF CONCEPT FOR IMPROVED ASD OUTCOMES.

Way H, Williams G, Hausman-Cohen S, et al.

Considerable evidence is emerging that Autism Spectrum Disorder (ASD) is most often triggered by a range of different genetic variants that interact with environmental factors such as exposures to toxicants and

changes to the food supply. Up to 80% of genetic variations that contribute to ASD found to date are neither extremely rare nor classified as pathogenic. Rather, they are less common single nucleotide polymorphisms (SNPs), found in 1-15% or more of the population, that by themselves are not disease-causing. These genomic variants contribute to ASD by interacting with each other, along with nutritional and environmental factors. Examples of pathways affected or triggered include those related to brain inflammation, mitochondrial dysfunction, neuronal connectivity, synapse formation, impaired detoxification, methylation, and neurotransmitter-related effects. This article presents information on four case study patients that are part of a larger ongoing pilot study. A genomic clinical decision support (CDS) tool that specifically focuses on variants and pathways that have been associated with neurodevelopmental disorders was used in this pilot study to help develop a targeted, personalized prevention and intervention strategy for each child. In addition to an individualΓÇÖs genetic makeup, each patientΓÇÖs personal history, diet, and environmental factors were considered. The CDS tool also looked at genomic SNPs associated with secondary comorbid ASD conditions including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections/pediatric acute-onset neuropsychiatric syndrome (PANDAS/PANS). The interpreted genomics tool helped the treating clinician identify and develop personalized, genomically targeted treatment plans. Utilization of this treatment approach was associated with significant improvements in socialization and verbal skills, academic milestones and intelligence quotient (IQ), and overall increased ability to function in these children, as measured by autism treatment evaluation checklist (ATEC) scores and parent interviews

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J Am Acad Child Adolesc Psychiatry. 2021.

PREDICTORS OF TREATMENT ENGAGEMENT AND OUTCOME AMONG ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: AN INTEGRATIVE DATA ANALYSIS.

Sibley MH, Coxe SJ, Stein MA, et al.

Objective: To identify patient- and treatment-level factors that predict intervention engagement and outcome for adolescents with attention-deficit/hyperactivity disorder (ADHD), guiding efforts to enhance care.

Method: Integrative data analysis was used to pool data from 4 randomized controlled trials of adolescent ADHD treatment with participants (N = 854) receiving various evidence-based behavioral therapy packages in 5 treatment arms (standard [STANDARD], comprehensive [COMP], engagement-focused [ENGAGE]), community-based usual care (UC), or no treatment (NOTX). Participants also displayed varying medication use patterns (negligible, inconsistent, consistent) during the trial. Regression and latent growth curve analyses examined treatment- and patient-level predictors of engagement and outcome.

Results: Compared with COMP, ENGAGE was associated with higher parent engagement in behavioral therapy (d = 1.35-1.73) when delivered in university, but not community, clinics. Under some conditions, ENGAGE also predicted youth engagement in behavioral therapy (d = 1.21) and lower likelihood of negligible medication use (odds ratio = 0.49 compared with NOTX). UC was associated with poorer parent engagement compared with COMP (d = 0.59) and negligible medication use (odds ratio = 2.29) compared with NOTX. Compared with COMP, ENGAGE (in university settings) was consistently associated with larger ADHD symptom improvements (d = 0.41-0.83) at 6-month follow-up and sometimes associated with larger grade point average (d = 0.68) and parent-teen conflict (d = 0.41) improvements. Consistent medication use during behavioral therapy was associated with larger improvements in ADHD symptoms (d = 0.28) and parent-teen conflict (d = 0.25-0.36). An ADHD+internalizing clinical profile predicted larger improvements in grade point average (d = 0.45). Family adversity predicted poorer parent and youth engagement (rate ratio = 0.90-0.95), negligible medication use (odds ratio = 1.22), and smaller improvements in grade point average (d = 0.23). African American race predicted smaller improvements in parent-teen conflict (d = 0.49).

Conclusion: Engagement-focused behavioral therapy and consistent medication use most frequently predicted stronger clinical engagement and outcomes for adolescents with ADHD. Youths who are African American or who experience family adversity may demonstrate treatment-related disparities for certain outcomes; youths with ADHD+internalizing symptoms may demonstrate excellent academic outcomes following behavioral therapy. Data sharing: The full ADHD TIDAL dataset is publicly available through the National Data Archive (https://nda.nih.gov), including a data dictionary. The study protocol is also publicly available: https://doi.org/10.1186/s12888-020-02734-6

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J Am Acad Child Adolesc Psychiatry. 2021.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND EXTERNALIZING PROGRESSION IN THE LAMS STUDY: A TEST OF TRAIT IMPULSIVITY THEORY.

Bell ZE, Fristad MA, Youngstrom EA, et al.

Objective: To test differential prospective prediction of growth in externalizing behavior, including oppositional defiant disorder, conduct disorder, and substance use disorders, by earlier hyperactive-impulsive (HI) vs inattentive (IN) symptoms of attention-deficit/hyperactivity disorder (ADHD).

Method: Participants in the Longitudinal Assessment of Manic Symptoms (LAMS) Study (N = 685 at study entry), including 458 boys and 227 girls ages 6ΓÇô12, completed full parent report and self-report assessments every year for 8 years on the Schedule for Affective Disorders and Schizophrenia for School-Age Children. Three sets of analyses were conducted. First, hierarchal regression (block entry) was used to test independent associations between HI symptoms and later externalizing outcomes, controlling for IN symptoms, and IN symptoms and later externalizing outcomes, controlling for HI symptoms. Second, logistic regression was used to test progression of DSM externalizing disorders. Third, tests of mediation were used to assess potentiation of externalizing progression through environmental risk mediators (eg, family environment, neighborhood violence).

Results: Consistent with hypotheses derived from trait impulsivity theories of externalizing behavior, HI symptoms of ADHD were associated independently with long-term externalizing outcomes, whereas IN symptoms were not. Between months 48 and 96, ADHD-HI/combined symptom subtype diagnoses predicted later oppositional defiant disorder diagnoses, oppositional defiant disorder diagnoses predicted later conduct disorder diagnoses, and conduct disorder diagnoses predicted later substance use disorder diagnoses. Evidence for environmental risk mediation (eg, parental monitoring, neighborhood violence) was also found.

Conclusion: Findings support trait impulsivity models of externalizing progression, whereby ADHD-HI/combined symptoms subtypes predispose to increasingly severe externalizing behaviors, which are magnified in contexts of environmental risk

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J Formos Med Assoc. 2021.

NEURAL SUBSTRATES UNDERPINNING INTRA-INDIVIDUAL VARIABILITY IN CHILDREN WITH ADHD: A VOXEL-BASED MORPHOMETRY STUDY.

Chiang HL, Lin HY, Tseng WYI, et al.

Background/purpose: Increased intra-individual variability (IIV) in reaction time (RT) is a key feature of attention-deficit/hyperactivity disorder (ADHD). However, little is known about neurobiology underpinnings of IIV in ADHD.

Methods: We assessed 55 youths with ADHD, and 55 individually-matched typically developing control (TDC) with the MRI and Conners' Continuous Performance Test. The ex-Gaussian distribution of RT was estimated to capture IIV with the parameters (sigma) and (tau). The regional brain volumes, analyzed by voxel-based morphometry, were correlated with IIV parameters.

Results: We found both distinct and shared correlations among ADHD and TDC. For grey matter, there were significant ¤â-by-group interactions in the cingulate cortex and thalamus and also a-by-group interaction in the right inferior frontal gyrus. There was also shared negative associations between ¤â and regional volumes of the right posterior cerebellum and a positive association between ¤ä and the right anterior insula. For white matter, there was a significant by-group interaction in the genu of the corpus callosum and significant by-group interactions in the right anterior corona radiata, the left splenium of the corpus callosum, and bilateral posterior cerebellum. There were also shared patterns that increased ¤ä was associated with increased regional volumes of the right anterior corona radiata and decreased regional volumes of the right posterior limb of the internal capsule.

Conclusion: This study highlights that brain regions responsible for the motor, salience processing and multimodal information integration are associated with increased IIV in youths with ADHD

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Kranion. 2020;15:5-12.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN ADULTS.

Fernández-Mayoralas DM, Jaon AF.

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurobiological disorder frequent in childhood and adulthood. The main symptoms are attention disorder and/or impulsivity and/or hyperactivity. There are different subtypes of ADHD according to the degree of presence of these three symptoms. The social, personal, family and occupational disruption observed in these patients are necessary for classification and depends on clinical severity, early and adequate diagnosis and treatment. The early detection improves the prognosis and reduces morbidity. There are different therapeutic approaches with high proved effectiveness. This current article develops the theoretical and practical bases for an appropriate approach of adult ADHD and an assessment of the different treatment options

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Medical Forum Monthly. 2021;32:155-59.

FREQUENCY OF SOURCES OF REFERRAL OF CHILD PSYCHIATRIC CASES AT HYDERABAD.

Shaikh H, Junejo J, Dhingra LC, et al.

Objective: This study is designed to determine the frequency of sources of referral of child psychiatric cases.
Study Design: Cross-sectional study.
Place and Duration of Study: This study was conducted at the Sir Cowasji Jehangir Institute of Psychiatry (CJIP) and Liaquat University Hospital (LUH), Hyderabad from June 2018 to Feb 2019.
Materials and Methods: 175 children with psychiatric problems were included in this study. History was taken for the duration of symptoms and the source of referrals was inquired. All information was noted in the proforma.
Results: 67.43% (118/175) sources of referral were parents, schoolteachers were responsible for 10.29% (18/175), and doctors for 22.29% (39/175).
Conclusion: Mental disorders are among the most burdensome of all classes of disease because of their high prevalence, chronicity, early age of onset, and resulting in serious impairment and disability

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Molecules. 2021 Jun;26.

PLS-DA MODEL FOR THE EVALUATION OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS THROUGH BLOOD SERUM FTIR SPECTRA.

Ogruc IG, Karadag A, Kaygisiz E, et al.

Attention deficit and hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. It affects ~10% of the world's population of children, and about 30-50% of those diagnosed in childhood continue to show ADHD symptoms later, with 2-5% of adults having the condition. Current diagnosis of ADHD is based on the clinical evaluation of the patient, and on interviews performed by clinicians with parents and teachers of the children, which, together with the fact that it shares common symptoms and frequent comorbidities with other neurodevelopmental disorders, makes the accurate and timely diagnosis of the disorder a difficult task. Despite the large effort to identify reliable biomarkers that can be used in a clinical environment to support clinical diagnosis, this goal has never been achieved hitherto. In the present study, infrared spectroscopy was used together with multivariate statistical methods (hierarchical clustering and partial least-squares discriminant analysis) to develop a model based on the spectra of blood serum samples that is able to distinguish ADHD patients from healthy individuals. The developed model used an approach where the whole infrared spectrum (in the 3700-900 cm(-1) range) was taken as a holistic imprint of the biochemical blood serum environment (spectroscopic biomarker), overcoming the need for the search of any particular chemical substance associated with the disorder (molecular biomarker). The developed model is based on a sensitive and reliable technique, which is cheap and fast, thus appearing promising to use as a complementary diagnostic tool in the clinical environment

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Monatsschr Kinderheilkd. 2021.

DRUG TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: BENEFITS AND RISKS.

Frey M.

Attention deficit hyperactivity disorder (ADHD) as a-áclinical diagnosis requires conscientious diagnostics, taking developmental, psychological and gender-specific characteristics into account. The assessment of the severity of ADHD enables the indications for drug treatment against the background of the multimodal treatment regimen. If the indications exist, the benefit is clearly established. Methylphenidate is the first choice in otherwise healthy and not previously treated patients between 6-áand 17-áyears of age. In particular, weight and growth progression and possible cardiac side effects must be considered during treatment. The treatment of ADHD is multimodal and medication is accompanied by appropriate psychosocial interventions according to the overall constellation

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Neuroimage Clin. 2021;30:102662.

NEURAL BASIS OF WORKING MEMORY IN ADHD: LOAD VERSUS COMPLEXITY.

Mukherjee P, Hartanto T, Iosif AM, et al.

Working memory (WM) deficits are key in attention deficit hyperactivity disorder (ADHD). Nevertheless, WM is not universally impaired in ADHD. Additionally, the neural basis for WM deficits in ADHD has not been conclusively established, with regions including the prefrontal cortex, cerebellum, and caudate being implicated. These contradictions may be related to conceptualizations of WM capacity, such as load (amount of information) versus operational-complexity (maintenance-recall or manipulation). For instance, relative to neurotypical (NT) individuals, complex WM operations could be impaired in ADHD, while simpler operations are spared. Alternatively, all operations may be impaired at higher loads. Here, we compared the impact of these two components of WM capacity: load and operational-complexity, between ADHD and NT, behaviorally and neurally. We hypothesized that the impact of WM load would be greater in ADHD, and the neural activation would be altered. Participants (age-range 12-23 years; 50 ADHD (18 females); 82 NT (41 females)) recalled three or four objects (load) in forward or backward order (operational-complexity) during functional magnetic resonance imaging scanning. The effects of diagnosis and task were compared on performance and neural engagement. Behaviorally, we found significant interactions between diagnosis and load, and between diagnosis, load, and complexity. Neurally, we found an interaction between diagnosis and load in the right striatum, and between diagnosis and complexity in the right cerebellum and left occipital gyrus. The ADHD group displayed hypo-activation compared to NT group during higher load and greater complexity. This informs mechanisms of functional problems related to WM in adolescents and young adults with ADHD (e.g., academic performance) and remedial interventions (e.g., WM-training)

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NeuroImage Clin. 2021;31.

INCREASED INTERHEMISPHERIC SOMATOMOTOR FUNCTIONAL CONNECTIVITY AND MIRROR OVERFLOW IN ADHD.

Chen C, Lidstone D, Crocetti D, et al.

Mirror overflow is a developmental phenomenon defined as unintentional movements that mimic the execution of intentional movements in homologous muscles on the opposite side of the body. In children with attention-deficit/hyperactivity disorder (ADHD), mirror overflow is commonly excessive, abnormally persistent, and correlated with ADHD symptom severity. As such, it represents a promising clinical biomarker for disinhibited behavior associated with ADHD. Yet, the neural underpinnings of mirror overflow in ADHD remain unclear. Our objective was to test whether intrinsic interhemispheric functional connectivity between homologous regions of the somatomotor network (SMN) is associated with mirror overflow in school age children with and without ADHD using resting state functional magnetic resonance imaging. To this end, we quantified mirror overflow in 119 children (8ΓÇô12 years old, 62 ADHD) during a finger sequencing task using finger twitch transducers affixed to the index and ring fingers. Group ICA was used to identify right- and left-lateralized SMNs and subject-specific back reconstructed timecourses were correlated to obtain a measure of SMN interhemispheric connectivity. We found that children with ADHD showed increased mirror overflow ($p < 0.001$; $d = 0.671$) and interhemispheric SMN functional connectivity ($p = 0.023$; $d = 0.521$) as compared to typically developing children. In children with ADHD, but not the typically developing children,

there was a significant relationship between interhemispheric SMN functional connectivity and mirror overflow (t = 2.116; p = 0.039). Our findings of stronger interhemispheric functional connectivity between homologous somatomotor regions in children with ADHD is consistent with previous transcranial magnetic stimulation and diffusion-tractography imaging studies suggesting that interhemispheric cortical inhibitory mechanisms may be compromised in children with ADHD. The observed brain-behavior correlation further suggests that abnormally strong interhemispheric SMN connectivity in children with ADHD may diminish their ability to suppress overflow movements

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NeuroImage Clin. 2021;31.

CUMULATIVE EXPOSURE TO ADHD MEDICATION IS INVERSELY RELATED TO HIPPOCAMPUS SUBREGIONAL VOLUME IN CHILDREN.

Fotopoulos NH, Devenyi GA, Guay S, et al.

Background: Although there is some evidence for a normalization of brain structure following exposure to ADHD medication, literature on the effects of duration and dose of continued use on the brain is scarce. Here, we investigated the association between cumulative exposure to medication (range 1 week to 4.69 years) and cortical structures and subcortical volumes in a clinical sample of children with ADHD taking medication (n = 109). To the best of our knowledge, this is the first structural MRI study investigating the effects of cumulative exposure to medication on subregional volumes in children treated for ADHD.

Methods: Cumulative exposure to ADHD medication (CEM) was defined as the product of duration on medication (days) and dose (mg/day), yielding the area under the curve (total mg). Cortical thickness and surface area measurements (CIVET-1.1.12), and subcortical volumes in 51 regions (MAGeT-Brain) were analyzed using general linear modelling.

Results: Significant effects of CEM were found in two subregions of the left hippocampus, the CA1 (df = 95; q = 0.003) and the strata radiatum/lacunosum/moleculare (df = 95; q = 0.003). Specifically, higher CEM was associated with smaller volumes within these subregions. No effects of medication exposure were detected on cortical thickness or surface area.

Conclusions: Although this study is cross-sectional, the results found within this sample of children show that prolonged ADHD medication use at higher doses is significantly associated with smaller hippocampus volumes in specific subregions. More research is required to determine whether these results are reproduced in other samples of children of ADHD, and further, whether these are beneficial or off-target effects of the medication

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Neuropsychiatr Dis Treat. 2021;17:1751-62.

THE EFFECT OF VILOXAZINE EXTENDED-RELEASE CAPSULES ON FUNCTIONAL IMPAIRMENTS ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS IN FOUR PHASE 3 PLACEBO-CONTROLLED TRIALS.

Nasser A, Hull JT, Liranso T, et al.

Purpose: The ADHD Rating Scale (ADHD-RS) assesses 18 symptoms of inattention and hyperactivity/impulsivity and has been used in many clinical trials to evaluate the treatment effect of drugs on ADHD. The fifth edition of this scale (ADHD-RS-5) also assesses the impact of inattention and hyperactivity/impulsivity symptoms on six domains of functional impairment (FI): family relationships, peer relationships, completing/returning homework, academic perfor- mance at school, controlling behavior at school, and self-esteem. Here, we report the effect of viloxazine extended-release capsules (viloxazine ER), a novel nonstimulant treatment for ADHD in children and adolescents (ages 6-17 years), on FI from a post hoc analysis of four randomized, double-blind, placebo-controlled Phase 3 clinical trials (N=1354).

Patients and Methods: ADHD-RS-5 investigator ratings of ADHD symptoms and FIs were conducted at baseline and weekly post-baseline for 6-8 weeks in the four trials. Change from baseline (CFB) in ADHD-RS-5 FI scores (Total score [sum of 12 FI items] and Inattention and Hyperactivity/Impulsivity subscale scores [sum of 6 corresponding FI items]) and the 30% and 50% Responder Rates (ADHD-RS-5 FI Total score) were compared between viloxazine ER and placebo.

Results: The reduction (improvement) in ADHD-RS-5 FI scores (Total and subscale scores) and the percentage of responders (30% and 50%) at Week 6 were significantly greater in each viloxazine ER dose group vs placebo. In the 100-400 mg/day viloxazine ER groups, improvements were found as early as Week 1 (100-mg/day) or Week 2 (200-, 400-mg/day) of treatment. Analysis of individual items of ADHD-related FIs demonstrated that the effect of viloxazine ER was observed across all domains of impairment.
Conclusion: Significant improvements observed in ADHD-related FIs are consistent with the reduction in inattention and hyperactivity/impulsivity symptoms demonstrated in the viloxazine ER Phase 3 pediatric trials. Therefore, viloxazine ER provides clinically meaningful improvement of ADHD symptoms and functioning in children and adolescents with ADHD, starting as early as Week 1-2 of treatment

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Neuropsychiatr Dis Treat. 2021;17:1965-75.

DO TEACHERS CONFIRM PARENT'S RATINGS OF ADHD DSM-IV CRITERIA? A STUDY OF A MEXICAN POPULATION.

Chamorro Y, Bola+¦os L, Trejo S, et al.

Background and Objective: Collecting information from different raters is important for diagnosing ADHD, but several factors can lead to gathering discrepant information. Our aim was to determine the agreement between parent and teacher's when rating the list of ADHD symptoms (criterion A, DSM-IV) in a sample of Mexican school-age children. We explored whether inter-rater agreement varied by childrenΓÇÖs age and sex, and each symptom of inattention, hyperactivity, and impulsivity.
Methods: A total of 789 children (335 girls) from six elementary school grades grouped as G1 [grades 1-2], G2 [grades 3-4], and G3 [grades 5-6]) were rated by their parents and teachers. We identified inter-rater reliability by using Cohen's kappa coefficient by school level, sex, and ADHD symptoms. We explored the presence of symptoms considering parents and teachers ratings, individually and collapsed, using the AND/OR rules.
Results: Low inter-rater agreement was observed. Moderate levels were observed in G1, but not in G2 or G3. Both groups of informants reported that more boys than girls met these criteria, but agreement by sex was still low, as were the results of the analyses by individual symptoms. Among the children that met the ADHD criteria, an inattention symptom was the one most frequently reported by both raters, whereas among non-ADHD children, a hyperactive symptom was the one most often reported.
Discussion: The exclusive use of questionnaires fails to provide convergent information between raters. We highlight the importance of conducting comprehensive clinical histories when diagnosing ADHD in order to explore what these discrepancies show about the relationship symptoms/context

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Neuropsychiatrie. 2021.

PRACTITIONER'S REVIEW: MEDICATION FOR CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER (ASD) AND COMORBID CONDITIONS.

Popow C, Ohmann S, Plener P.

Alleviating the multiple problems of children with autism spectrum disorder (ASD) and its comorbid conditions presents major challenges for the affected children, parents, and therapists. Because of a-ácomplex psychopathology, structured therapy and parent training are not always sufficient, especially for those patients with intellectual disability (ID) and multiple comorbidities. Moreover, structured therapy is not available for a-álarge number of patients, and pharmacological support is often needed, especially in those children with additional attention deficit/hyperactivity and oppositional defiant, conduct, and sleep disorders

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Neurosci Lett. 2021;760.

POLYGENIC RISK OF GENES INVOLVED IN THE CATECHOLAMINE AND SEROTONIN PATHWAYS FOR ADHD IN CHILDREN.

Wang Y, Wang T, Du Y, et al.

It is general acknowledged that genes play a vital role in the etiology of attention deficit/hyperactivity disorder (ADHD). The relationship between the genes involved in catecholamine (dopamine, noradrenaline)/serotonin transmissions and ADHD has been widely described in medical literature. A pathway-based study was conducted in this study to test the association of gene-gene interaction and the cumulative effect of genetic

polymorphisms within the dopamine, norepinephrine, and serotonin neurotransmitter pathways with ADHD susceptibility. A case-control study was conducted among Chinese children, and 168 ADHD patients and 233 controls were recruited using a combination diagnosis according to the DSM-IV ADHD rating scale. Classification and regression tree (CART) analysis was conducted to explore the gene-gene interaction, and logistic regression modal was applied to estimate the polygenic risk of the potential multiple genetic variants. The results of CART analyses indicated that the children carrying the combination of ADRA2A rs553668GG/GA and SLC6A4 rs6354 GG/GT genotypes displayed a 6.15-fold increased risk of ADHD, compared to those with the combination of ADRA2A rs553668 AA and ANKK1 rs1800497 AA genotypes. The unfavorable alleles of ADRA2A rs553668 G, DRD2 rs1124491 G and SLC6A4 rs6354 G showed cumulative effects on ADHD, and the OR for ADHD may increase by 1.42 times when the number of unfavorable allele number increased by one. Those findings reveal the importance of the gene-gene interactions and polygenic effects of many common variants to ADHD susceptibility, even the effect of each variant is very small

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Nord J Psychiatry. 2021.

THE ASSOCIATION BETWEEN PRAGMATIC LANGUAGE IMPAIRMENT, SOCIAL COGNITION AND EMOTION REGULATION SKILLS IN ADOLESCENTS WITH ADHD.

Çiray RO, et al.

Objective: Attention Deficit and Hyperactivity Disorder (ADHD) is associated with significant pragmatic language impairment and theory of mind deficits, but there are only a handful of studies have investigated the relationship between them in these conditions. This study aimed that investigate two different aspects of Theory of Mind (ToM) (ToM decoding and reasoning), pragmatic language impairment, and emotion regulation in patients with ADHD.

Method: Seventy adolescents with ADHD were compared to matched 64 healthy controls. We administered Social Responsiveness Scale-2 (SRS-2), Difficulties in Emotion Regulation Scale (DERS), Kiddie-SADS, Conners Parent Rating Scale, Children's Communication Checklist-2 (CCC-2), Faux Pas, Comprehension Test, and Reading Mind in the Eyes Test (RMET) to all study participants.

Results: The CCC-2 scores were found to be statistically significantly higher in the ADHD group than in healthy controls. ADHD group had lower performance in the Faces Test and RMET compared to healthy controls, which did not survive from false discovery rate correction. We also found that CCC-2 performance and Conners scores were significant predictors of social responsiveness.

Conclusion: Our results point to widespread impairment in pragmatic language use and communication from many perspectives. These results might be important to understand the difficulties in social functioning and interpersonal relationship in adolescents with ADHD.Key points ADHD is associated with significant impairment in pragmatic language use and social cognitive functions. ToM-Decoding (RMET) is impaired much more than ToM-Reasoning (Faux Pas) in ADHD. Pragmatic language skills and severity of ADHD may be significant predictors of social responsiveness. Emotion regulation problems may affect communication and pragmatic language use

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Nord J Psychiatry. 2021.

EVALUATION OF PERIPHERAL INFLAMMATORY MARKERS, SERUM B12, FOLATE, FERRITIN LEVELS AND CLINICAL CORRELATIONS IN CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD) AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Topal Z, Tufan AE, Karadag M, et al.

Aim: The aim of the current study is to compare serum B12, folate, and ferritin levels and peripheral inflammatory indicators between children with Autism Spectrum Disorders (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and healthy controls (HC) and to evaluate the correlation of those with symptoms.

Materials and Methods: A total of 203 children were evaluated (ASD = 72; ADHD = 61; HC = 70). Diagnoses of ASD and ADHD were ascertained according to Schedule for Affective Disorders and Schizophrenia for School-Age ChildrenΓÇôPresent and Lifetime Version (K-SADS-PL). Control group was chosen among the

healthy children who applied to general pediatrics outpatient clinic. Gilliam Autism Rating Scale-2 is used to assess autistic symptoms and Atilla Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale is used for ADHD symptoms.
Results: Neutrophil levels (p = 0.014) and neutrophil/lymphocyte ratio (NLR) (p = 0.016) were higher in the ADHD and ASD groups compared to HC. Neutrophil values explained 70.1% of the variance across groups while NLR explained a further 29.9% of the variance. NLR significantly correlated with social interaction problems in ASD (r = 0.26, p = 0.04). There were no significant differences between groups in terms of vitamin B12, folate and ferritin levels.
Conclusion: Our results may support involvement of inflammation in the underlying pathophysiology of neurodevelopmental disorders. However, these parameters should be analyzed in a wider population to clarify the effect on the etiology and symptomatology of neurodevelopmental disorders

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Nutrients. 2021 Jun;13.
FUSSY EATING AMONG CHILDREN AND THEIR PARENTS: ASSOCIATIONS IN PARENT-CHILD DYADS, IN A SAMPLE OF CHILDREN WITH AND WITHOUT NEURODEVELOPMENTAL DISORDERS.
Thorsteinsdottir S, Olsen A, Olafsdottir AS.
Parents are important agents in shaping children's eating habits. However, the associations between children's and parents' eating behaviors are complex and may be convoluted for various reasons, such as parenting feeding styles, stressful mealtimes, and children's neurodevelopmental disorders (ND), such as Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD). The purpose of this study was to analyze associations between parents and their children's fussy eating, in a cross-sectional sample of children, with and without ND. Ninety-seven parents answered screening questionnaires prior to an intervention study. Associations were investigated using two-way ANOVAs and chi-square analyses. Overall, children with ND accepted fewer food items and consumed unhealthier foods more frequently than children without ND. Fussy eating parents had children who accepted fewer food items and consumed unhealthier foods more frequently than children whose parents were not fussy eaters. Interaction effects were not significant. A higher proportion of fussy eating parents, than non-fussy eating parents, had children who had difficulties with combined foods and hidden ingredients. The findings highlight the need for further investigation into the relationships between parents' influence on their children's eating behavior and food consumption, as well as possible reciprocal impacts

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Paediatr Anaesth. 2021;31:282-89.
HYPOTENSION AND ADVERSE NEURODEVELOPMENTAL OUTCOMES AMONG CHILDREN WITH MULTIPLE EXPOSURES TO GENERAL ANESTHESIA: SUBANALYSIS OF THE MAYO ANESTHESIA SAFETY IN KIDS (MASK) STUDY.
Gleich SJ, Shi Y, Flick R, et al.
Background: The potential adverse effects of exposures to general anesthesia on the developing human brain remain controversial. It has been hypothesized that hypotension accompanying anesthesia could be contributory. We hypothesized that among children exposed to multiple anesthetics prior to age 3, children developing adverse neurodevelopmental outcomes would be more likely to have intraoperative hypotension.
Methods: Two previously published study cohorts were utilized for analysis: the retrospective and prospective Mayo Anesthesia Safety in Kids cohorts. The two lowest consecutive systolic blood pressure measurements were abstracted and standardized by calculating a z-score for noninvasive blood pressure reference ranges for children. The lowest systolic blood pressure z-score (continuous variable) and intraoperative hypotension (lowest systolic blood pressure z-score <1.0) were used to assess the association of intraoperative hypotension with the incidence of learning disabilities or attention-deficit/hyperactivity disorder(retrospective cohort) and factor scores/cluster membership (prospective cohort).
Results: One hunderd and sixteen and 206 children with multiple exposures to general anesthesia were analyzed in the retrospective and prospective cohorts with mean lowest systolic blood pressure z-scores 0.26 (SD 1.02) and 0.62 (SD 1.10), respectively. There was no overall association of the lowest z-score or hypotension with learning disabilities or attention-deficit/hyperactivity disorder in the retrospective cohort. In

the prospective cohort, there was no overall association of the lowest systolic blood pressure or hypotension with factor scores or cluster membership.
Conclusions: We did not find evidence to support the hypothesis that, among children exposed to multiple anesthetics prior to age 3, children developing adverse neurodevelopmental outcomes would be more likely to have intraoperative hypotension compared with those who did not

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Paediatr Perinat Epidemiol. 2021;35:26-27.

LONG-TERM FOLLOW-UP OF CHILDREN CONCEIVED WITH ASSISTED REPRODUCTIVE TECHNIQUES-ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND 9TH GRADE SCHOOL PERFORMANCE IN THE SWEDISH POPULATION.

Wang C, Johansson ALV, Malmros CA, et al.

Objective: To examine the relationship between use of assisted reproductive techniques (ART) and offspring Attention Deficit Hyperactivity Disorder (ADHD) and 9th grade school performance in a nation-wide cohort with ability to account for a wide range of background factors, including underlying infertility. Design Register-based cohort study. Setting and Participants All children born in Sweden between 1983 and 2006. Exposures In-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), reported by IVF-clinics, medical records, and mothers at the first antenatal visit.
Main Outcomes and Measures: Cases of ADHD were identified in registers via specialist diagnosis and/or use of ADHD medication. The school register provided final grade average (0-20) and eligibility for upper secondary school. Children conceived with ART were compared to naturally conceived children (1) from the population, and (2) from couples with known trouble conceiving, while adjusting for background factors.
Results: The study included a total of 2 420 101 children. Overall, children conceived with ART were at lower risk of ADHD (Hazard Ratio (HR) = 0.81 [95% CI 0.75-0.88]) and did slightly better in lower secondary school (average grade mean difference (MD) = 1.10 [95% CI 1.01-1.20]; eligibility Odds Ratio (OR) = 1.45 [95% CI 1.31-1.61]), but once maternal characteristics were taken into account they rather appeared at a slight disadvantage. In the comparison to children of couples with known trouble conceiving, a similar overall advantage was simply attenuated toward the null (HR = 0.94 [95% CI 0.86-1.02]; MD = 0.05 [95% CI -0.04-1.15]; OR = 1.01 [95% CI 0.90-1.10]). Further comparison of children conceived with IVF alone vs IVF and ICSI showed no differences in the risk of ADHD.
Conclusions: This study provides additional reassurance concerning offspring neurodevelopment following ART, finding no indication for concern about children's risk of ADHD or overall performance in school

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Paediatr Perinat Epidemiol. 2021;35:13.

DOES EXPOSURE TO ORGANOPHOSPHATE ESTERS DURING PREGNANCY INCREASE THE RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN OFFSPRING?

Choi G, Keil AP, Richardson DB, et al.

Background: Recent studies have linked organophosphate esters (OPEs) during pregnancy to offspring hyperactivity and attention problems. Such behaviors are often found in children with attention-deficit hyperactivity disorder (ADHD). However, prenatal exposure to OPEs has not been investigated as a risk factor for clinically diagnosed ADHD.
Aim: To evaluate associations between prenatal OPEs exposure and childhood ADHD diagnosis in a case-cohort substudy of the Norwegian Mother, Father and Child (MoBa) cohort, run by the Norwegian Institute of Public Health.
Methods: We identified ADHD cases in MoBa through linkage to the Norwegian patient registry and sampled a sub-cohort among the eligible population in MoBa as controls. Diphenyl phosphate (DPHP) and bis(1,3-dichloro- 2- propyl) phosphate (BDCIPP) concentrations were measured in maternal urine collected at 17 weeks' gestation. Binary exposure indicators were created for DPHP using the median, and BDCIPP using the limit of detection. We estimated adjusted odds ratios (aORs) with logistic regression, considering the season of urine collection, child sex, birth year, maternal depression, and phthalate metabolite concentrations. Missing covariates were multiply imputed and estimates were pooled using Rubin's rules. Effect measure modification by child sex was investigated.

Results: DPHP was detected in nearly all samples (98%), with a higher geometric mean among ADHD cases (0.70 ng/mL; N = 297) as compared to the sub-cohort (0.52 ng/mL; N = 555). BDCIPP was detected in 26% of the ADHD cases and 21% of the sub-cohort. Children whose mothers had above the median DPHP concentrations during pregnancy were more likely to be diagnosed with ADHD (aOR: 1.55 [95% CI: 1.08, 2.22]). We did not observe strong evidence of an association between BDCIPP and ADHD (1.17 [0.78, 1.76]), nor modification by child sex.
Conclusions: DPHP exposure during pregnancy may increase the risk of ADHD in offspring

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Pediatrics. 2021;148.

ASSISTED REPRODUCTIVE TECHNIQUES, ADHD, AND SCHOOL PERFORMANCE.

Wang C, Johansson ALV, Rodriguez-Wallberg KA, et al.

OBJECTIVES: To examine the long-term impact of assisted reproductive techniques (ART) on offspring neurodevelopment, accounting for parental factors and the role of infertility.
METHODS: Linkage of national registers allowed follow-up of >2.4 million children born in Sweden 1986-2012. Information on ART was retrieved from fertility clinics, medical records, and maternal self-report. Attention-deficit/hyperactivity disorder (ADHD) was identified from specialist diagnosis and/or use of medication through 2018. School performance was assessed from records of ninth year final grade averages (0ΓÇô20) and eligibility for upper secondary school through 2017.
RESULTS: Children conceived with ART had lower risk of ADHD (hazard ratio 0.83; 95% confidence interval [CI]: 0.80 to 0.87) and did better in school (grade mean difference 1.15; 95% CI: 1.09 to 1.21 and eligibility odds ratio 1.53; 95% CI: 1.45 to 1.63) compared with all other children. Differences in parental characteristics explained and even reversed associations, whereas no disadvantage was seen when the comparison was restricted to children of couples with known infertility (adjusted hazard ratio 0.95; 95% CI: 0.90 to 1.00, adjusted mean difference 0.05; 95% CI: -0.01 to 0.11, and adjusted odds ratio 1.03; 95% CI: 0.96 to 1.10). Among children conceived with ART, there was furthermore no indication that intracytoplasmic sperm injection (compared with standard in vitro fertilization) or frozen (compared with fresh) embryo transfer had any adverse influence.
CONCLUSIONS: With this nationwide, long-term follow-up, we provide additional reassurance concerning offspring neurodevelopment after use of ART, finding no indication for concern about risk of ADHD or school performance in adolescence

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Pharmacology and Therapeutics. 2021.

EVIDENCE-BASED PHARMACOLOGICAL TREATMENT OPTIONS FOR ADHD IN CHILDREN AND ADOLESCENTS.

Mechler K, Banaschewski T, Hohmann S, et al.

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity, causing functional impairment. Its prevalence lies at approximately 5% in children and adolescents and at approximately 2.5% in adults. The disorder follows a multifactorial etiology and shows a high heritability. Patients show a high interindividual and intraindividual variability of symptoms, with executive deficits in several cognitive domains. Overall, ADHD is associated with high rates of psychiatric comorbidities, and insufficient treatment is linked to adverse long-term outcomes. Current clinical guidelines recommend an individualized multimodal treatment approach including psychoeducation, pharmacological interventions, and non-pharmacological interventions. Available medications include stimulants (methylphenidate, amphetamines) and non-stimulants (atomoxetine, guanfacine, clonidine). While available pharmacological treatment options for ADHD show relatively large effect sizes (in short-term trials) and overall good tolerability, there is still a need for improvement of current pharmacotherapeutic strategies and for the development of novel medications. This review summarizes available pharmacological treatment options for ADHD in children and adolescents, identifies current issues in research and evidence gaps, and provides an overview of ongoing efforts to develop new medications for the treatment of ADHD in children and adolescents by means of a systematic cross-sectional analysis of the clinical trials registry www.clinicaltrials.gov

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Pharmacol Biochem Behav. 2021;208.

METHYLPHENIDATE AND ATOMOXETINE TREATMENT NEGATIVELY AFFECT PHYSICAL GROWTH INDEXES OF SCHOOL-AGE CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Deng L, Zhou P, Zhu L, et al.

Aim: To determine the effects of drug therapy on the physical growth of school-age children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Method: The medical records of 86 participants (average age: 8.9 -¦ 2.2 years) with ADHD prescribed methylphenidate (MPH) or atomoxetine (ATX) for ΓëÑ24 weeks from the Children's Hospital of Chongqing Medical University were analysed.

Results: The Z-scores of height, weight and body mass index (BMI) of children with ADHD decreased significantly over the first six months of MPH treatment (P < 0.001). The slopes of the fitting lines after the first six months of MPH (0.18, 0.58 and 0.69, respectively) returned over the entire treatment (the slopes changed to 0.027, 0.26 and 0.20, respectively). For ATX, the Z-scores of height of children decreased significantly over the first six months (P < 0.001), but the Z-scores of weight and BMI did not (P > 0.05). The slopes of the fitting lines after the first six months of ATX (0.058, 0.032 and 0.0094, respectively) changed over the entire treatment (slopes were 0.16, 0.52 and 0.26, respectively). Children taking MPH were more likely to report decreased appetite (P < 0.05). The weight and BMI of the children receiving MPH were significantly correlated with decreased appetite (P < 0.01).

Conclusion: The physical growth indexes (PGIs) of school-age children and adolescents with ADHD were negatively affected while taking MPH, and these effects were gradually mitigated with continued treatment. ATX hardly had negative effects on weight and BMI. Neither MPH nor ATX had a significant negative effect on the height of children in long-term ADHD treatment. It is necessary for clinicians to consider children's diet during treatment

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PLoS ONE. 2021;16.

SUSTAINED BENEFITS OF COGNITIVE TRAINING IN CHILDREN WITH INATTENTION, THREE-YEAR FOLLOW-UP.

Jurigova BG, Gerdes MR, Anguera JA, et al.

The goal of this study was to test for long-term benefits three years after the completion of a cognitive training intervention (Project: EVOΓäó) in a subset of children with Sensory Processing Dysfunction (SPD). Our initial findings revealed that children with SPD who also met research criteria for Attention Deficit Hyperactivity Disorder (SPD+IA) showed a significant decrease in parent-observed inattentive behaviors, which remained stable in a ninemonth follow-up assessment. Forty nine caregivers of participants who completed the Project: EVOΓäó training were contacted to be included in this follow up study. Each was emailed an invitation to complete the Vanderbilt ADHD Diagnostic Parent Rating Scale, which yielded a completion rate of 39/49 (80%). A Generalized Estimating Equations analysis was used to assess changes in symptoms over time, specifically to determine whether the initial improvements were retained. The SPD+IA cohort continued to show sustained benefits on their parent-reported scores of inattention, with 54% of SPD+IA individuals no longer meeting criteria for ADHD three years following intervention. These findings provide initial insights into the potential long-term benefits of a digital health intervention for children with attentionbased issues

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Psychiatry Res. 2021;303.

THE RELATIONSHIP BETWEEN INTELLIGENCE AND GLOBAL ADAPTIVE FUNCTIONING IN YOUNG PEOPLE WITH OR WITHOUT NEURODEVELOPMENTAL DISORDERS.

Ñsberg Johnels J, Yngvesson P, Billstedt E, et al.

Previous studies have shown an association between IQ and adaptive global functioning, i.e. how well a person is functioning in different domains of life. However, it is unclear to what extent such an association applies in children with neurodevelopmental disorders (NDDs). The study group consisted of 550 population-screened children assessed with the K-SADS, WISC-IV, and the C-GAS. Approximately half of the sample had been diagnosed with one or several NDDs (ADHD, autism, language disorder and tic disorder). A factorial ANOVA with IQ level and the presence of NDD was conducted, with C-GAS score as the dependent variable. Results revealed a significant interaction effect between IQ-group and NDD-status. In the non-NDD

group (49% girls), higher IQ scores were clearly linked with better global adaptive functioning. Among children with NDDs (35% girls), however, higher IQ scores were not clearly associated with better functioning. Thus, the association between IQ and adaptive functioning were found to differ depending on the presence of NDD. These results have implications for the interpretation of IQ test results in neurodevelopmental assessments and point towards the importance of providing support based on an assessment of needs and functioning rather than scores from IQ tests

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Psychol Assess. 2021 Jul.

THE INTERTEACHER RELIABILITY OF ASSESSMENTS OF ADOLESCENTS.

Morris S, Ling M, Sheen J, et al.

Teachers are uniquely placed to comment on the psychosocial functioning of their students. In particular, teacher report of symptoms and functional impairment is crucial in a diagnostic assessment of Attention-deficit Hyperactivity Disorder (ADHD). For adolescents, however, schooling structures and other factors can influence the reliability of teacher reports. Clarity is needed for both clinicians and researchers regarding the interteacher reliability across different domains in the assessment of adolescents. This study investigated interrater reliability of teacher reports of adolescents using data from the 72-month follow-up of the National Institute of Mental Health (NIMH) Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) when participants were 13–15.9 years old. For adolescents with a history of ADHD (MTA; N = 177–210), and a normative comparison group (Local Normative Control Group [LNCG]; N = 100–125), intraclass correlations (ICC) were examined between Math and English teacher reports of ADHD symptoms, externalizing behavior, scholastic competence, and social functioning. Results indicate poor to moderate reliability in the assessment of adolescents with a history of ADHD for core ADHD symptoms, social functioning and scholastic competence, and moderate to good reliability of externalizing behavior. Interteacher reliability was better for the normative comparison group in all domains except social functioning, which was also poor to moderate. Clinicians and researchers should be aware of potential inconsistencies in teacher reports and where possible collect multiple teacher reports to maximize reliability. Further implications for research and clinical practice are explored.

Teacher-reported symptoms and functioning of adolescents are important for the assessment and management of Attention-deficit Hyperactivity Disorder (ADHD), however, there are likely to be discrepancies between the ratings different teachers provide. This study demonstrates that teacher reports of adolescent functioning vary considerably, particularly regarding social functioning and ADHD symptoms. (PsycInfo Database Record (c) 2021 APA, all rights reserved)

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Psychol Med. 2021 Jun;51:1279-88.

SMALLER TOTAL BRAIN VOLUME BUT NOT SUBCORTICAL STRUCTURE VOLUME RELATED TO COMMON GENETIC RISK FOR ADHD.

Mooney MA, Bhatt P, Hermosillo RJM, et al.

Background: Mechanistic endophenotypes can inform process models of psychopathology and aid interpretation of genetic risk factors. Smaller total brain and subcortical volumes are associated with attention-deficit hyperactivity disorder (ADHD) and provide clues to its development. This study evaluates whether common genetic risk for ADHD is associated with total brain volume (TBV) and hypothesized subcortical structures in children.

Methods: Children 7–15 years old were recruited for a case–control study (N = 312, N = 199 ADHD). Children were assessed with a multi-informant, best-estimate diagnostic procedure and motion-corrected MRI measured brain volumes. Polygenic scores were computed based on discovery data from the Psychiatric Genomics Consortium (N = 19 099 ADHD, N = 34 194 controls) and the ENIGMA + CHARGE consortium (N = 26 577).

Results: ADHD was associated with smaller TBV, and altered volumes of caudate, cerebellum, putamen, and thalamus after adjustment for TBV; however, effects were larger and statistically reliable only in boys. TBV was associated with an ADHD polygenic score [ß = -0.147 (-0.27 to -0.03)], and mediated a small proportion of the effect of polygenic risk on ADHD diagnosis (average ACME = 0.0087, p = 0.012). This

finding was stronger in boys (average ACME = 0.019, p = 0.008). In addition, we confirm genetic variation associated with whole brain volume, via an intracranial volume polygenic score.
Conclusion: Common genetic risk for ADHD is not expressed primarily as developmental alterations in subcortical brain volumes, but appears to alter brain development in other ways, as evidenced by TBV differences. This is among the first demonstrations of this effect using molecular genetic data. Potential sex differences in these effects warrant further examination

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Res Dev Disabil. 2021;115.

DURATION OF BREAST FEEDING AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN UNITED STATES PRESCHOOL-AGED CHILDREN.

Brasfield J, Goulding SM, Kancherla V.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by difficulties sustaining attention and controlling hyperactivity and impulsive behavior. Population-based studies concerning the association between breast-feeding duration and ADHD among preschool-aged children in the United States (U.S.) have been sparse.
Aims: To determine whether there is an association between the duration of breast feeding and ADHD in U.S. children aged 2ΓÇô5 years.
Methods and procedures: We used nationally representative data from the 2016, 2017, and 2018 National Survey of Children's Health (NSCH) to examine the association between breast-feeding duration and ADHD in U.S. preschool-aged children. Sample characteristics were compared using Rao-Scott chi-square test, and adjusted prevalence odds ratios and 95 % confidence intervals were estimated using unconditional logistic regression.
Outcomes and results: Of the 20,453 children eligible for our study, 1.5 % had received a diagnosis of ADHD and 77.5 % were reported to have been fed human milk as infants. Prevalence odds of ADHD were 57 % lower among children fed human milk for 6-12 months compared to children never fed human milk after controlling for potential confounders. Among children with durations of breast feeding lasting less than 6 months or lasting 12 months or longer, prevalence odds of ADHD were not significantly lower than the comparison group, children who were never fed human milk, after controlling for potential confounders.
Conclusions and implications: We noted an inverse association between breast feeding durations of 6-12 months and parent-reported diagnosis of ADHD in preschool-aged children in the U.S. Future studies should use longitudinal designs to examine ADHD and duration of breast-feeding measures

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Res Dev Disabil. 2021;116.

VISUAL ATTENTION SPAN AND PHONOLOGICAL SKILLS IN CHINESE DEVELOPMENTAL DYSLEXIA.

Cheng C, Yao Y, Wang Z, et al.

Background: It has been debated whether visual attention span deficit was independent from phonological deficit in alphabetic developmental dyslexia. Yet, this issue has never been examined in Chinese developmental dyslexia.
Aim: The aim of the present study was to concurrently investigate visual attention span deficit and phonological deficit in Chinese developmental dyslexia, and examine the relationship between them.
Methods: A total of 45 Chinese dyslexic and 43 control children aged between 8 and 11 years old participated in this study. A visual one-back paradigm with both verbal stimuli (character and digit strings) and nonverbal stimuli (color dots and symbols) was employed for measuring visual attention span. Phonological skills were measured by three dimensions: phonological awareness, rapid automatized naming, and verbal short-term memory.
Results: Chinese dyslexic children showed deficits in verbal visual attention span and all three dimensions of phonological skills, but not in nonverbal visual attention span. Phonological skills significantly contributed to explaining variance of reading skills and classifying dyslexic and control memberships. Almost all Chinese dyslexic participants who showed a deficit in visual attention span also showed a phonological deficit.

Conclusion: The study suggests that visual attention span deficit is not independent from phonological deficit in Chinese developmental dyslexia

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Research on Child and Adolescent Psychopathology. 2021 Jul;49:835-48.

DISTINCT PATTERNS OF IMPAIRED COGNITIVE CONTROL AMONG BOYS AND GIRLS WITH ADHD ACROSS DEVELOPMENT.

DeRonda A, Zhao Y, Seymour KE, et al.

This study examined whether girls and boys with ADHD show similar impairments in cognitive control from childhood into adolescence and the developmental relationship between cognitive control and ADHD symptoms. Participants include 8–17-year-old children with ADHD (n = 353, 104 girls) and typically developing (TD) controls (n = 241, 86 girls) with longitudinal data obtained from n = 137. Participants completed two go/no-go (GNG) tasks that varied in working memory demand. Linear mixed-effects models were applied to compare age-related changes in cognitive control for each GNG task among girls and boys with ADHD and TD controls and in relation to ADHD symptoms. Boys with ADHD showed impaired response inhibition and increased response variability across tasks. In contrast, girls with ADHD showed impaired response inhibition only with greater working memory demands whereas they displayed increased response variability regardless of working memory demands. Analysis of age-related change revealed that deficits in cognitive control under minimal working memory demands increase with age among girls with ADHD and decrease with age among boys with ADHD. In contrast, deficits in cognitive control with greater working memory demands decrease with age among both boys and girls with ADHD compared to TD peers. Among children with ADHD poor response inhibition during childhood predicted inattentive symptoms in adolescence and was associated with less age-related improvement in inattentive symptoms. These findings suggest that girls and boys with ADHD show differential impairment in cognitive control across development and response inhibition in childhood may be an important predictor of ADHD symptoms in adolescence

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Revista de Neuro-Psiquiatria. 2020;83:148-56.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS. A CLINICAL REVIEW.

Rusca-Jordín F, Cortez-Vergara C.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition whose main symptoms are inattention, hyperactivity, and impulsivity. ADHD has been associated with a model of pathophysiological heterogeneity, in which, among others, executive functions are mostly affected, generating significant difficulties in responding to certain stimuli, planning and organizing a variety of actions, reflecting on possible consequences, and inhibiting the first, initial automatic response to substitute it with a more appropriate one. ADHD accounts for up to 50% of consultations in child psychiatry, and its prevalence has been estimated between 2% and 12% of the pediatric population. It is multifactorial in origin and, in 70% of the cases, it can coexist with other psychiatric and neurological disorders. The diagnosis is basically clinical and requires, ideally, a careful medical examination as well as exhaustive interviews with parents or caregivers and teachers, as well as, the interview of the child or adolescent whenever possible. Every child or adolescent with ADHD should have a comprehensive, individualized treatment plan that considers the chronicity and impact of the condition, and involves psychopharmacological and / or therapeutic behavioral measures to improve the central manifestations of ADHD and a possible associated functional decline

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Sci J Kurdistan Univ Med Sci. 2021;26:114-25.

INVESTIGATION OF PREDICTORS OF INJURY LEADING TO MOTORCYCLIST HOSPITALIZATION: A CASE-CONTROL STUDY.

Hasanzadeh S, Asgharijafarabadi M, Sadeghi-Bazargani H.

Background and Aim: Traffic and its related problems are among the most important public health concerns in the world and prevention of these problems are necessary. GSEM model is a method to test of theoretical models and causal modeling exactly. The objective of the present study was to investigate the predictors of injuries leading to hospitalization of motorcyclists considering MRBQ as a mediator in this case-control study, using a generalized structural equation modeling (GSEM).

Methods: In this case-control study, we selected 303 cases (motorcyclists admitted for a traumatic condition) and 153 controls (motorcyclists admitted for a non-traumatic condition) using a cluster random sampling method in Tabriz, Iran. We used motorcycle-riding behavior questionnaire (MRBQ), Attention-deficit/hyperactivity disorder (ADHD) questionnaire, and a researcher-made checklist. GSEM model was used to examine the direct linear and indirect linear relationships of variables in the conceptual model, considering the binary response variable of the model. Data analysis was performed by STATA14 software.
Results: The predictors of injury were: MRBQ, ADHD, and demographic charcteristics. The results indicated significant linear and direct relationships between odds of injury and cell phone answering (OR= 2.22, P= 0.010), hyperactive child (OR= 1.65, P= 0.057), dark hour riding (OR= 1.01, P= 0.001) and MRBQ (OR= 1.27, P= 0.092), while there were significant inverse relationships between injury and marital status (OR= 0.43, P= 0.002), and academic education (OR= 0.29, P= 0.001).
Conclusions: According to the results of our study, intervention programs on the ADHD, use of cell phone while driving, and dark hour riding are highly recommended

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Seizure. 2021;91:325-31.

CLINICAL AND NEUROPSYCHOLOGICAL CHARACTERISTICS OF CHILDREN WITH EPILEPSY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Park KJ, Kim MJ, Yum MS, et al.

Objectives: This study aimed to explore the clinical and neuropsychological characteristics cognition, behavior, parenting-related stress, and sleep of children with epilepsy, attention-deficit/hyperactivity disorder (ADHD), or both.
Methods: We retrospectively reviewed the electronic medical records of 33 children with epilepsy and ADHD, 113 with epilepsy alone, and 294 with ADHD alone. The children were required to complete the Advanced Test of Attention (ATA), and their parents completed the ADHD Rating Scale (ARS), Child Behavior Checklist (CBCL), Children's Sleep Habits Questionnaire (CSHQ), Disruptive Behavior Disorder (DBD) Scale (DBD), Social Responsiveness Scale (SRS), and Parenting Stress Index-Short Form (PSI-SF).
Results: Auditory Commission Errors made during the ATA were higher in children with epilepsy and ADHD than in those with epilepsy alone. On the SRS, all the subscales except Social Awareness were significantly higher in children with epilepsy and ADHD or ADHD alone than in those with epilepsy alone. The Oppositional Defiant and Conduct Disorder subscales on DBD, Attention Problems, and Aggressive Behaviors on CBCL were significantly higher in children with both epilepsy and ADHD than in those with epilepsy alone. The Parent-Child Dysfunctional Interaction subscales on the PSI-SF were significantly greater in children with both epilepsy and ADHD than in those with epilepsy alone. The subscales on the CSHQ did not significantly differ between children with both epilepsy and ADHD and those with epilepsy alone.
Conclusions: In children with epilepsy, comorbid ADHD was associated with negative effects on response inhibition, aggressive behavior, and parenting-related stress

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Soc Sci Med. 2021;284.

WHY CAN'T YOU SIT STILL? THE EFFECT OF DAILY PHYSICAL ACTIVITY ON CHILDHOOD INATTENTION/HYPERACTIVITY AND THE EDUCATIONAL GENDER GAP.

Chen K, Phipps S.

Despite the compelling evidence of the long-run consequences of childhood inattention/hyperactivity and harmful side effects of stimulant medication, relatively little is known about accessible non-pharmacological options to reduce inattentive/hyperactive behaviours. This study evaluates the effect of daily exercise on inattentive/hyperactive behaviours among young children by leveraging evidence from a quasi-experiment generated when 3 Canadian provinces adopted mandatory requirements for all students in grades 1 through 6 to participate in 20ΓÇô30 min of daily physical activity at school between 1994 and 2009. By exploiting plausibly exogenous variations in the timing of implementation and duration of physical activity mandated as well as over 20,000 observations on a sample of nationally representative children, our difference-in-differences estimates indicate that brief bouts of daily exercise at school effectively reduce inattention/hyperactivity in children with the beneficial effect enhanced by the duration of exercise mandated.

Importantly, most of the exercise effect is concentrated on boys. Since boys' higher rates of inattention/hyperactivity contribute to the explanation for boys lagging academic motivation and achievement, we argue that providing more scope for physical activity during the school day might be a feasible policy option not only for reducing inattentive/hyperactive behaviours, but also for helping to close the educational gender gap in the longer run

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Transl Psychiatry. 2021 Jul;11:382.

GUT MICROBIOTA SIGNATURE IN TREATMENT-NAÃ¯VE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Richarte V, SÃ¡nchez-Mora C, Corrales M, et al.

Compelling evidence supports alterations in gut microbial diversity, bacterial composition, and/or relative abundance of several bacterial taxa in attention-deficit/hyperactivity disorder (ADHD). However, findings for ADHD are inconsistent among studies, and specific gut microbiome signatures for the disorder remain unknown. Given that previous studies have mainly focused on the pediatric form of the disorder and involved small sample sizes, we conducted the largest study to date to compare the gastrointestinal microbiome composition in 100 medication-naÃ¯ve adults with ADHD and 100 sex-matched healthy controls. We found evidence that ADHD subjects have differences in the relative abundance of several microbial taxa. At the family level, our data support a lower relative abundance of Gracilibacteraceae and higher levels of Selenomonadaceae and Veillonellaceae in adults with ADHD. In addition, the ADHD group showed higher levels of Dialister and Megamonas and lower abundance of Anaerotaenia and Gracilibacter at the genus level. All four selected genera explained 15% of the variance of ADHD, and this microbial signature achieved an overall sensitivity of 74% and a specificity of 71% for distinguishing between ADHD patients and healthy controls. We also tested whether the selected genera correlate with age, body mass index (BMI), or scores of the ADHD rating scale but found no evidence of correlation between genera relative abundance and any of the selected traits. These results are in line with recent studies supporting gut microbiome alterations in neurodevelopment disorders, but further studies are needed to elucidate the role of the gut microbiota on the ADHD across the lifespan and its contribution to the persistence of the disorder from childhood to adulthood

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Transl Psychiatry. 2021 Jul;11:410.

IDENTIFICATION OF PLEIOTROPY AT THE GENE LEVEL BETWEEN PSYCHIATRIC DISORDERS AND RELATED TRAITS.

Polushina T, Banerjee N, Giddaluru S, et al.

Major mental disorders are highly prevalent and make a substantial contribution to the global disease burden. It is known that mental disorders share clinical characteristics, and genome-wide association studies (GWASs) have recently provided evidence for shared genetic factors as well. Genetic overlaps are usually identified at the single-marker level. Here, we aimed to identify genetic overlaps at the gene level between 7 mental disorders (schizophrenia, autism spectrum disorder, major depressive disorder, anorexia nervosa, ADHD, bipolar disorder and anxiety), 8 brain morphometric traits, 2 cognitive traits (educational attainment and general cognitive function) and 9 personality traits (subjective well-being, depressive symptoms, neuroticism, extraversion, openness to experience, agreeableness and conscientiousness, children's aggressive behaviour, loneliness) based on publicly available GWASs. We performed systematic conditional regression analyses to identify independent signals and select loci associated with more than one trait. We identified 48 genes containing independent markers associated with several traits (pleiotropy at the gene level). We also report 9 genes with different markers that show independent associations with single traits (allelic heterogeneity). This study demonstrates that mental disorders and related traits do show pleiotropy at the gene level as well as the single-marker level. The identification of these genes might be important for prioritizing further deep genotyping, functional studies, or drug targeting

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Yeni Symp. 2020;58:11-19.

The Comparison of Self-Efficacy Beliefs of Adolescents With and Without Attention-Deficit Hyperactivity Disorder (ADHD), Parents Parental Self-Efficacy Beliefs, and ADHD Symptoms.

Yaşam Karadağ, H. Güzel

The Comparison of Self-Efficacy Beliefs of Adolescents With and Without Attention-Deficit Hyperactivity Disorder (ADHD), Parents Parental Self-Efficacy Beliefs, and ADHD Symptoms Objective: In this study, it was aimed to compare the self-efficacy beliefs of adolescents with and without attention-deficit hyperactivity disorder (ADHD), parentsΓÇÖ parental self-efficacy beliefs, and ADHD symptoms. Method: The clinical sample consisted of 46 adolescents diagnosed with ADHD between the ages of 14-17 and parents of 42 adolescents; control sample consisted of 43 adolescents without any diagnosis and their parents. Adolescent participants have completed the socio-demographic form and Self-Efficacy Scale in Adolescents; their parents have completed the Parental Self-Efficacy Scale, Wender Utah Rating Scale and Adult Attention Deficit and Hyperactivity Disorder Self-Report Scale. Results: As a result, it was found that adolescents with diagnosed ADHD have lower general and academic self-efficacy belief scores than those in the control group. Whereas it was showed that there is a significant positive relationship between self-efficacy belief scores of female adolescents in clinical and control group and the parental self-efficacy belief scores of their parents, there isn't a significant relationship between male adolescents and their parents parental self-efficacy belief scores in ADHD and control group. The parental self-efficacy belief scores of parents in clinical group were significantly lower than those in the control group. Finally, it was reported that parents with adolescents diagnosed with ADHD have adult ADHD symptoms more than those in control group whereas there was a significant difference between the fathers in terms of childhood ADHD symptoms, but no difference between the mothers of the two groups. Conclusion: The results of this study are important in terms of addressing the self-efficacy beliefs of adolescents with and without ADHD together with the parental self-efficacy beliefs of their mothers and fathers

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frontiers in Pediatrics

ORIGINAL RESEARCH
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Breastfeeding in Pediatric Acute-Onset Neuropsychiatric Syndrome: An Italian Observational Study

Manuel Murciano[1†], *Davide Maria Biancone*[2†], *Francesca De Luca*[2], *Denise Piras Marafon*[3], *Cristiana Alessia Guido*[2,4] *and Alberto Spalice*[2*]

[1] *Emergency Paediatric Department, Bambino Gesù Children's Hospital, Rome, Italy,* [2] *Child Neurology Division, Department of Pediatrics, "Sapienza" University of Rome, Rome, Italy,* [3] *Rheumatology Unit, Bambino Gesù Children's Hospital, Rome, Italy,* [4] *Department of Developmental and Social Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy*

Objective: Pediatric acute-onset neuropsychiatric syndrome (PANS) is a condition defined by sudden onset of obsessive–compulsive symptoms and/or severe eating restrictions, along with at least two other cognitive, behavioral, or neurological symptoms. Its pathogenesis is unknown but it seems triggered by infections, metabolic disturbances, and other inflammatory reactions. PANS represents a neurodevelopmental problem and infant feeding can play a role. Breast milk is the ideal food for infants and influences children's brain, cognitive, and socio-emotional development.

Methods: We enrolled 52 children diagnosed with PANS. We interviewed their parents in order to investigate perinatal history, infant feeding, neurologic development, and confounding factors like socio-economic status and region of origin. We subgrouped PANS patients into three subsets: those who only received human milk (HMO), those who only received infant formula, and those who received mixed feeding.

Results: The cohort is composed of 78.9% males, with a median age of 11 years (range 7–17). We found some neurodevelopmental problems (13.5%): walking disorders, ASD, ADHD, oppositional attitude, and delayed psychomotor development. We found scholar performance deficits (25%), including language problems like dysgraphia, dyslexia, and dyscalculia. The achievement of some milestones in the development of the infant is affected in 73.1% of cases. Breastfeeding is not homogeneously practiced in Italy because of social, economic, and cultural phenomena. The richest and the poorest families (100%) in the sample choose breastfeeding, probably with a different approach and for different reasons (awareness or need). In the group of PANS patients fed with HMO, compared to the rest of the patients, we registered fewer cases of growth problems (0 vs. 12.9%; $p = 0.14$), school performance problems or the need for school support (19.1% vs. 29%; $p = 0.42$), and a delay in the age of babbling/speaking (range 4–20 vs. 7–36 months; $p = 0.066$).

Conclusion: This is the first study that investigates the role of breastfeeding in the development of PANS. Promoting breastfeeding is important in the general population

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Piero Pavone,
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University of Padua, Italy

***Correspondence:**
Alberto Spalice
alberto.spalice@uniroma1.it

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

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and also in PANS patients because it has an important social and global health impact, also during adult life. Further studies with a bigger population are needed to investigate the mechanisms underlying PANS and the role that breastfeeding may play in their short- and long-term neurodevelopment.

Keywords: pediatric acute-onset neuropsychiatric syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, breast feeding, neurodevelopment, milk, infant formula, children

ARTICLE SUMMARY

This study investigates the role that breastfeeding may play in short- and long-term neurodevelopment in PANS patients, from birth to 15 years.

WHAT'S KNOWN ON THIS SUBJECT

PANS is a condition defined by sudden onset of obsessive–compulsive symptoms and/or severe eating restrictions, along with at least two other cognitive, behavioral, or neurological symptoms. The pathogenesis of PANS is unknown. Breast milk influences children's brain, cognitive, and socio-emotional development.

WHAT THIS STUDY ADDS

This study describes the neurodevelopmental evolution and problems among 52 PANS patients from intra-uterine life till adolescence and focuses on infant feeding, human milk, and formula, looking for a correlation with neurologic infant milestones and scholar outcomes.

INTRODUCTION

Pans and Pandas

Pediatric acute-onset neuropsychiatric syndrome (PANS) is a condition defined by sudden onset of obsessive–compulsive symptoms and/or severe eating restrictions, along with at least two other cognitive, behavioral, or neurological symptoms (1) (see **Figure 1**).

The pathogenesis of PANS is unknown, but it seems triggered by infections, metabolic disturbances, and other inflammatory reactions. Children diagnosed with PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections) have an acute onset of neuropsychiatric symptoms, specifically obsessive–compulsive disorders (OCDs) or tics. PANDAS is classified as a subset of PANS (4, 5) (see **Figure 2**).

In 2012, PANS clinical criteria were described (6) and then updated during the 2013 PANS Consensus Conference (2, 3). The PANS definition no longer includes tic disorders as a primary criterion or the restriction of cases to prepubescent children, but it emphasizes OCD and restrictive eating. This classification is helpful to standardize cohorts of patients presenting typical symptoms (2, 3, 6). The inclusion of abrupt onset of psychiatric symptoms as a criterion seems to distinguish a subset of children from others referred for evaluation for PANS.

PANS describes the clinical presentation of a subcategory of childhood OCD. PANS or PANDAS syndrome should be considered whenever symptoms of OCD, food restrictions, or tics occur and are accompanied by other emotional and behavioral changes, frequent urination, motor abnormalities, and/or changes in writing. Some authors in the literature have also correlated the close connection of the pathology with ENT (ears, nose, and throat) symptoms and the reduction of behavioral disorders after medical or surgical treatment (7–9).

Even if the pathogenesis of PANS is not clear, several studies hypothesize a mechanism known as "molecular mimicry" or rather the immunological cross-reactivity between host and bacterial antigens, above all regarding the PANDAS subgroup (10–15). It is known that the lymphocytic responses against microbial pathogens can be auto-reactive to the basal ganglia and the surrounding brain tissues (16, 17). Many PANS patients have concurrent autoimmune/inflammatory diseases: the most common are arthritis and thyroiditis. These patients have higher levels of antinuclear, anti-histone, and anti-thyroid antibodies than the general population (18). Symptoms appear to improve administering anti-inflammatory and immunosuppressive therapies (19, 20). In allergic diseases, there is a Th2-mediated immunological response (21), but the involvement of this pathway in PANS pathogenesis is not clear.

Breastfeeding, Infant Formula, and Neurodevelopment

There are no previous studies known to the authors that have investigated the role of breastfeeding in the development of PANS. Breast milk is the ideal food for infants (22, 23). It is safe and clean and contains antibodies that help protect the infant against many common childhood illnesses (24–28). Breast milk influences children's brain, cognitive, and socio-emotional development (29). WHO (World Health Organization) and UNICEF (United Nations International Children's Emergency Fund) recommend to mothers to start breastfeeding in the first hour of life and to continue to do so exclusively for the first 6

Abbreviations: PANS, Pediatric acute-onset neuropsychiatric syndrome; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections; OCD, Obsessive–compulsive disorders; ENT, ears, nose, and throat; HMO, human milk only; MF, mixed feeding; IFO, infant formula only; ARA, arachidonic acid; WHO, World Health Organization; UNICEF, United Nations International Children's Emergency Fund; LC-PUFA, long-chain polyunsaturated fatty acid; DHA, docosahexanoic acid; S/C, Sieroproteins/Caseins ratio; GOS, galacto-oligosaccharides; FOS, fructo-oligosaccharides; EPA, eicosapentaenoic acid; EU, European Union; IQ, intelligence quotient.

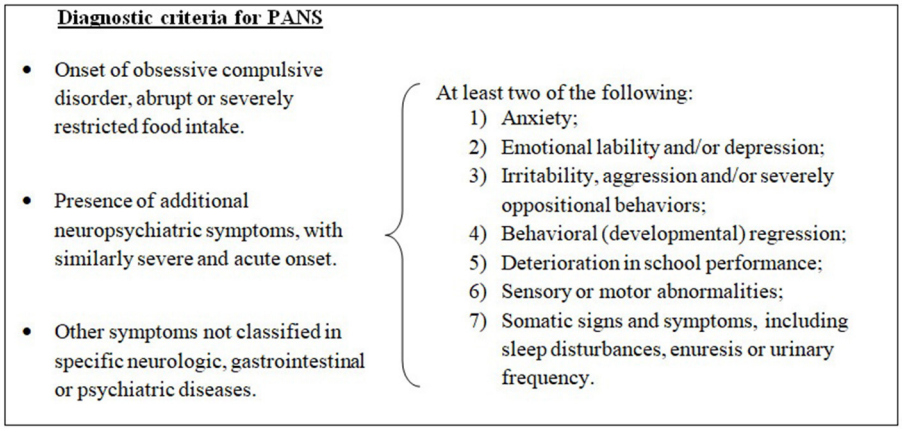

FIGURE 1 | Diagnostic criteria for pediatric acute-onset neuropsychiatric syndrome (PANS), modified from 2013 PANS Consensus Conference (2, 3).

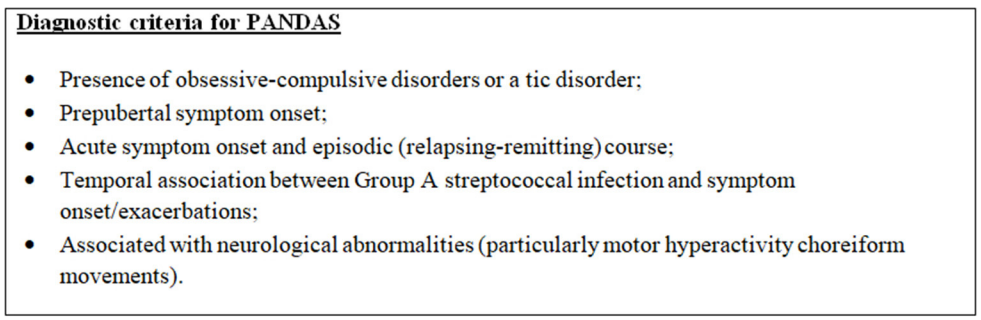

FIGURE 2 | Diagnostic criteria for Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS), modified from 2013 PANS Consensus Conference (2, 3).

months. It is essential for the survival, growth, and development of the baby in the first year of life, with an impact that affects adult life (30).

When exclusive breastfeeding is insufficient or may not be available, suitable, or solely adequate, additional milk intake should be provided. The choice of an adequate infant formula (23, 31), which mimics breast milk nutritional composition (23) (see **Table 1**), should be administrated considering the infant's characteristics and specific nutritional needs (32).

Breast milk contains essential nutrients for neurological and cognitive development (33, 34). LC-PUFAs (long-chain polyunsaturated fatty acid) (15% of human milk fats) represent fundamental factors for the development of the central nervous system and the retina. Brain matter is made up of 60% lipids, and its composition can be influenced by diet (35–42). Breastfed babies have a higher concentration of DHA (docosahexanoic acid) in the brain than babies who receive food without LC-PUFA supplementation (43, 44).

Positive links between breastfeeding and cognitive development are clear, with long-term effects until adulthood (45–49), particularly in premature babies (50). Exclusive breastfeeding can increase the growth of white matter in the brain from 20 to 30% (51).

Six-year-old children who had received infant formula added in LC-PUFA in the first 4 months of life or had been breastfed showed reactions significantly in the association test (52, 53). They were also more efficient at understanding and solving problems in other intelligence tests and can be very significant for their learning abilities in the school setting.

The children of mothers who took more DHA during breastfeeding presented a better understanding of speeches at the age of three and better verbal and non-verbal intelligence at the age of seven (54). Breastfed babies from mothers who ate high-fat fish weekly showed better visual and motor skills at the age of 3 years. Another study found associations between breastfeeding and polymorphisms of the FADS2 gene (involved in fatty acid metabolism), increased attention span at the age of 12, less hyperactive behavior at the age of three, and a trend toward higher IQ (42).

Several factors influence the availability of breastfeeding in Italy (55, 56). The most common reasons of exclusive breastfeeding discontinuation include the perception of insufficient milk, misinterpretation of infant crying, returning to work or school, early introduction of solid foods, and lack of support (57).

TABLE 1 | Comparison between breast milk and infant formula on the market in Italy around 2008, in the period in which the patients in the study were infants.

Formula 2012	Aptamil® 1	Humana® 1	Mellin® 1	Nidina® 1	Nipiol® 1	Human Milk
Kcal/dl	66	68	66	67	69	70
Proteins source	S/C 60/40	S/C 60/40	S/C 60/40	S/C 70/30	S/C 52/48	S/C 70/40
Proteins g/dl	1.3	1.7	1.3	1.2	1.4	1.2
Lipids source	Palm, canola, coconut, and sunflower oil; fish oil. DHA 6.4 mg/dl; ARA 11 mg/dl; EPA 1.4 mg/dl	Palm, rapeseed, sunflower and palm kernel oil; fish oil. DHA 7 mg/dl; ARA 7 mg/dl	Palm oil, rapeseed, coconut, sunflower; fish oil. DHA 6.4 mg/dl; ARA 6.4 mg/dl; EPA 1.4 mg/dl	Vegetable oils; fish oil. DHA 8.2 mg/dl; ARA 8.2 mg/dl	Vegetable oils (including soybean oil)	Traces of fatty acids with 8 C atoms; Polyunsaturated fatty acids 14%; DHA; ARA; EPA
Lipids g/dl	3.4	3.5	3.4	3.6	3.6	3.8
Carbohydrates source	Lactose 7 g/dl; Glucose 0.2 g/dl. GOS/FOS (9/1) 0.8 g/dl	Lactose 6.7 g/dl; Maltodextrins 0.2 g/dl; Glucose 0.2 g/dl. GOS 0.5 g/dl	Lactose 7 g/dl; Glucose 0.2 g/dl. GOS/FOS (9/1) 0.8 g/dl	Lactose 7.5 g/dl	Lactose 5.4 g/dl; Maltodextrins 2.3 g/dl	Lactose 7 mg/dl; Oligosaccharides 0.5 mg/dl
Carbohydrates g/dl	7.4	7.1	7.4	7.5	7.7	7.0
Sodium mg/dl	17	19	17	25	20	15
Potassium mg/dl	45	68	65	77	60	55
Calcium mg/dl	47	65	47	39	65	30
Phosphorus mg/dl	26	44	26	23	45	14
Nucleotides mg/dl	3.2	-	3.2	2	-	7
Osmolarity mOsm/l	300	293	-	275	n.d.	79

S/C, Sieroproteins/Caseins ratio; GOS, galacto-oligosaccharides; FOS, fructo-oligosaccharides.

The abrupt stop of breastfeeding leads to adverse health consequences for women, children, the community, and the environment; to a greater spending on national health systems; and to health inequalities (7, 58, 59).

Those issues assume much importance among PANS population because they can worsen morbidity and psychosocial burdens in patients who have behavioral disturbances (60, 61) and also need both pharmacological (62) and psychological therapy, especially cognitive behavioral therapy (63, 64).

AIMS

The aim of this study is to verify if a correlation exists between infant feeding and PANS age of onset. We also want to investigate if breastfeeding can be a protective factor for PANS symptoms and neurodevelopmental problems.

The immunologic system commitment in PANS (18) is known but still unclear, and it is possible that there is a connection between this syndrome and breastfeeding, which is involved in the development of children's immunologic and nervous system.

Another end point is to investigate if PANS children who received breastfeeding have better or worse neurologic impairments, compared to the ones who did not.

Family socio-economic status may affect the adherence to breastfeeding, the children's neurodevelopment, and possibly the development of PANS symptoms. So, we analyzed the family socio-economic status and perinatal health problems because both can be considered confounding factors and to investigate how they can be related to PANS.

MATERIALS AND METHODS

Since November 2019, we have enrolled 52 children diagnosed with PANS, between 7 and 17 years of age, referred to our center. We interviewed the patients' parents by telephone in order to investigate perinatal history, infant feeding, neurologic development, onset of symptoms, and confounding factors like socio-economic status and region of origin. Also, scholar achievement and other related problems were investigated.

We stratified the patients into three groups, depending on the kind of feeding they were exposed to during the first 4 months of life: group 1 receiving human milk only (HMO); group 2 receiving mixed feeding (MF), which is both human milk and infant formula; and group 3 receiving infant formula only (IFO).

Diagnosis of PANS or PANDAS was performed according to the 2013 PANS Consensus Conference (6).

Other major conditions represent exclusion criteria and have been excluded through targeted diagnostic analysis. Some of the most important conditions excluded are acute rheumatic fever (65), rheumatologic diseases, immunologic impairment, anti-phospholipids syndrome, acute or chronic infections, acute pharyngitis, encephalitis, meningitis, and presence of auto-antibodies in a blood sample. All patients had a negative culture of the pharyngeal swab at the time of the enrolment.

Most of the patients present tics and OCD symptoms spectrum, but some patients also presented other psychiatric conditions (like oppositional behaviors, selectivity for clothes or food).

We asked parents some information about family income bracket since it was found that socio-economic status can affect

TABLE 2 | Characteristics of the study population and of the subgroups.

	Total	**Human milk only (HMO)**	**Mixed feeding (MF)**	**Infant formula only (IFO)**
	***N* = 52**	***N* = 21**	***N* = 26**	***N* = 5**
Gender, male[a]	41 (78.9)	15 (71.4)	22 (84.6)	4 (80.0)
Age at onset (years)[b]	6.0 (1.5–10.0)	5.0 (1.5–8.0)	7.0 (1.5–10.0)	5.0 (3.0–5.0)
Age (years)[b]	11 (7-17)	10 (7-17)	11 (9-17)	10 (9-12)
Region of origin[a]				
Northern Italy	5 (9.6)	2 (9.5)	2 (7.7)	1 (20.0)
Central Italy	35 (67.3)	11 (52.4)	20 (76.9)	4 (80.0)
Southern Italy and Islands	12 (23.1)	8 (38.1)	4 (15.4)	0 (0.0)
Tic[a]	50 (96.2)	20 (95.2)	25 (96.2)	5 (100.0)
OCD[a] (obsessive-compulsive disease)	25 (48.1)	12 (57.1)	11 (42.3)	2 (40.0)
Other neuro-psychiatric symptoms[a]	30 (57.7)	11 (52.4)	16 (61.5)	3 (60.0)
Gluten sensitivity or Celiac disease[a]	4 (7.7)	2 (9.5)	2 (7.7)	0 (0.0)
Father age at birth (years)[b]	36 (25–53)	36 (30–47)	36 (27–53)	36 (25–38)
Mother age at birth (years)[b]	34 (20–41)	33 (28–41)	35 (24–40)	32 (20–36)
Siblings[b]	1 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)
First-born[a]	24 (46.2)	11 (52.4)	11 (42.3)	2 (40.0)
Twins[a]	4 (7.7)	0 (0.0)	3 (11.5)	1 (20.0)
Birth weight (g)[b]	3,300 (700–4,370)	3,470 (2,640–4,370)	3,190 (2,200–4,030)	3,000 (700–3,720)
Birth length (cm)[b]	50 (32–56)	50 (41–56)	50 (42–54)	50 (32–56)
Birth weight[a]				
SGA (small for gestational age)	7 (13.5)	2 (9.5)	5 (19.2)	0 (0.0)
AGA (adequate for gestational age)	39 (75.0)	16 (76.2)	18 (69.2)	5 (100.0)
LGA (large for gestational age)	6 (11.5)	3 (14.3)	3 (11.5)	0 (0.0)
Apgar 1'[b]	9 (3–10)	9 (4–10)	9 (6–10)	9 (3–9)
Apgar 5'[b]	10 (1–10)	10 (7–10)	10 (8–10)	10 (1–10)
Pregnancy problems[a]	22 (42.3)	11 (52.4)	9 (34.6)	2 (40.0)
Neonatal problems[a]	17 (32.7)	7 (33.3)	7 (26.9)	3 (60.0)
Income bracket classes[a]				
Class 1	4 (7.7)	2 (9.5)	2 (7.7)	0 (0.0)
Class 2	14 (26.9)	5 (23.8)	8 (30.8)	1 (20.0)
Class 3	23 (44.2)	10 (47.6)	9 (34.6)	4 (80.0)
Class 4	8 (15.4)	2 (9.5)	6 (23.1)	0 (0.0)
Class 5	3 (5.8)	2 (9.5)	1 (3.9)	0 (0.0)
Weaning age (months)[b]	6 (4–8)	6 (4–7)	6 (4–8)	6 (4–8)
Weaning problems[a]	3 (5.8)	0 (0.0)	3 (11.5)	0 (0.0)
Allergies[a]	11 (21.2)	3 (14.3)	8 (30.8)	0 (0.0)
Growth problems[a]	4 (7.7)	0 (0.0)	3 (11.5)	1 (20.0)
Neuromotor development problems[a]	38 (73.1)	16 (76.2)	18 (69.2)	4 (80.0)
- Head maintenance (months)[b]	3 (1–8)	3 (2–8)	3 (1–5)	3 (3–4)
- Sitting position (months)[b]	6 (4–10)	6 (5–10)	6 (4–9)	5 (5–7)
- Crawl (months)[b]	9 (6–20)	9 (8–11)	9 (6–20)	9 (8–15)
- Toddle/walk (months)[b]	13 (10–24)	12 (1–18)	13 (10–24)	15 (11–18)
- Babbling (months)[b]	12 (4–36)	12 (4–20)	12 (8-36)	15 (7–20)
School performance problems or support[a]	13 (25.0)	4 (19.1)	6 (23.1)	3 (60.0)

[a]*Number (%);* [b]*Median (1°-3° quartile).*

the development of children. We grouped all the cases into five classes of annual income bracket:

- Class 1: 10,000€−15,000€;
- Class 2: 15,000€−30,000€;
- Class 3: 30,000€−50,000€;
- Class 4: 50,000€−70,000€;
- Class 5: 70,000€−100,000€.

We found the composition of infant formula that parents reported to have been using for their children and which were on the market in Italy around 12 years ago, when most of our

TABLE 3 | Comparison between the subgroups of the study cohort: HMO vs. MF+IFO groups.

	Human milk only (HMO)	Mixed feeding (MF) + Infant formula only (IFO)	HMO vs. (MF+IFO)
	***N* = 21**	***N* = 31**	***p*-value**
Gender, male[a]	15 (71.4)	26 (83.9)	0.32
Age at onset (years)[b]	5.0 (1.5–8.0)	6.0 (1.5–10.0)	0.35
Age (years)[b]	10 (7–17)	11 (9–17)	0.24
Region of origin[a]			0.10
Northern Italy	2 (9.5)	3 (9.7)	1.0
Central Italy	11 (52.4)	24 (77.4)	0.059
Southern Italy and Islands	8 (38.1)	4 (12.9)	0.048
Tic[a]	20 (95.2)	30 (96.8)	1.0
OCD[a] (obsessive-compulsive disease)	12 (57.1)	13 (41.9)	0.28
Other neuro-psychiatric symptoms[a]	11 (52.4)	19 (61.3)	0.52
Gluten sensitivity or Celiac disease[a]	2 (9.5)	2 (6.5)	1.0
Father age at birth (years)[b]	36 (30–47)	36 (25–53)	0.70
Mother age at birth (years)[b]	33 (28–41)	34 (20–40)	0.84
Siblings[b]	1 (0–3)	1 (0–2)	0.72
First-born[a]	11 (52.4)	13 (41.9)	0.46
Twins[a]	0 (0.0)	4 (12.9)	0.14
Birth Weight (g)[b]	3,470 (2,640–4,370)	3,100 (700–4,030)	0.38
Birth Length (cm)[b]	50 (41–55)	50 (32–56)	0.76
Birth weight[a]			0.72
SGA (small for gestational age)	2 (9.5)	5 (16.1)	0.69
AGA (adequate for gestational age)	16 (76.2)	23 (74.2)	0.87
LGA (large for gestational age)	3 (14.3)	3 (9.7)	0.68
Apgar 1'[b]	9 (4–10)	9 (3–10)	0.47
Apgar 5'[b]	10 (7–9)	10 (1–10)	0.19
Pregnancy problems[a]	11 (52.4)	11 (35.5)	0.23
Neonatal problems[a]	7 (33.3)	10 (32.3)	0.94
Income bracket classes[a]			0.78
Class 1	2 (9.5)	2 (6.5)	1.0
Class 2	5 (23.8)	9 (29.0)	0.68
Class 3	10 (47.6)	13 (41.9)	0.69
Class 4	2 (9.5)	6 (19.4)	0.45
Class 5	2 (9.5)	1 (3.2)	0.56
Weaning age (months)[b]	6 (4–7)	6 (4–8)	0.67
Weaning problems[a]	0 (0.0)	3 (9.7)	0.26
Allergies[a]	3 (14.3)	8 (25.8)	0.49
Growth problems[a]	0 (0.0)	4 (12.9)	0.14
Neuromotor development problems[a]	16 (76.2)	22 (71.0)	0.68
- Head maintenance (months)[b]	3 (2–8)	3 (1–5)	0.30
- Sitting position (months)[b]	6 (5–10)	6 (4–9)	0.49
- Crawl (months)[b]	9 (8–11)	8 (6–20)	0.23
- Toddle/walk (months)[b]	12 (11–18)	13 (10–24)	0.29
- Babbling (months)[b]	12 (4–20)	12 (7–36)	0.066
School performance problems or support[a]	4 (19.1)	9 (29.0)	0.42

[a]*Numero (%)—Fisher's exact test;* [b]*Median (1° – 3° quartile)—Mann-Whitney U test.*

patients were infants. We show these data in **Table 1**, comparing them with breast milk.

The neurodevelopmental problems (13.5%) that we found among the 52 patients are as follows: walking disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), oppositional attitude, and delayed psychomotor development. The latter, as specified in **Tables 2**, **3**, includes the delay in the development of the infant's developmental

milestones: head maintenance, sitting position, crawl, toddle/walk, and babbling. In these disorders, we have not taken into account tics and OCD, as they are typical manifestations of PANS.

Other reported comorbidities are asthma, craniosynostosis, plagiocephaly, and obesity.

Ethics Statement

All subjects' parents gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by Ethics Committee of Policlinico Umberto I.

Statistical Analysis

The distribution of the factors under study was evaluated by means of the Shapiro–Wilk test and the indices of asymmetry (skewness) and kurtosis (kurtosis). Since the main factors did not follow a Gaussian distribution, the quantitative variables were described using the medians and the interquartile range (first and third quartiles) and compared by the Mann–Whitney test. Absolute and percentage frequencies were calculated for qualitative variables, and comparison between groups was performed with Chi-square test or Fisher's exact test, when appropriate. $p < 0.05$ (two-tailed test) were considered statistically significant. The data were collected in an Excel database, and the statistical analysis was carried out with the Stata software version 15.1 (StataCorp, College Station, TX).

Limitations of the study: this is a retrospective study with a small population sample, and some patients had neonatal problems. Strengths of the study: this is an innovative study that investigates an unexplored field, with good-quality statistical analysis and no lack of data.

RESULTS

Since November 2019, 52 children between 7 and 17 years of age (median 7 years), referred to our center and diagnosed with PANS, have been enrolled in this study.

The patients are 41 males (78.9%) and 10 females (21.1%) (male/female ratio, 4.1:1). See **Table 2** for the characteristics of the population.

Of the entire cohort, 32.7% presented neonatal problems: prematurity, testicular agenesis, vomiting, bronchodysplasia, sepsis, lower limb tremors, jaundice, fetal distress at birth, respiratory distress, perinatal asphyxia, bandolier cord, breech birth, difficulty in feeding, hypotonia, neonatal hematemesis, gastroesophageal reflux, infant colic, and anemia.

By analyzing patient origin, we noticed that 5 (9.6%) children come from the Northern regions of Italy, 35 (67.3%) come from the Central regions, and 12 (23.1%) come from the Southern regions or Italian Islands (Sicily and Sardinia), as shown in **Figure 3**.

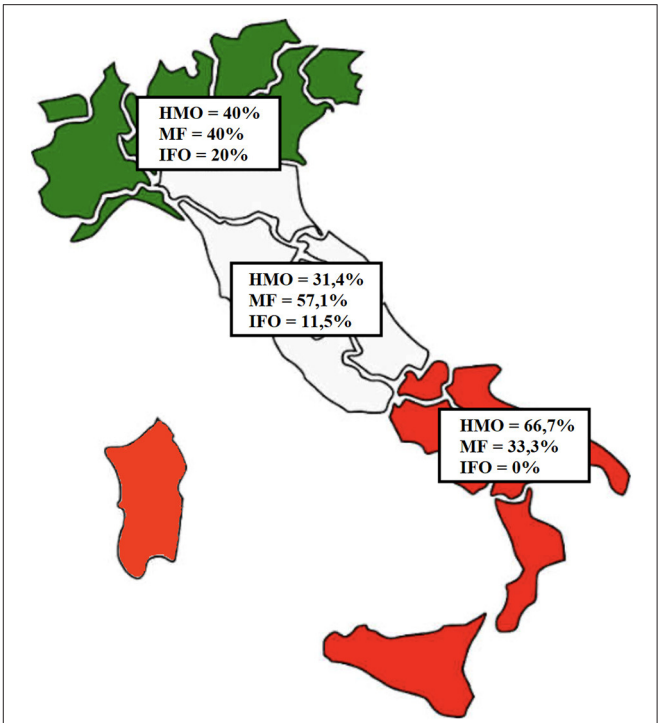

FIGURE 3 | Distribution of the patients based on region of origin. In green, Northern regions (five patients); in white, Central regions (35 patients); in red, Southern regions (12 patients).

Three groups have been identified among the study population, depending on the kind of feeding they were exposed to during the first 4 months of life: group 1 (21 patients, 40.4%) receiving human milk only (HMO); group 2 (26 patients, 50%) receiving mixed feeding (MF) (i.e., both human milk and infant formula); and group 3 (5 patients, 9.6%) receiving infant formula only (IFO).

Average age at onset is different among the groups: the total is 5.8 years (1.5–10); IFO is earlier, around 4.6 years; HMO is 5.4 years; and MF is older, around 6.3 years.

The IFO group only has five patients, so any statistical analysis and comparison with the other groups appear useless. Therefore, we decided to analyze together the group of patients who received IFO and MF and compare them with the patients who received HMO.

Comparing the two groups in **Table 3** [HMO vs. (MF+IFO)], it emerges that the distribution of males is similar in both groups (71.4 vs. 83.9; $p = 0.32$). The age of onset of symptoms is similar in all the groups and ranges from 5 to 6 years.

Breastfeeding is preferred in all regions of Italy, especially in the Southern and Central regions. Food weaning during infant age occurred between 4 and 8 months of life but only three children (5.8%) presented weaning difficulties, and all of them received mixed feeding (11.5% of MF group). Three out of five patients who received only infant formula (60% of the IFO group) had a history of perinatal disease.

The average onset of verbal ability (like babbling and speaking) is around 12 months in both groups but with different age distribution widths, appearing earlier in the HMO group (range 4–20 months) and later in the MF+IFO group (range 7–36 months) ($p = 0.066$).

Although not statistically significant, the following results were observed (see **Table 3**).

Neonatal problems were found in 32.7% among the overall population, 33.3% among HMO, 26.9% among MF, and 60% among IFO; this may be a study bias, but it is also expected data. Growth problems are present in the MF (11.5%) and IFO (20%) groups but not in HMO. Neurodevelopmental problems are present in HMO (76.2%), MF (69.2%), and IFO (80%).

The time to reach neuro-motor milestones (like head maintenance, reaching sitting position, crawling, and toddling/walking) did not appear to be significantly different among the groups.

Regarding socio-economic status, we analyzed the distribution among family annual income bracket from the poorest (Class 1) to the richest (Class 5) class: 7.7, 26.9, 44.2, 15.4, and 5.8%, respectively (see **Figure 5**). The poorest and richest income brackets prefer exclusive breastfeeding.

Finally, the presence of school performance problems or the need for school support were reported in 13 children (25%): 4 (19.1%) in the HMO group, 6 (23.1%) in the MF group, and 3 (60%) in the IFO group.

School performance problems were reported in 25% of patients. PANS onset occurred in preschool age (<6 years) in 44.2% of cases, and it occurred after the start of school (6 years old or more) in 55.8%. Among the group with preschool onset, only 20.7% presented school performance problems; conversely, it occurred in 30.4% in the group with PANS onset during school age.

These results are not all statistically significant (probably due to the small number of patients), but consistent with our hypothesis since the benefits of fatty acids in the diet are highlighted above all from school age.

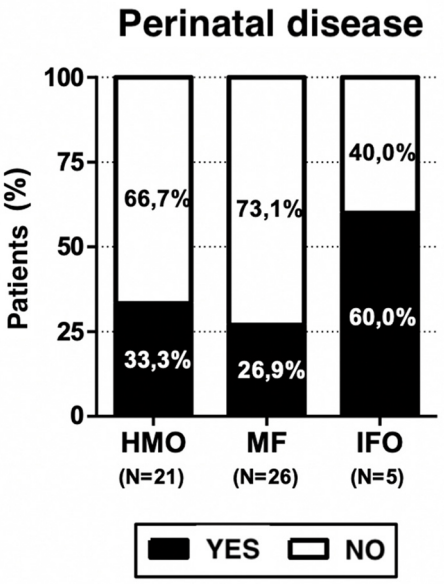

FIGURE 4 | Prevalence of perinatal disease among the study population.

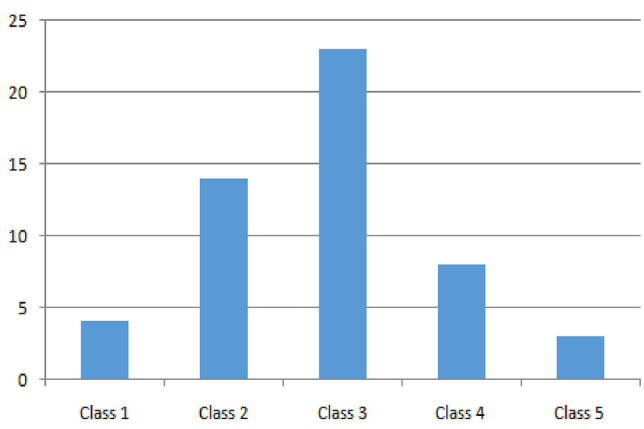

FIGURE 5 | Distribution of patients by income group, from the poorest (Class 1) to the richest (Class 5).

DISCUSSION

The different infant feeding approaches among Italians may be attributed to various reasons that are social, economic, and cultural in nature.

As already specified above, the IFO group only has five patients, so any statistical analysis and comparison with the other groups appear useless. Therefore, we decided to analyze together the group of patients who received IFO and MF, and compare them with the patients who received HMO.

Three out of five patients who received infant formula only (60% of IFO group) had a history of perinatal disease (see **Figure 4**). On the one hand, it is expected because newborns with perinatal problems often need infant formula; on the other hand, it represents a bias because we have no evidence on how those perinatal problems can affect the neurodevelopment of the children with respect to the other groups, HMO and MF, which presented 33.3 and 26.9% cases, respectively. It is very unlikely that this explains the other main results of the paper because only one (out of five) IFO-fed patient presented with severe Apgar (3–1 min and 1–5 min), bronchodysplasia, and sepsis. One patient presented with lower limb tremors, and one presented with breech position and physiological jaundice, but in any case, the Apgar score was at least 9.

Weaning problems are present only in three patients, all in the MF group (11.5%); these data can be explained with the need to support breastfeeding with infant formula if weaning difficulties occur.

Growth problems are present in the MF and IFO groups but not in HMO; it supports the beneficial activity of breastfeeding and it can be the expression of feeding supplementation needed in children with growth issues.

Neurodevelopmental problems are present in 73.1% of the study population; in detail, HMO, 76.2%; MF, 69.2%; and IFO, 80%. So, the IFO group appears to be more affected; we have

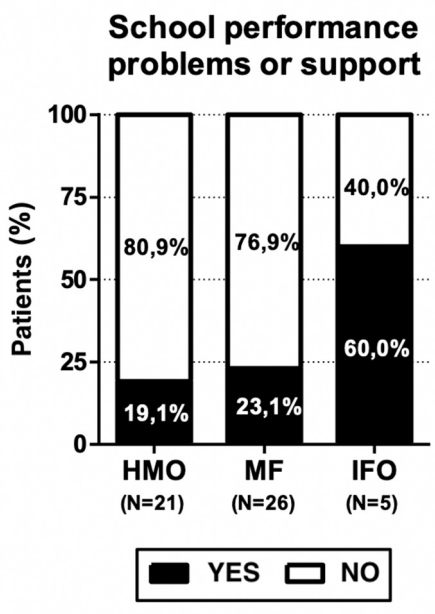

FIGURE 6 | Prevalence of school performance problems among the study population.

to remember that it is the same group with 60% of perinatal problems, and it can represent a confounding factor.

The time to reach neuro-motor milestones (like head maintenance, keeping sitting position, crawling, toddling, or walking) did not appear to be significantly different among the groups.

As expected, the distribution among family annual income bracket is pretty normal (see **Figure 5**), but it is peculiar to notice how the poorest and the richest families prefer exclusive breastfeeding. These data can be explained in many ways: in general, the action of pediatricians during recent decades in family education may have played an important public health role; moreover, the poorest parents probably find adequate and cheap nutrition for their babies in breastfeeding, while the richest ones are probably better instructed.

The presence of school performance problems and the need for school support were reported in 13 children (25%): 4 (19.1%) patients in the HMO group, 6 (23.1%) in the MF group, and 3 (60%) in the IFO group (see **Figure 6**). These results are not statistically significant due to the small number of patients, but consistent with our hypothesis since the benefits of fatty acids in the diet are highlighted above all from school age.

The school problems registered in this study are as follows: the need for school support, loss of school years, dysgraphia, dyscalculia, dyslexia, attention deficit, autism spectrum disorder, and oppositional attitude.

CONCLUSIONS

PANS is an underdiagnosed and little known condition among physicians; its incidence is unknown, and this makes it difficult to collect an adequate amount of evidence. Moreover, the follow-up of PANS patients is still short because it is a nosological entity known for a relatively short time and its causes are not that clear.

There are no studies known to the authors that have investigated the role of breastfeeding in the development of PANS. PANS patients have an immunological commitment that can influence the neurological development in children. Breastfeeding has a known immunologic action and a positive influence on the neurodevelopment, so it can be beneficial for PANS children or to prevent PANS onset.

Since the benefits of fatty acids in the diet are evident starting from school age, in line with the working hypothesis, the lack of some fundamental nutrients could play a role in the onset of some educational performance deficits and also of language in its various forms (dysgraphia, dyslexia, dyscalculia, etc.). This lack could also affect the achievement of some milestones in the development of the infant (i.e., babbling). In the group of PANS patients fed only with human milk, we registered fewer cases of growth problems, school performance problems or the need for school support, and a delay in the age of babbling/speaking.

We want to highlight the benefits of breastfeeding in babies and the importance of DHA and all LC-PUFA intake during breastfeeding, since PANS symptoms and PANS diagnosis are typical for those between 3 and 16 years and the benefits of this nutritional elements are evident in adolescence.

Breastfeeding is preferred in all Italian regions, but its diffusion is not homogeneous; it can be explained by social, economic, and cultural phenomena that characterize the different parts of the nation.

The richest and poorest families choose breastfeeding, probably with a different approach and for different reasons (awareness for the former, need for the latter), but this highlights the fact that the health education furnished by pediatricians is precious.

This study offers a food for thought not foreseen *a priori* regarding the topic of breastfeeding in Italy and in Europe, that is, how scientific societies have changed their approach through the years and how it has been received by society and by the various segments of the population.

Promoting breastfeeding is important in the general population as well as in PANS patients because it has an important social and global health impact, also during adult life.

Further studies with a bigger population are needed to investigate the mechanisms underlying PANS and the role that breastfeeding may play in the short- and long-term neurodevelopment of these patients.

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 Policlinico Umberto I, Sapienza University of Rome,

Italy. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MM, DB, FD, and AS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. All authors designed the data collection instruments, collected data, carried out the initial analyses, reviewed and revised the manuscript, conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Link Between Topographic Memory and the Combined Presentation of ADHD (ADHD-C): A Pilot Study

*Noemi Faedda[1], Cecilia Guariglia[2,3], Laura Piccardi[2,3], Giulia Natalucci[1], Serena Rossetti[4], Valentina Baglioni[1], Danilo Alunni Fegatelli[5], Maria Romani[1], Miriam Vigliante[1] and Vincenzo Guidetti[1]**

[1] Section of Child and Adolescents Neuropsychiatry, Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, [2] Department of Psychology, Sapienza University of Rome, Rome, Italy, [3] Cognitive and Motor Rehabilitation and Neuroimaging Unit, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Fondazione Santa Lucia, Rome, Italy, [4] Department of Dynamic and Clinical Psychology, Sapienza University of Rome, Rome, Italy, [5] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Background: Topographic memory is the ability to reach various places by recognizing spatial layouts and getting oriented in familiar environments. It involves several different cognitive abilities, in particular executive functions (EF), such as attention, working memory, and planning. Children with attention deficit hyperactivity disorder (ADHD) show impairments in inhibitory control, regulation of attention, planning, and working memory.

Aim: The aim of this study was to evaluate the topographic memory in children with ADHD-combined subtype (ADHD-C).

Method: Fifteen children (8–10 years) with a diagnosis of ADHD-C (DSM-5) (ADHD-C group) were compared to 15 children with typical development (TD group) of the same age. All children performed Raven's colored progressive matrices (CPM) test to obtain a measure related with cognitive functioning. The walking Corsi test (WalCT), a large-scale version of the Corsi block-tapping test, was used to assess topographic memory in experimental environment.

Results: A higher impairment was observed in ADHD-C than TD with significant differences in the WalCT, in particular on the topographic short-term memory (TSTM) task, on the topographic learning (TL) task, and on the repetition number (RN) task during the TL task. Perseverative errors were reported in performing the square-sequence in the WalCT. Zero-order correlations showed a positive correlation between TSTM and auditory attention, and memory of design of NEPSY-II and digit span of WISC-IV. No statistically significant differences were found between the ADHD-C group and TD group in the TL task in the WalCT condition.

Conclusion: In ADHD-C, initial topographic learning was compromised whereas the long-term retention of learned topographical material seemed to not be impaired. In particular, these impairments seem to be linked with difficulties in sustained attention, in spatial memory for novel visual materials, in a poor working memory, and in perseverative behaviors.

Keywords: navigational memory, executive function, attention deficit hyperactivity disorder, navigational skills, topographic memory

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Veit Roessner, University Hospital Carl Gustav Carus, Germany

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Joanne Cotton, University of Cambridge, United Kingdom
Augusto Pasini, University of Rome Tor Vergata, Italy

***Correspondence:**
Vincenzo Guidetti
vincenzo.guidetti@uniroma1.it

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INTRODUCTION

Development of Topographic Memory and Spatial Cognition

Human spatial cognition is a fundamental ability in humans. The visual and tactile world consists of objects situated in space, so it is essential from the first months of life to understand the characteristics of the surrounding area and object positions in it. This knowledge allows children to mentally and physically organize objects in their world. Indeed spatial awareness and spatial relations allow children to locate objects and navigate successfully in their environment, while spatial language allows children to express specific needs and describe the world (1).

Topographic memory is one component of spatial cognition that corresponds to the ability to reach various places in the environment, recognize spatial layouts, orient in familiar environments (2, 3), and to encode and maintain online sequences of environmental cues that are central during navigation (4, 5).

Topographic memory involves several cognitive processes and skills such as the ability to retain the spatial layout of an environment, to memorize and recognize complex visuo-spatial configurations, to find a shortcut between two locations, or to create an interconnected network among different paths (6–8). For a successful topographic memory, individuals have to access at least two types of spatial representations: the online representation of their position in the environment, and the offline representation of the environment (9). Therefore, it is essential that the individual create a stable mental representation of the environment, representing a "cognitive map" (7, 10, 11).

Indeed, human navigation develops gradually at distinct time points (12, 13), in parallel with the development of executive functions (EF) and language (5). By the age of 6–9 months, children are just able to use path integration, that is the ability to memorize their movements in the environment, and to get oriented on the basis of geometric features of the environment. They become able to deal with a spatial array from a novel viewpoint using landmarks only at 5 years old (5). Cognitive mapping starts to develop very late, at 7–8 years of age, and is fully functional by the age of 10 (12). However, the accuracy and the efficiency of navigational abilities continues to improve into adolescence, depending, at least in part, on the maturation of sensory and motor systems, combined with environmental feedback. In order to navigate in a successful way, humans must be able to process, integrate, and manipulate information derived from internal and external factors pertaining to time and space. The body's sensations and perceptions, environmental signals, and landmarks or reference points, are equally important for reaching a place and memorizing a path (13).

Links Between Spatial Navigation and ADHD

Successful navigation is known to be strictly connected with the activity of several brain areas such as parieto-medial temporal networks (14), the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC) (15), and the medial temporal lobe structures. Several neuroimaging studies have also revealed an increased activity in prefrontal areas during spatial navigation tasks (16–20). As described above, human navigation is constituted by multicomponent abilities, which need several cognitive processes, such as attention, memory, perception, and decision-making, for correct development and functioning. Indeed, even a single impairment in these processes may negatively affect navigation (21–24). Recently, in the adult population, several variable levels of navigational skills were reported and a specific developmental disorder, developmental topographical disorientation (DTD), was described. This disorder is characterized by a life-long inability in orientation despite otherwise well-preserved cognitive functions, and without other neurological conditions (25–31). This suggests the importance of understanding if and how the development of navigational skills is affected by the development of the other cognitive domains, particularly executive functions with specific attention toward working memory that is known to be important in maintaining online navigational information.

In this regard, the investigation of the spatial navigation in children, presenting this selective impairment, may shed light on those factors causative of the development of navigational skills. For this purpose, the study of topographic memory in children with attention deficit hyperactivity disorder (ADHD) could be crucial as a disorder of EFs, which are proposed to be a core deficit of this pathology (32, 33). Willcutt et al. (34) conducted a meta-analysis to evaluate the performance in executive function tasks in children and adolescents with ADHD showing weaknesses in several key EF domains, but the strongest and most consistent effects were obtained on measures of response inhibition, vigilance, spatial working memory, and some measures of planning. One of the most prominent cognitive weaknesses in patients with ADHD appears to be visuospatial working memory (VSWM), including short-term memory (STM) and central executive (CE) function (35). ADHD-combined subtype (ADHD-C), described as the more pervasive and impairing form of the disorder (36), shows significantly higher impairing rates in the functioning of vigilance, sustained attention, visual attention task, especially inhibition and shifting, visuo-spatial short-term memory, working memory, short-term memory compared to TD, and the other ADHD subtypes (37–41). Pasini et al. (42) conducted a study on attention and executive functions profile in drug-naive ADHD subtypes, founding that ADHD patients, inattentive and combined subtypes, differ from controls on response inhibition, divided attention, phonological, and visual object working memory and on variability of reaction times (43).

Attention and executive functions (EF), in particular inhibition and VSWM, play a critical role in the development of topographic memory, so it is important to investigate the development of topographic memory in children with ADHD that tend to fail in tasks both requiring an attentional load and involving EF (44–46). Furthermore, deficits in *executive functions* could also affect learning processes. In particular, several studies and clinical evidence (47–50) showed that children with ADHD present an impairment in sustained attention, flexibility, problem solving, and lower levels of task persistence, which has an impact on learning processes.

To investigate the development of navigational skills in ADHD children, it is important to consider that the age period of 8–10 years represents a crucial developmental phase for both executive functions and navigational skills [e.g., (4, 51–54)]. Previous studies found that the abilities to bind geometric environmental features, landmark identity, and directional estimations get developed at the age of 6–8 years, in accordance with the development of visuospatial processing and language (5, 7). Egocentric information, which includes spatial information about the location of the subject in the environment, is gradually supplemented with allocentric coding, which involves spatial information about the reciprocal object's positions (55). Furthermore, the relation-place strategies required for cognitive mapping start to develop around 7–8 years of age and are fully functioning by the age of 10 (56–60). It is important to note that several previous studies showed a cortical maturation delay in ADHD children, in particular in the prefrontal regions involved in attention, planning, and navigational abilities [e.g., (61–64)].

AIM AND HYPOTHESIS

The aim of this study was to evaluate the topographic memory in children with ADHD-C compared with a group of typical developmental (TD) children. To this purpose, we used the WalCT (4, 51, 65, 66), a test widely used both in clinical and experimental settings to study topographic memory. This study was novel in its attempt to compare the performance of children with ADHD-C with a control group without any ADHD symptoms on topographical memory. The aim was to address the following questions:

1) Does the ADHD-C group perform poorly on the topographic short-term memory task compared to TD children?

   Based on previous studies that confirmed a strong relationship between working memory and navigation (4, 67–74) and based on previous results showing low working-memory performances in children with ADHD [e.g., (75)], poor performance on the topographic short-term memory (TSTM) task in children with ADHD-C compared to TD children was expected. To support of this hypothesis, Kofler et al. (76) found that impaired working memory in children with ADHD determined consistent difficulties in anticipating, planning, enacting, and maintaining goal-directed actions, all fundamental abilities for successful navigation.
2) Does the ADHD-C group perform poorly on topographic learning task compared to TD children?

   To our knowledge, this study is the first that assesses, in children with ADHD-C, not only some aspects of topographic short-term memory, but also the ability to learn new paths. It is known that sustained attention and flexibility in problem solving play an important role in learning and that these abilities seem to be compromised in children with ADHD (47, 49, 50). For such a reason, we also expected to find deficits in learning paths in children with ADHD-C but not in children with TD.
3) Does the ADHD-C group perform poorly on the topographic delayed recall (TDR) task compared to TD children?

   Few studies have assessed long-term memory (both learning and delayed recall) in children with ADHD. A recent meta-analysis (77) found that adults with ADHD performed significantly worse than controls on verbal but not on visual long-term memory and memory acquisition subtests. A long-term memory deficit was strongly statistically related to memory acquisition deficits. In contrast, no retrieval problems were observable suggesting that memory deficits in adults with ADHD reflect a learning deficit induced at the stage of encoding. Furthermore, Skowronek (78) showed equal or enhanced performance on long-term episodic tasks in children with ADHD compared to TD children. Based on this evidence, we hypothesize that we will not find any differences in long-term memory between the two groups.
4) Are there any correlations between topographic memory and executive function performances in the ADHD-C group?

   Topographic memory involves several different cognitive abilities, in particular executive functions (EFs), such as attention and working memory (21, 22, 24). To date no studies have evaluated the correlations between topographic memory and executive function performances in ADHD-C children, we expected a positive correlation between topographic short-term memory (TSTM) and the "attention and executive function" domain of NEPSY-II and topographic short-term memory (TSTM) and the working memory index of WISC-IV.

It is important to note that some navigational tasks might be impaired in both groups (children with ADHD and TD) because of age/stage of development. In particular, we considered the ability to use cognitive maps. Indeed, Lehnung et al. (56) showed that 10-year-old children tended to use cognitive-map strategies at greater rates and generally made fewer errors than younger children in a spatial orientation task, furthermore children who suffered from a traumatic brain injury before 10 years of age showed greater long-term impairments in the ability to orient themselves by means of cognitive maps. Newcombe (13) reported that by around 12 years, we can observe adult-level performance and adult patterns of individual differences on cognitive mapping tasks and these abilities continue to improve, along with the adaptive combination of various kinds of input, at least until adolescence. Each of these lines of development depends at least in part on the maturation of sensory and motor systems, combined with environmental feedback. Taken together, these findings suggest that several complex spatial cognition abilities develop rapidly between 7 and 12 years of age (79). Furthermore, different complex navigational skills depend on the development and maturation of several networks and brain areas such as the hippocampus, retrosplenial cortex, and prefrontal cortex (PFC) whose development is prolonged, continuing into adolescence [e.g., (15, 51, 80)].

In addition, the relation-place strategies required for cognitive mapping start to develop around 7 or 8 years of age and are fully functional by the age of 10 (56–60). Therefore, both groups, with ADHD-C and TD children, might have difficulties in transforming egocentric information into an allocentric representation of the experimental setting.

TABLE 1 | Descriptive statistics of the sample.

	ADHD-C	TD
Boys	12	10
Girls	3	5
Age	8.73 (M)	8.87 (M)
Raven	24.67	27.67
SES	Class 2: household income	Class 2: household income

MATERIALS AND METHODS

Participants

For this study, we assessed a sample of 100 children and adolescents (aged between 5.1 and 15.4 years), that had been referred to the Department of Human Neuroscience with a diagnostic suspicion of ADHD by parents, teachers, or a pediatrician. All children and parents underwent an initial interview with a child neuropsychiatrist who recorded the child's medical history, followed by an evaluation performed by a multidisciplinary team of experts constituted by a neuropsychiatrist and four psychologists. For the diagnosis, several neuropsychological and emotional tests were administered (see **Supplementary Material**).

After this assessment, for the ADHD-C group, patients needed to meet the following criteria for hyperkinetic disorder (HKD) for ICD-10 (81) and ADHD-C (48): six (or more) symptoms of hyperactivity and impulsivity and six (or more) symptoms of inattention persisting for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts social and academic/occupational activities. We chose to focus on the ADHD-C subtype because it defines a more pervasive and generally more impairing form of the disorder (36). In particular, some studies highlighted an association between specific subtypes of ADHD and TD and specific executive function impairments (38–40). In particular, children and adolescents with the ADHD-C subtype seemed to show significantly more impaired functioning on perseverative errors, visual attention tasks, especially inhibition and shifting, visuo-spatial short-term memory, working memory, and shortterm memory compared to TD and the other ADHD subtypes (38–41, 82). Furthermore, besides having a diagnosis of ADHD-C, the individuals included in the study had to meet the following criteria of inclusion: age 8–10, I.Q. $\geq$85, an average score on Raven's colored progressive matrices (percentile rank $\geq$ 37.5 = category average) (83), no previous treatment, no other diagnosis of a comorbidity, no primary visual or hearing impairments, and no other neurological or organic disease. After they were initially screened to determine their eligibility based on the aforementioned criteria, a sample of 15 children (age range: 8–10 y, M= 8.73, s.d.: 0.70; M:12; F:3) with a diagnosis of ADHD-C (experimental group: EG), based on DSM-5 (48) were recruited from the Department of Human Neuroscience.

We conducted an informal interview with parents of children that took part in the study as the control group (TD group) before the enrolment screening. None of these children had ever been previously reported for emotional, behavioral, or learning difficulties. No primary visual and hearing impairments, neurological and organic disease, or other neurodevelopmental issues were described. The individuals included in the study as TD had to meet the following criteria of inclusion: age 8–10, an average score on Raven's colored progressive matrices (percentile rank $\geq$ 37.5 = category average) (83), no emotional, behavioral, or learning difficulties, no primary visual or hearing impairments, no other neurodevelopmental, neurological, or organic disease. A typical developmental (TD) sample of 15 children (age range: 8–10 y, M = 8.87, s.d.: 0.83; M:10 F:5), with an average score on Raven's colored progressive matrices (percentile rank $\geq$ 37.5 = category average) [see **Table 1**; (84, 85)] without ADHD took part in the study as the comparison group (TD group).

We administered Raven's colored progressive matrices to both groups to obtain a measure of non-verbal intelligence and to exclude the presence of a visuospatial deficit. All subjects were of Caucasian origin and came from families with middle-class socio economic status (class 2: household income = €28,000–55,000; current Italian economic parameters), confirmed during the interview with parents. TD children were recruited from primary schools, describing the study protocol individually to their parents. **Table 1** reports the descriptive statistics for the sample.

An informed written consent form, requiring active consent from caregivers, was signed. Each child, before taking part in the study, give an informed verbal assent. This research has been revised and approved by the Local Ethics Committees (Protocol number:416/16) in accordance with the tenets of the latest Declaration of Helsinki.

Instruments

Neuropsychological Testing Administered to ADHD and TD Children

Raven's Colored Progressive Matrices (CPM)

All children in both the groups performed Raven's CPM to obtain a cognitive functioning measurement. The CPM is internationally recognized as a culture-fair test of non-verbal intelligence (84, 85) designed for the use of children between the ages of 5½ and 11½. The test consists of 36 items in three sets (A, Ab, B), with 12 items per set (86). As reported in **Table 1**, the ADHD-C group and TD group fell in the average range (ADHD-C group, raw score = 24.67, TD group, raw score = 27.67).

The Walking Corsi Test (WalCT)

The WalCT (4, 5, 51, 65, 66) (**Figure 1**), a large-scale version of the Corsi block-tapping test [CBT: (87)] was used to assess short- and long-term topographic memory. Specifically, the WalCT measures the memory of short paths in the navigational vista space, which is, according to Wolbers and Wiener (88), the portion of the navigational space that can be seen from a single location or with little exploratory movements.

It was set up in a wide room of the Department of Human Neuroscience. It was composed of nine green squares (30 × 30 cm) that were placed on a carpet on the floor, reproducing the

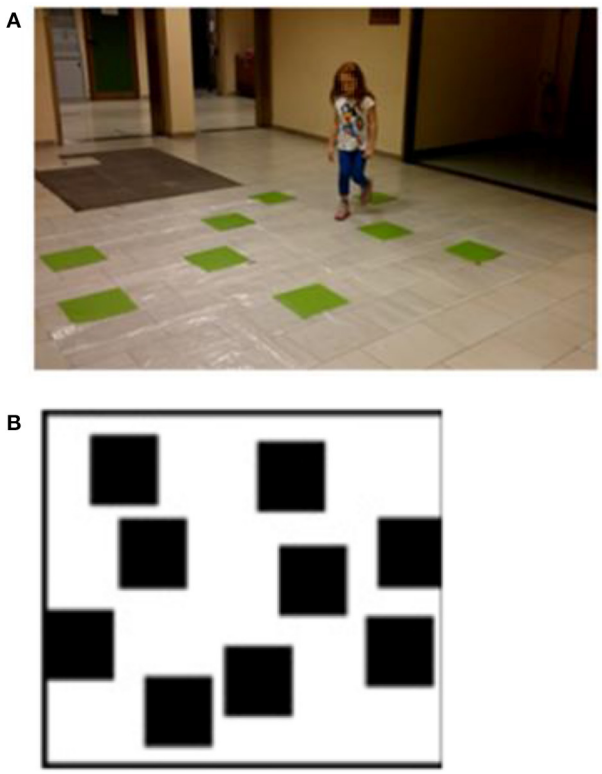

FIGURE 1 | (A) Walking Corsi test (WalCT). The WalCT was the apparatus used for measuring topographical memory. Nine black squares (30 × 30 cm) were placed on a 2.50 × 3.00 m white carpet. The scaled position and the relative spatial layout of the squares were the same as in the Corsi block-tapping test (CBT). **(B)** The outline map of the WalCT on which children had to draw the previously learned path. Written informed consent was obtained from the parents of the child represented in the figure for publication of this experiment. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

same standard positions as used in the CBT (see **Figure 1A**). In this test, the subject had to walk and reach different locations. The experimenter illustrated the sequence by walking on the carpet and stopping on each square for 2 s. Then, the subject had to repeat the same sequence as the experimenter by walking and stopping on the squares included in the sequence.

Following standard procedures (51, 65, 66), participants performed three different tasks, assessing:

1) *Topographic short-term memory (TSTM),* in which a square span was obtained, that is, the number of squares in the longest sequence of squares that a child was able to repeat in the correct order immediately after the presentation.

   During the task, the number of squares to be reproduced gradually increased in length (from a 2-square sequences to a 9-square sequences). Children were required to reproduce the square sequences shown by the examiner by actually stepping on the green squares included in the sequence previously shown by the examiner.

2) *Topographic learning (TL),* in which participants were asked to learn a fixed supra-span sequence (a path), which was calculated by considering the square span of the child + 2 squares according to standard procedures (5, 89). In each trial, after the examiner presented the sequence, the child was invited to walk on the carpet to reproduce it, stepping out of the carpet when he/she had finished. In each trial, the number of correct black squares reproduced in the sequence was calculated as the final score. During the task no feedback about the correctness of performance was provided. The learning criterion (indicating that learning was achieved) corresponded to three consecutive correct reproductions in a row of the sequence; in case the child did not reach the learning criterion the sequence was repeated for a maximum of 18 trials (5, 89).
3) *Topographic delayed recall (TDR)* of the supra-span sequence, in which 5 min later (the child and examiner spent this time out of the room where the WalCT was placed), participants were required to show the learned sequence. The examiner did not remind the child of the sequence and the child had to reproduce what he/she remembered of the long previously learnt sequence.

   At the end of the TDR task, the children had to use a felt-tip marker to retrace the pathway they had learned on the outline map of the WalCT (**Figure 1B**).

The whole protocol was administered in a single session on ∼30 min at the Department of Human Neuroscience.

Neuropsychological Testing Administered to ADHD Children

For the aim of this study, descriptions and scores of the "attention and executive function" and "memory and learning" domains of NEPSY II (90) and the working memory indexes of WISC IV (91, 92) are reported.

NEPSY II

Attention and Executive Functions

In NEPSY II (90), the subtests administered to the children with ADHD in the domain "attention and executive function" were as follows:

Animal sorting (AS): assessing the ability to formulate basic concepts, to sort those concepts into categories, and to shift from one concept to another.
Auditory attention (AA): assessing selective auditory attention and the ability to sustain it (vigilance).
Visual attention (VA): assessing the ability to sustain selective visual attention.
Response set (RS): the first task assesses the ability to shift and maintain a new and complex set involving both the inhibition of previously learned responses and correctly responding to matching or contrasting stimuli. In the second task, the child listens to a series of words and touches the appropriate circle when he/she hears a target word.
Design fluency (DS): assessing the child's ability to generate unique designs by connecting up to five dots, presented in two arrays: structured and random.

Inhibition (IN): assessing the ability to inhibit automatic responses in favor of novel responses and the ability to switch between response types (90).

The scores of the children with ADHD on the "attention and executive function" subtests of NEPSY II (90) are reported in **Table A1**.

Memory and Learning

In NEPSY II (90) the subtests administered to children with ADHD in the "memory and learning" domain are as follows:

List memory (LM): assessing verbal learning and memory, rate of learning, and the role of interference in recall for verbal material.
Memory for designs (MFD): assessing the spatial memory for novel visual material.
Memory for faces (MFF): assessing the ability to encode facial features, as well as face discrimination and recognition.
Memory for names (MFN): assessing the ability to learn the names of children over three trials.
Narrative memory (NM): assessing the memory for organized verbal material under free recall, cued recall, and recognition conditions.
Sentence repetition (SR): assessing the ability to repeat sentences of increasing complexity and length.
Word list interference (WLI): assessing the verbal working memory, repetition, and word recall following interference (90).

The scores of the children with ADHD on the "memory and learning" subtests of NEPSY II (90) are reported in **Table A2**.

WISC IV

Working memory indexes This index is a measure of an individual's ability to hold verbal information in short-term memory and to manipulate that information. It consists of two subtests:

Digit span (DS): The examiner reads a series of numbers and the child has to repeat them. Then, the examiner again reads a series of numbers but this time the child is required to say them back in reverse order.
Letter number sequencing (LNS): The examiner reads a series of letters and numbers and the child is required to repeat them back with the letters in alphabetical order and the numbers in numerical order (The WISC IV and WAIS IV Subtests, Weiss, data, 2003). **Table A3** reports the working memory indexes (WMI) of WISC IV (91, 92) of children with ADHD.

Statistical Analysis

To compare the performances of the two groups (ADHD-C vs. TD group) in the WalCT, we used the g formula of Hedges and Olkin (93), which can be interpreted with the same rules as Cohen's d (94). Indeed, Hedges' g and Cohen's d are extremely similar except when the sample size is small, in this case, Hedges' g outperforms Cohen's d (95). Values for Hedges' g that range from 0.20 to 0.49 are reported as small effect sizes. Values that range from 0.50 to 0.79 are reported as moderate effect sizes, and values of 0.80 or more are reported as large effect sizes. Rosenthal (96) added a classification of very large, defined as being equivalent to or >1.30. In addition to the effect size, we computed the 95% confidence interval (CI) for the effect size, which is usually interpreted as the range of values that encompass the population, or the true value, estimated by a certain statistic with a given probability (97–99). According to Nakagawa and Cuthill (100), when we have a mean difference of 28 with 95% CI = −1 to 59, the result is not statistically significant (at an α level of 0.05) because the CI includes zero, while another mean difference of 28 with 95% CI = 9–49 is statistically significant because the CI does not include zero. Differences in the number of perseverative errors, committed by the two groups during WalCT, were evaluated by the Chi-square (Chi^2) test. Zero-order correlation was conducted to measure the strength and direction of association that exists between the ADHD-C group's performances in the WalCT and the performances in NEPSY II (90) (attention, executive function, and memory and learning domains) and in the WISC-IV (working memory index) (91, 92).

Statistical Power of the Sample

To our current knowledge, this is the first study evaluating topographic memory in children with ADHD-C of a school age (ranging from 8 to 10 years) thus we conducted a *post-hoc* power analysis (i.e., OBSERVED power) based on the effect size, sample size, and parameter estimate from the data set, which found the following observed power for the variables considered: TSTM (0.93), TL (0.67), RN (0.76), OM (0.26), WalCT perseverative errors (0.88).

Preliminary Results

Regarding the control variables of age and Raven score, the two groups were balanced for age but not for Raven score with a moderate Hedges' g (ADHD-C group: M = 24.67, SD = 5.67; TD group: M = 27.67, SD = 2.44; g: −0.67; CI = −1.40 to 0.07).

However, in examining the 95% CI for the effect size, for the Raven score, a mean difference of −3 with a 95% CI = −1.40 to 0.07 was not statistically significant because the CI included zero. Furthermore, the two groups were balanced for gender; the ADHD group was composed of three girls and 12 boys and the TD group consisted of five girls and 10 boys [$Chi^2_{(1)} = 0.682$; $p > 0.05$]. All children of both groups were of Caucasian origin and came from families with middle-class socio economic status.

RESULTS

NEPSY II

Attention and Executive Function Domain

In our sample, the majority of children with ADHD showed below-average performances in the attention and executive function domain of NEPSY II (90), in particular 67% of children performed below average on the animal sorting (AS) subtest, 80% on the auditory attention (AA) subtest, 40% on the visual attention (VA) subtest, 80% on the responses et (RS) subtest, 60% on the design fluency (DF) subtest, and 74% on the inhibition (IN) subtest (**Table A1**).

TABLE 2 | Hedges' g-comparison between groups: diagnosis by the WalCT.

	ADHD-C ($n = 15$)				TD ($n = 15$)				Means comparisons between groups				
Variables	**M**	**SD**	**Skewness**	**Kurtosis**	**M**	**SD**	**Skewness**	**Kurtosis**	**Diff. means**	**Df**	**Hedges' g***	**95%CI**	**Hedges' g**
TSTM	3.53	0.83	0.31	−0.23	4.93	0.80	0.13	−1.35	−1.40	28	**−1.67**	−2.50	−0.84
TL	89.89	6.24	−0.55	−0.57	95.13	3.80	−0.83	−0.36	−5.24	28	**−0.99**	−1.75	−0.23
RN	9.13	4.69	0.58	−0.89	5.07	1.49	0.92	−0.20	4.06	28	**1.14**	0.36	1.91
OM	43.95	48.00	0.37	−2.05	67.30	43.65	−0.74	−1.38	−23.34	28	−0.50	−1.22	0.23

**For the interpretation of Hedges' g: > 0.20 is a small effect; > 0.50 is a medium effect; > 0.80 is a large effect. Rosenthal (96) added a classification of "very large" defined as being equivalent to or >1.30. Values in bold are significant.*

TABLE 3 | Perseverative errors (PE) in the WaLCT ADHD-C vs. TD.

	Actual	Expected	Adjusted residual*
ADHD-C ($n = 15$)			
Error count = 0	5	9	−3
Error count > 0	10	6	3
TD ($n = 15$)			
Error count = 0	9	13	3
Error count > 0	6	2	−3

**The adjusted residuals are the raw residuals (or the difference between the observed counts and expected counts) divided by an estimate of the standard error. Chi (1) = 8.88, p = 0.003.*

TABLE 4 | Significant zero-order correlations between ADHD-C's performances on WalCT and NEPSY II and on WalCT and WISC-IV.

		AA	RS	MFD	DS
TST	*r*	0.55	0.19	0.67	0.54
	p	**0.03**	0.49	**0.01**	**0.04**
TDR	*r*	−0.22	−0.66	0.07	−0.05
	p	0.42	**0.01**	0.8	0.87

r, Pearson correlation; p =Sig. (2-tailed) TSTM, topographic short-term memory; TDR, topographic delayed recall; AA, auditory attention; RS, response set; MFD, memory for designs; DS, digit span. Values in bold are significant.

Memory and Learning Domain

In the memory and learning domain of NEPSY II (90), 60% of children performed below average on the list memory (LM) subtest, 47% on the design fluency (DF) subtest, 40% on the memory for designs (MFD) subtest, 33% on the memory for faces (MFF) subtest, 20% on the memory for names (MFN) subtest, 47% on the narrative memory (NM) subtest, 47% on the sentence repetition (SR) subtest, and 47% on the word list interference (WLI) subtest (**Table A2**).

WISC- IV

Below average performances on the working memory index of the WISC-IV (91, 92) were reported by 40% of children with ADHD, 27% on the digit span (DS) subtest and 33% on letter number sequencing (LNS) (**Table A3**).

Walking Corsi Test (WalCT)

By comparing the ADHD group with the TD group, it emerged that the ADHD group had significantly lower performance in several tasks. In particular, the Hedges' g ranged from 0.50 to 1.67 (i.e., from medium effect to very large effect) on the topographic short-term memory (TSTM) task, topographic learning (TL) task, repetition number task during the TL task, and the WalCT outline map task (**Table 2**); however, in examining the 95% CI for the effect size, for the WalCT outline map task, a mean difference of 23.34 with a 95% CI = −1.22 to 0.23 was not statistically significant because the CI included zero (**Table 2**). All children of both groups correctly performed the topographic delayed recall (TDR) task without errors, so this score was not inserted into the table. The skewness and kurtosis statistics appeared to be very dependent on the sample size. Smaller sample sizes can give results that are very misleading. The statistics for skewness and kurtosis simply did not provide any useful information beyond that already given by the measures of location and dispersion (101).

For the perseverative errors in the WalCT, the Chi^2 test showed significant differences between the two groups with respect to the distribution of the levels of the variables [$Chi^2_{(1)} = 8.88$, $p = 0.003$]. In particular, the ADHD group committed a significantly higher number of perseverative errors than the TD group in the WalCT (**Table 3**).

Zero-order correlations showed a positive correlation between the topographic short-term memory (TSTM) task and auditory attention (AA) task ($r = 0.55$, $p = 0.03$), and the memory of design task ($r = 0.67$, $p = 0.01$) of NEPSY II, and the digit span task ($r = 0.54$, $p = 0.04$) of WISC-IV (**Table 4**). Furthermore, a correlation between delayed recall and response set (RS) ($r = -0.66$, $p = 0.01$) of NEPSY II was found (**Table 4**).

DISCUSSION

To our knowledge, the current study is the first to assess the topographic memory in children with a diagnosis of ADHD-C using the WalCT (4, 51, 65, 66), testing the subject's ability to get oriented while really walking and moving through the environment. We found that the presence of an ADHD-C diagnosis negatively affected topographic memory performances in the WalCT. In regard to the first hypothesis of this work, we

found an impairment in the topographic short-term memory in children with ADHD-C. This finding is in line with previous studies on working memory and visuospatial short-term memory in children with ADHD (e.g., (35, 102)). Kofler et al. (76) found that impaired working memory in children with ADHD determined consistent difficulties in anticipating, planning, enacting, and maintaining goal-directed actions, all fundamental abilities for a successful navigation. Zero-order correlations were conducted to measure the association between the ADHD-C group's performances in the WalCT and the performances in NEPSY II (90) and in WISC-IV (91, 92), confirmed this finding. Indeed, we found a positive correlation between the ADHD-C group's performances on TSTM and on digit span of WISC-IV (working memory index). During the digit span task, the child had to repeat a dictated series of digits forwards and another series backwards. The forward condition assessed span capacity, and the backward condition evaluated the ability to manipulate information in working memory (103). Rosenthal et al. (96) compared the performances on forward digit recall and on backward digit recall in children with ADHD, finding that the ADHD-predominantly inattentive group was able to recall significantly more digits backward than the ADHD-combined type group, showing a specific deficit in working memory. They also found an association between working memory and cortical thickness of the left medial temporal lobe in a sample of children with ADHD during the backward digit span subtest of WISC-IV (104). A recent study (105) found that human spatial navigation training is associated with changes in cortical thickness. Participants exhibited large improvements in navigation performance after 4 months of training, and these improvements were partly maintained 4 months after the end of training. In according to neural plasticity, younger adults showed higher performance than older adults. Considering this evidence, it would be interesting to assess if spatial navigational training in children with ADHD-C might increase cortical thickness, and in turn improve working memory ability. Taking into account that for pre-school children with TD a navigational training program fostered the acquisition of survey representation that is typically developed much later (106).

Furthermore, our finding showed that TSTM appears to be correlated with auditory attention (AA). It assessed the selective auditory attention and the ability to maintain concentrated attention over prolonged periods of time (vigilance or sustained attention). Children with ADHD-C could show a lower TSTM than TD because they could not sustain their concentration during the presentation of the sequences by the examiner. So, they were able to repeat only the first squares presented. To support of this hypothesis, Tucha et al. (107) assessed attention functioning in children with ADHD—predominantly hyperactive-impulsive type and children with ADHD—combined type, and showed that in comparison to healthy participants, they were impaired in measures of vigilance, divided attention, selective attention, and flexibility. Also, Pasini et al. (42), found that an ADHD-C and ADHD-I group showed an impairment in divided attention, response inhibition (prepotent response and interference control), and phonological and visual-object working memory.

Eventually, TSTM appears to be correlated with the memory for designs (MFD) task of NEPSY II that assessed spatial memory for novel visual material. In memory for designs, the child is shown a grid with four to ten designs on a page, which is then removed impeding the child from seeing the material to remember. The child then selects the designs from a set of cards and places the cards on a grid in the same location as previously shown (108).

A low score on MFD may suggest difficulty with route memorization for details, with location of visual stimuli details in the two-dimensional space and with learning for visuospatial information. Although there are few studies using tests to assess visuo-spatial working memory (VSWM) in children with ADHD-C, our findings are consistent with Westerberg et al. (35), who showed that in a specific sample of boys with ADHD-C and with no comorbidity (like our sample expect for the gender), VSWM is an important component of ADHD symptomatology. Also (37) investigated visuo-spatial and verbal WM performance in children with combined-type ADHD and their matched controls, finding that children with ADHD-C had deficits, relative to controls, on tasks designed to assess visuo-spatial WM. It is important to highlight that a delay in cortical maturation in children with ADHD has been reported by several authors [e.g., (62–64)] which showed a marked delay in children with ADHD in attaining peak thickness in particular in the prefrontal regions important for attention, planning, and navigational abilities: the median age of the attained peak thickness of cortical points for the ADHD group was 10.5 years, which was significantly later than the median age of 7.5 years for TD children.

Furthermore, children with ADHD-C performed significantly worse than controls in topographic learning (TL), they made more mistakes in executing the square-sequence path and needed a significantly higher number of repetitions to learn the path than children with typical development.

It is known that the maintenance of attention and cognitive flexibility play an important role in learning (47, 49, 50). Cognitive flexibility (CF) allows us to rapidly adapt our thoughts and behaviors in response to changing environmental demands and goals (109, 110), and CF is related specifically to working memory and inhibitory control (111). Cognitive flexibility plays a relevant role in learning and in complex problem solving. It allows us to select the strategy we need to adapt to different situations, capturing information from the environment, and responding in flexible ways by adjusting our behavior to the changes and demands of the situation. Perseverative errors committed by participants on executive function tasks such as the Wisconsin card sort test [WCST, (112)] are said to reflect cognitive inflexibility. An interesting finding of this work, that could have important consequences for clinical practice, is the fact that children with ADHD-C committed more perseverative errors during the topographic learning (TL) tasks than the TD children, showing more cognitive inflexibility. It is recognized that children with ADHD have difficulty in changing their responses even when the feedback suggests that their response is ineffective or maladaptive (75, 82, 113–115). Ahmadi et al. (82) investigated the differences between

ADHD subtypes in terms of executive function profile, finding that children with the ADHD combined type showed more perseverative responses and perseverative errors than children with the ADHD predominantly inattentive type and TD children. In the study conducted by Lawrence et al. (113), children's performance on both neuropsychological and real-life measures of executive function and processing speed were compared, finding that problems in goal-directed behavior during real-life measures (number of deviations from designated route) were related to problems in set-shifting on the WCST (perseverative responding). Vallesi et al. (115) demonstrated that drug-naïve ADHD children were less able than TD children to switch from quick to accurate decision making, when required by the task demands, showing a deficit in the flexible regulation of strategic behavior. According to Fuster (116) and Barkley (33), perseverative errors in children with ADHD could be due to an interaction between behavioral inhibition and working memory; they fail to hold in mind information on the success of their response immediately preceding trials (retrospection), which then feeds forward to influence or even stop immediate future responses. On this topic, a growing body of research has focused on neural correlates of error detection reflected in the event-related potential (ERP). In particular, two ERP components seem to be involved in error processing: error-related negativity (ERN) reflecting a "monitoring system" to detect errors, and error positivity (Pe) reflecting a "remedial action system" to compensate for errors (117). Children with ADHD seem to have no compromises in early error monitoring processes related to error detection, whereas they show abnormal response strategy adjustments (117). In accordance with these findings, recent research demonstrated that it is very difficult to learn from our mistakes. Monfardini et al. (118) administered the same task in rhesus macaques and humans in which they could see that two items concealed a reward (a coin for humans, a candy for macaques). The authors found that choice-induced preference strongly affected individual learning. The monkeys and humans performed much more poorly after an initial negative choice than after an initial positive choice, indeed, poor learning from errors due to over-valuation of personal choices is among the decision-making biases shared by humans and animals.

Furthermore, Robaey et al. (119) based on their finding suggested a different strategy to help children with ADHD symptoms better orientate in space. They found a significant interaction between the presence of ADHD symptoms and learning strategy in virtual navigation tasks suggesting that children with ADHD symptoms primarily rely on caudate nucleus-dependent response learning strategies at the expense of hippocampus-dependent spatial strategies. They suggest that promoting a response strategy (counting, using anon-spatial systematic pattern of open and closed pathways, etc.) could help them to be better oriented when introducing them to a new spatial environment.

Unlike previous studies (120, 121), we did not find differences in the delayed recall between the two groups. From our results, it would seem that once the children have learned the path, they have no difficulty in keeping it in their memory and repeating it after 5 min. Although several long-term memory (LTM) tests used this interval of time or even shorter (e.g., Rey Figure Memory Recall) and in accordance with Miller's and Atkinson and Shiffrin's definition of short-term memory (STM), 5 min are a short time of delay and it is possible that some differences may emerge with longer time intervals. Future studies should also take into account different long-term intervals of time. Based on our findings, ADHD-C seemed to be associated with impaired initial topographic learning, probably due in particular to selective auditory attention and to the ability to maintain attention over prolonged periods of time (vigilance or sustained attention), to poor working memory and spatial memory for novel visual material, and perseverative behavior (cognitive inflexibility), whereas long-term retention of the learned topographical material was not compromised. This finding is consistent with previous studies that found that children with ADHD tend to display intact LTM if the material is encoded successfully (122, 123), suggesting that if children with ADHD have encoded information into long-term memory, they have no difficulties in retaining and retrieving that information (124).

We did not find significant differences between the two groups on the WalCT outline map task. Generally, all children of both groups showed difficulties in reproducing the learned path on the map. This finding is consistent with previous studies that showed how some aspects of human navigation are acquired later mainly because the neural bases underlying different processes have different maturational rates. Indeed, the neural structures that allow path integration and reorientation are already fully developed in toddlers, whereas more complex navigational skills require the activity of neural areas (such as the prefrontal cortex, PFC) which present a prolonged development, continuing into adolescence (51, 54).

CONCLUSIONS

Based on our findings it would seem that children with ADHD-C have a poor topographic span and a specific impairment in learning a new path, but when it is acquired, they have no difficulty in keeping it in their memory and repeating it after 5 min. In fact, children with ADHD-C presented significantly worse performances than controls in the topographic short-term memory (TSTM) and topographic learning (TL) tasks but not in topographic delayed recall (TDR). These impairments are probably due to the difficulty of maintaining their attention over prolonged periods of time (sustained attention), a spatial memory for novel visual material, poor working memory and visuo-spatial working memory, and perseverative behaviors. In regard to perseverative behaviors, children with ADHD-C tend to repeat the committed errors even if feedback suggests that their response is ineffective or maladaptive. Based on these results and on the conducted studies by Monfardini et al. (118), it would be interesting to design topographic training for children with ADHD-C based on the observation of errors of other subjects, in order to assess if they are able to overcome the bias linked to the choice-induced preference and commit fewer perseverative errors, learning the new path faster.

This study presents some limitations: the sample size does not allow for generalizations about findings and for such a reason we could not investigate the presence of individual differences (such as gender) on topographic memory in our sample, although previous studies found no gender differences in children aged 4–11 years on WalCT performance (4, 51). We followed strict criteria of inclusion in the sample recruitment: diagnosis of ADHD-C (DSM-5), age 8–10, IQ ≥85, an average score on Raven's colored progressive matrices (84, 85), no previous treatment, no other diagnosis of comorbidity, no primary visual or hearing impairments, and no other neurological or organic disease. These criteria led to the recruitment of a small sample of children with ADHD-C. In particular, it is very difficult to find a child with pure ADHD, because the presence of a comorbid disorder in neurodevelopmental disorders, and in particular, in ADHD children is more the rule than the exception (125). Also, the average age of diagnosis for ADHD is usually 6–8 years, so it is difficult to recruit children with pure ADHD-C who received their first diagnosis after the age of 8. As for the control group, we conducted a formal interview with parents and teachers to obtain information about the children but the influence of emotional variables (i.e., anxiety) was not considered in the neurocognitive performance.

Further studies should compare different subtypes of ADHD [predominantly inattentive ADHD (ADHD/I) vs. hyperactive-impulsive subtype (ADHD/HI) vs. ADHD-C] to evaluate if there are differences between these groups in topographic memory and to better understand the role of attention, hyperactivity, and impulsivity in navigational performances.

Eventually, several previous studies showed cortical maturation delay in ADHD children, particularly in prefrontal regions, relevant for the attention, planning, and navigational abilities that often disappear during adolescence [e.g., (61–64, 126–129)]. It would be interesting to assess further studies on topographic memory in older ADHD children compared with younger ADHD children in order to investigate whether part of the difficulties displayed by young ADHD-C children could be explained by a developmental delay that improves over time.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Of Policlinico Umberto I, Rome, Italy (Protocol number:416/16). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MV recorded clinical data. NF conducted the research and wrote the manuscript with LP. SR and DA analyzed clinical data and conducted the statistical analysis. VG, GN MR, and CG coordinated and supervised the work and critically reviewed the manuscript. VB revised the English language editing. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.647243/full#supplementary-material

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Review article

Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies

Giulio Emilio Brancati [a], Giulio Perugi [a,*], Annarita Milone [b], Gabriele Masi [b], Gianluca Sesso [a,b]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[b] Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Pisa, Italy

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ABSTRACT

Background: Increasing attention has been recently paid to precursors of bipolar disorder (BD). Symptoms of attention-deficit/hyperactivity disorder (ADHD) have been reported among the most common prodromes of BD. The aim of this study was to estimate the risk of BD in youths affected by ADHD based on prospective studies.
Methods: A systematic review was conducted according to the PRISMA guidelines. A meta-analysis of single proportions was performed to compute the overall occurrence of BD in ADHD individuals. Binary outcome data were used to calculate risk estimates of BD occurrence in ADHD subjects *versus* Healthy Controls (HC).
Results: An overall proportion of BD occurrence of 10.01% (95%-confidence interval [CI]: 6.47%-15.19%; I^2 = 82.0%) was found among 1248 patients with ADHD over 10 prospective studies. A slightly higher proportion was found when excluding one study based on jack-knife sensitivity analysis (11.96%, 95%-CI: 9.15%-15.49%; I^2 = 54.1%) and in three offspring studies (12.87%, 95%-CI: 8.91%-18.23%). BD occurrence was not significantly associated with mean follow-up duration (p-value = 0.2118). A greater risk of BD occurrence in ADHD *versus* HC from six studies was found (risk ratio: 8.97, 95%-CI: 4.26-18.87, p-value < 0.0001).
Limitations: Few prospective studies have been retrieved in our search and most were not specifically aimed at assessing BD in followed-up ADHD patients.
Conclusions: Greater clinical attention should be paid to ADHD as an early precursor of BD since a substantial proportion of ADHD patients is expected to be diagnosed with BD during the developmental age.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) are highly prevalent conditions (Merikangas et al., 2010), that share a chronic course leading to significant impairment of educational, occupational and social functioning (Marangoni et al., 2015; Skirrow et al., 2012). ADHD and BD often co-occur in paediatric samples (Skirrow et al., 2012; Wingo and Ghaemi, 2007), particularly in the case of ADHD combined presentation (Donfrancesco et al., 2017). The high comorbidity between ADHD and BD is one of the main reason of misconceptions in the definition of boundaries between the two disorders, frequently leading to wrong diagnoses, especially during childhood, given the partial overlap of symptoms, especially when emotional dysregulation is a prominent feature.

Early follow-up studies of hyperactive children, before the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association, 1987), did not report elevated rates of BD or mood disorders as adult outcomes (Fischer et al., 2002; Mannuzza et al., 1998; Weiss et al., 1985). In contrast, later prospective studies, in parallel with a greater awareness of paediatric BD, supported the notion of a close relationship between ADHD and the subsequent development of BD, particularly during childhood and adolescence (Biederman, 1996; Biederman et al., 2004). Similar developmental pathways have been found in register-based ecological studies especially in patients with comorbid disruptive behaviour, anxiety and unipolar depressive disorders (Chen et al., 2015, 2014, 2013; Meier et al., 2018).

* Corresponding author at: Clinica Psichiatrica Università di Pisa, via Roma 67, 56100 Pisa, Italy.
E-mail address: giulio.perugi@med.unipi.it (G. Perugi).

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1.1. Comorbidity rates between ADHD and BD

High rates of ADHD comorbidity have been observed in paediatric patients with BD (Skirrow et al., 2012), where comorbidity rates range between 11% and 98%, with a weighted average rate of 62% (Kowatch et al., 2005). Estimates of ADHD comorbidity in paediatric patients with strictly defined BD type I ranged between 22% (Patel et al., 2006) and 61% (Birmaher et al., 2006). Lower but still rather high comorbidity rates have been reported at later ages: ADHD was observed in up to 23-25% of clinically-referred adult BD patients (Karaahmet et al., 2013; Pinna et al., 2019) and most reports consistently laid between 15% and 20% (Bernardi et al., 2010; McIntyre et al., 2010; Perugi et al., 2013; Tamam et al., 2006; Wingo and Ghaemi, 2007), but higher rates of approximately 28% have been reported in epidemiological samples (Merikangas et al., 2011).

On the other hand, in epidemiological and community settings, less than 2% of children and adolescents diagnosed with ADHD showed comorbidity with BD (Hassan et al., 2011; Reich et al., 2005), although a higher point-prevalence of 11% has been observed in clinically-referred ADHD patients (Biederman et al., 1996). Nevertheless, in adult ADHD clinical samples, higher BD comorbidity rates have been reported, ranging between 18% (Faraone et al., 2006b) and 47% (Wilens et al., 2003). A proportional increase in BD rate, approximately two or three times higher than that seen for other disorders, has been found in epidemiological studies (Skirrow et al., 2012), with up to 34% of ADHD patients diagnosed with BD (Bernardi et al., 2012). More recently, BD was found to be relatively prevalent (14%) in adults with ADHD from the Swedish national registers, resulting in a prevalence rate ratio of ~20 as compared with non-affected controls (Chen et al., 2018).

1.2. Characteristic features of ADHD-BD comorbid phenotype

Patients diagnosed with both ADHD and BD significantly differ from their non-comorbid counterparts. When compared with “pure” ADHD patients, ADHD patients with comorbid BD exhibited a younger age of ADHD onset and earlier treatment implementation, higher severity of inattentive and hyperactive/impulsive symptoms, externalizing problems and rule-breaking behaviours, more psychiatric hospitalizations, poorer educational and vocational functioning, more frequent substance use disorders, and higher rates of additional psychopathology – especially anxiety and disruptive behaviour disorders (Arnold et al., 2011; Doerfler et al., 2011; Donfrancesco et al., 2017; Halmøy et al., 2010; Jerrell et al., 2014; Serrano et al., 2013; Wilens et al., 2003, 1997).

On the other hand, when compared with BD patients without ADHD, BD patients with ADHD displayed a more severe and chronic course of mood disorder, shorter euthymic intervals, a greater number of both (hypo)manic and/or depressive mood episodes, higher rates of mixed depressive and borderline features, greater affective instability, behavioural impulsivity and violence, more suicide attempts and higher rates of comorbid conditions – such as anxiety disorders, disruptive behaviour disorders, substance and alcohol use disorders, higher rates of antidepressant-induced switch, poorer response to mood stabilizers, less treatment adherence, more legal problems and a lower level of personal, familial, occupational and social functioning with reduced quality of life (Bernardi et al., 2010; Jhanda et al., 2018; Karaahmet et al., 2013; Masi et al., 2012, 2006b; Nierenberg et al., 2005; Perroud et al., 2014; Perugi et al., 2013; Pinna et al., 2019; Sentissi et al., 2008; Tamam et al., 2006).

An earlier age at onset of BD in patients with comorbid ADHD was among the most replicated findings, with a mean difference of approximately five years (Masi et al., 2006a, 2006b; Perroud et al., 2014; Perugi et al., 2013; Pinna et al., 2019; Tamam et al., 2008). Among ADHD-BD patients more than a half showed a pre-adult onset of mood disorder (< 18 years), in contrast with less than one sixth of non-comorbid BD patients (Tamam et al., 2008). Even in patients with childhood and adolescent onset BD, ADHD was associated with pre-pubertal onset and specific clinical features (Masi et al., 2006a). A prepubertal onset of BD (< 12 years) was found indeed in more than a fourth of patients with comorbid ADHD, which conferred an odds ratio of approximately 5.5 in comparison with non-comorbid BD patients (Perugi et al., 2013). Early-onset BD is characterized by poorer prognosis, worse course of illness and greater delay to first treatment, that independently contribute to its long-term illness severity (Leverich et al., 2007; Post et al., 2010). Accordingly, a proper intervention at early stages of disease could improve the clinical and functional outcomes of BD (Elanjithara et al., 2011).

1.3. Aims of the study

In recent years, increasing attention has been paid to prodromal symptoms or precursors of BD, both using retrospective and prospective study designs. Interestingly, features possibly overlapping with the attention-deficit and hyperactivity domains, such as reduced concentration, academic difficulties, talkativeness, increased energy and overactivity, have been reported among the most common prodromal symptoms of BD (Van Meter et al., 2016), and ADHD has been proposed among the heterotypic risk factors of BD by the International Society of Bipolar Disorders task force on BD precursors (Faedda et al., 2019). Among ADHD patients, emotional dysregulation has been found to predict greater rates of subsequent diagnoses of BD (Biederman et al., 2009), possibly representing a specific manifestation pertaining to the bipolar spectrum in neurodevelopmental disorders. On the other hand, adult depressive patients with a history of ADHD are more likely to report lifetime (hypo)manic symptoms (Purper-Ouakil et al., 2017; Vannucchi et al., 2019) and childhood ADHD has been found to partially mediate the effect of parental BD on lifetime bipolar symptoms (Purper-Ouakil et al., 2017).

Despite this strong evidence, which relied, at best, on retrospective analysis of prospectively acquired register-based data, only a few well-powered prospective longitudinal studies have been conducted so far to assess the rate of BD occurrence in ADHD patients. Besides, to the best of our knowledge, no quantitative synthesis of these findings has been published so far, except for one meta-analysis of long-term outcomes of ADHD (Erskine et al., 2016), in which, however, BD outcome was not specifically addressed in the search strategy. Moreover, most of the included studies were conducted by the same research team on overlapping samples, thus limiting the reliability of the results, and the rate of prospective occurrence of BD in ADHD patients was not evaluated (Erskine et al., 2016). In the present study, instead, we first aimed to specifically estimate the occurrence rate of BD in children or adolescents affected by ADHD and, secondly, to assess whether ADHD confers a greater prospective risk of BD compared with healthy controls (HC), based on longitudinal studies conducted since the post-DSM-III-R era and beyond. Based on cross-sectional comorbidity studies, we hypothesized that about one or two ADHD patients in ten would be later diagnosed with BD.

2. Methods

2.1. Search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009) were used to conduct a systematic review of the literature and to search three bibliographic databases (PubMed, Scopus and Web of Science) from their inception date to 10th February 2020. The protocol was registered in the Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42021226493). We developed a search strategy using the following three groups of terms: 1) ‘bipolar’; 2) ‘ADHD’ OR ‘attention deficit’ OR ‘hyperkinetic disorder’ OR ‘hyperactivity’; 3) ‘longitudinal’ OR ‘prospective’.

Our strategy was to include all relevant titles and abstracts relating to group 1 AND group 2 AND group 3. The terms were adapted for each

database. We retrieved relevant abstracts using our search strategy and results were downloaded into Mendeley software. Any duplicate was removed. We also identified additional records through relevant citations in reference lists of screened papers and reviews. The authors discussed and reviewed the results of the initial search, including both reviews and original studies. If a previous review was found, its reference list was searched to identify and retrieve primary studies of interest. We also carefully searched reference lists of included original studies to identify relevant citations. If a title appeared potentially eligible but no abstract was available, the full-text article was retrieved. Two researchers (GS and GEB) scanned all titles and abstracts to identify relevant articles for full-text retrieval. Any disagreement was resolved by consensus.

2.2. Inclusion and exclusion criteria

Studies were selected if they met all the following inclusion criteria:

1 Study design: longitudinal prospective studies aimed at assessing the risk of developing BD in patients affected by ADHD;
2 Participants: only children and adolescents aged ≤ 18 years at first clinical assessment for ADHD diagnosis based on DSM-III-R or subsequent criteria; no a priori restrictions for participants' gender or intellectual functioning were applied;
3 Treatment: no a priori restrictions for previous or current ADHD medications were applied;
4 Comparison: no a priori restrictions were applied, only HC were taken into consideration for meta-analytic purposes;
5 Measures: either absolute number of BD diagnoses or Odds Ratios (OR) and/or Risk Ratios (RR) as compared with HC were accepted for meta-analytic procedures.

Studies were discarded if they met at least one of the following exclusion criteria:

1 No patients were diagnosed with ADHD prior to BD diagnosis;
2 The outcomes of ADHD patients were not separately reported or could not be inferred, nor were available on request;
3 BD patients were included at first clinical assessment and/or outcomes were not separately available for non-BD patients at study entry;
4 No lifetime BD diagnostic assessment was performed at follow-up visits or BD diagnoses were not separately reported (e.g. BD was grouped together with other mood disorders);
5 ADHD was retrospectively diagnosed;
6 Studies had a cross-sectional design or did not include longitudinal data analyses;
7 Data were retrospectively retrieved from prospective ecological cohorts (i.e. nation-wide registers);
8 Study participants were adults aged > 18 years at study entry;
9 The article was written in a language other than English, French, Spanish, Italian;

Among studies performed in overlapping samples, relevant studies were selected based, in order of importance, on 1) information available for meta-analytic purposes; 2) longer follow-up duration; 3) higher sample size.

When datasets were not fully available, relevant authors were contacted to try and attain the required data, so that all possible retrieved studies could be included. In case of insufficient data available, authors uncontactable or original data discarded, lost or irretrievable, studies were excluded from the meta-analyses.

2.3. Data collection process

For each study included in the meta-analyses, sample sizes at follow-up, demographic data (gender, age at first clinical assessment, age at last clinical assessment, duration of follow-up) were extracted from full-text papers both for ADHD patients and, if available, HC. When available, details on ADHD and BD clinical features (type, diagnostic criteria) and other clinical information (IQ, comorbid psychiatric conditions) were extracted. Finally, the number of ADHD patients and HC who had developed BD at last clinical follow-up assessment was extracted.

2.4. Meta-analysis procedures

A meta-analysis of single proportions from the included studies was performed to calculate the overall occurrence of BD in ADHD individuals using a generalized linear mixed model with logit transformation for pooling of studies. In the attempt to reduce the heterogeneity of the studies, a jack-knife sensitivity analysis was run using the leave-one-out method and the proportion meta-analysis was performed once more. Moreover, subgroup meta-analyses according to sample type (BD offspring *versus* clinical samples) were conducted to differentiate the effect of known family history of BD. Univariate meta-regressions were then performed to identify potential moderators that could affect BD occurrence, namely age, gender (% males) and mean follow-up duration.

Finally, a meta-analysis of binary outcome data from six of the included studies was conducted to calculate RR and OR estimates of BD occurrence in ADHD subjects *versus* HC. The Mantel-Hänszel method (Mantel and Hänszel, 1959), was used to calculate the pooled RR and OR and to assess statistical significance. A continuity correction was performed for those studies in which the outcome measure was zero and a value of 0.5 was added, as suggested by Gart and Zweifel (Gart and Zweifel, 1967).

For each meta-analysis, the Cochran Q test (p-value < 0.05) was employed for heterogeneity evaluation, as well as the I^2 index ($I^2 \leq$ 30%) was used to quantify the heterogeneity of the included studies. When studies were found to be statistically heterogeneous, then the random effects model was used to compute summary outcome measures with 95% confidence interval (CI) and to pool data. Otherwise, the fixed effect model was applied. All statistical analyses were performed using RStudio® software.

3. Results

3.1. Abstract screening and study selection

The PRISMA flowchart (Fig. 1) shows the process of identification and selection of papers. Of 963 abstracts retrieved using our search strategy, 361 were removed as duplicates. Thus, 602 studies were screened, of which 545 records were excluded based solely on title or abstract. A total of 57 full-text articles were thoroughly assessed for eligibility. Five additional records were identified through other sources (citations in reference lists of screened papers and reviews) and assessed for eligibility. Hence, 37 articles out of 62 were excluded (see Fig. 1 for further details). Among the remaining 25 studies, 19 had been performed on overlapping samples. Four of those studies were, thus, selected based, as previously specified, on 1) information provided, 2) longer follow-up, and 3) higher sample size. In conclusion, 10 studies were included in the systematic review (Table 1).

3.2. Meta-analyses results

3.2.1. Prospective occurrence of BD in ADHD patients

Forest and funnel plots of the proportion meta-analysis are displayed in Fig. 2A. This meta-analysis included single proportions of BD occurrence in individuals with ADHD from ten included studies that were highly heterogeneous, with I^2 index of 82.0% and Cochran Q test leading to a significant likelihood-ratio p-value < 0.0001. The random effects model was thus considered. The meta-analysis showed an overall

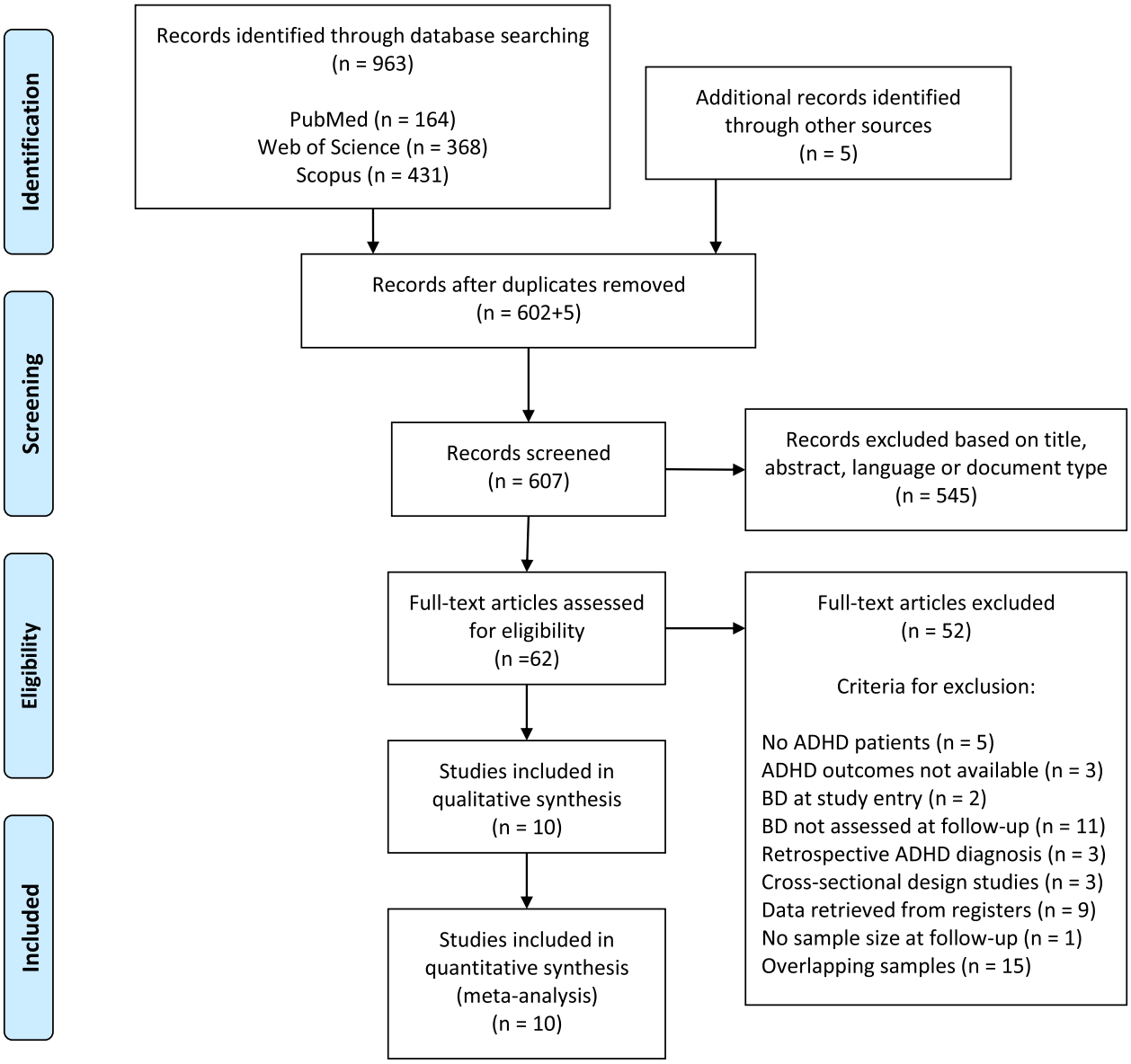

Fig. 1. PRISMA flowchart showing the process of identification and selection of papers.

proportion of BD occurrence of 10.01% (95% CI: [6.47%; 15.19%]). The funnel plot revealed a relative absence of studies in the left upper quadrant, that is, large sample studies with effect estimates that reduce the pooled proportion estimate.

A jack-knife sensitivity analysis was run to attempt to reduce the heterogeneity of the studies. I^2 indexes of all combinations of 9 studies using the leave-one-out method were computed and showed a substantial reduction in heterogeneity (I^2 index of 54.1%) when excluding from the sensitivity analysis the study performed by Klein et al. (2012) (Supplementary Fig. 1). Nonetheless, a random effects model was used once more since Cochran Q test still lead to a significant likelihood-ratio *p*-value = 0.0093. Forest and funnel plots of the proportion meta-analysis of nine studies are displayed in Fig. 2B. A slightly higher overall proportion of BD occurrence (11.96%; 95% CI: [9.15%; 15.49%]) was found when excluding the study by Klein et al. (2012). Moreover, the funnel plot of this meta-analysis revealed a more homogeneous distribution of studies across sample variance and estimate direction.

3.2.2. Subgroup analyses and meta-regressions

Forest plots of subgroup meta-analyses according to sample type are shown in Fig. 3. On one hand, a fixed effects model (Cochran Q test likelihood-ratio *p*-value = 0.5142) was applied to three studies including BD offspring with ADHD and showed an overall proportion of BD occurrence of 12.87% (95% CI: [8.91%; 18.23%]). On the other hand, a random effects model (I^2 = 88.3%; Cochran Q test likelihood-ratio *p*-value < 0.0001) was applied to the remaining seven studies including clinical samples of ADHD subjects and showed an overall proportion of BD occurrence of 8.62% (95% CI: [4.62%; 15.55%]).

On univariate meta-regressions, BD occurrence was not significantly associated with age at study entry (*p*-value = 0.4285) and gender (*p*-value = 0.9491), while a significant negative association was found with mean follow-up duration (β = –0.0823, SE = 0.0256, *p*-value = 0.0013). When excluding the study performed by Klein et al., 2012, according to the jack-knife sensitivity analysis, this association was not further confirmed (*p*-value = 0.2118).

3.2.3. Risk of BD occurrence in ADHD patients versus HC

Finally, a meta-analysis of binary outcomes was conducted with six

Table 1
Summary of included studies.

Study	Country	Sample type	FU	Age Range	Age (M ± SD)	Males (%)	IQ	ADHD diagnosis	BD diagnosis	HC
Arnold et al. 2020	USA	Subthreshold BD	M = 6.2	6–12	8.7 ± 1.9	75.5	≥ 70	K-SADS-PL-W	K-SADS-PL-W COBY study	No
Axelson et al. 2015	USA	BD offspring	M = 6.8	6–18	-	-	-	K-SADS-PL	K-SADS-PV	No
Biederman et al. 1996	USA	Clinical	4	6–17	10.6 ± 3.0	100.00	≥ 80	DSM-III-R	K-SADS-E	Yes
Biederman et al. 2008	USA	Clinical	5	6–18	11.1 ± 3.3	0.00	≥ 80	DSM-III-R	K-SADS-E SCID-IV	Yes
Duffy et al. 2007	Canada	BD offspring	M = 3.9	8–25	-	-	No ID	K-SADS-PL SADS-L DSM-IV	K-SADS-PL SADS-L DSM-IV	Yes
Halperin et al. 2011	USA	Clinical	M = 9.27	7–11	9.1 ± 1.3	87.1	> 70	DISC (DSM-III-R/DSM-IV)	K-SADS-PL	No
Klein et al. 2012	USA	Epidemiological	> 33	6–12	8.3 ± 1.6	-	≥ 85	DSM-IV	DSM-IV SCID-I-NP	Yes
Rudaz et al. 2020	Switzerland	MD offspring	M = 13.2	6–18	-	-	-	K-SADS-E DSM-IV	DSM-5	No
Shur-Fen G. et al. 2010	Taiwan	Clinical	M = 5.9	6–8	7.3 ± 2.8	82.8	> 80	DSM-IV	K-SADS-E	Yes
Tillman & Geller 2006	USA	Clinical	6	7–16	9.7 ± 2.0	79.0	≥ 70	DSM-IV	PEA-BP-I	Yes

Legend: FU duration, age range and age are expressed in years. Age range, age and males (%) refer to the characteristics of the ADHD sample at baseline. Diagnostic instruments and/or criteria are referred to in the ADHD and BD diagnosis columns. *Abbreviations*. ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; COBY = Course and Outcome of Bipolar Youth; DISC = Diagnostic Interview Schedule for Children; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HC = healthy controls; FU = follow-up; ID = intellectual disability; IQ = intelligence quotient; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version; K-SADS-PL-W = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version, with additional items from the Washington University St. Louis Version; K-SADS-PV = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Version; M = mean; MD = mood disorder; PEA-BP-I = prepubertal and early adolescent bipolar I disorder phenotype; SADS-L = Schedule for Affective Disorders and Schizophrenia, Lifetime Version; SCID-IV = Structured Clinical Interview for DSM-IV; SCID-I-NP = Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition; SD = standard deviation; USA = United States of America.

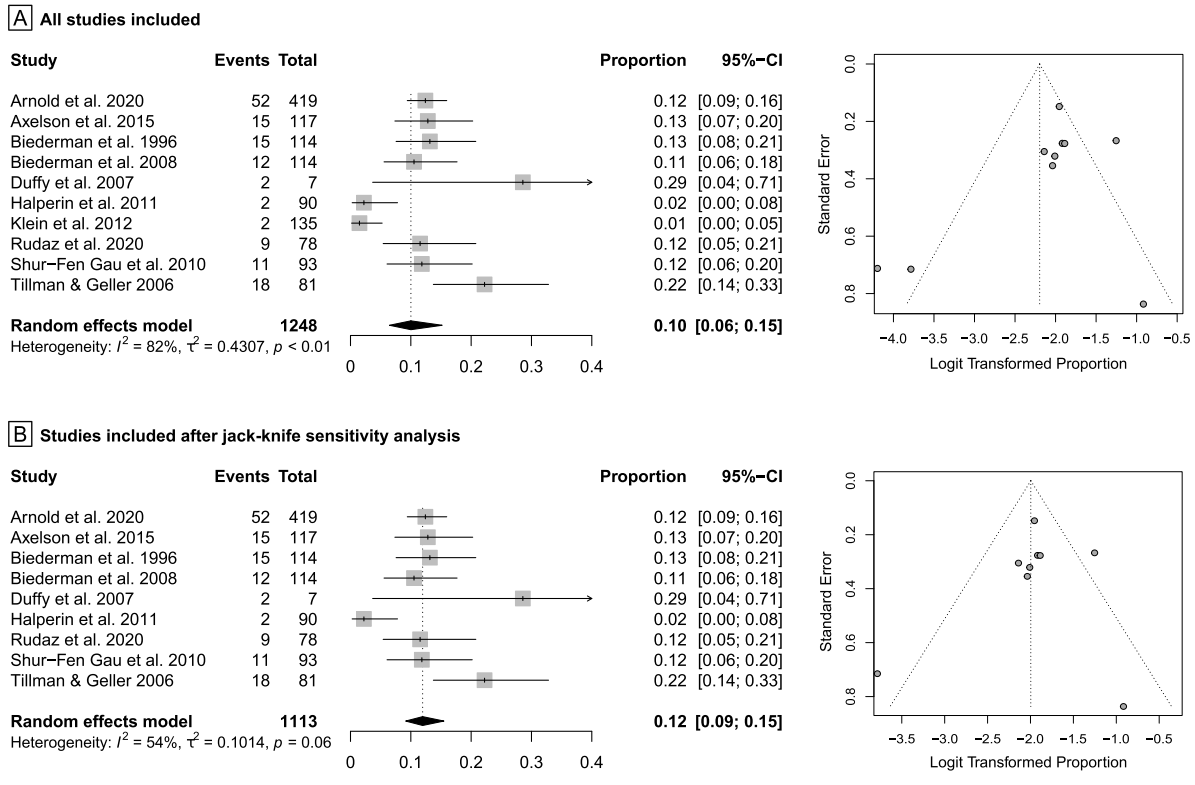

Fig. 2. Prospective occurrence of BD in ADHD patients: forest and funnel plots of the proportion meta-analyses including all studies (A; n = 10) and after excluding one study based on jack-knife sensitivity analysis (B; n = 9).

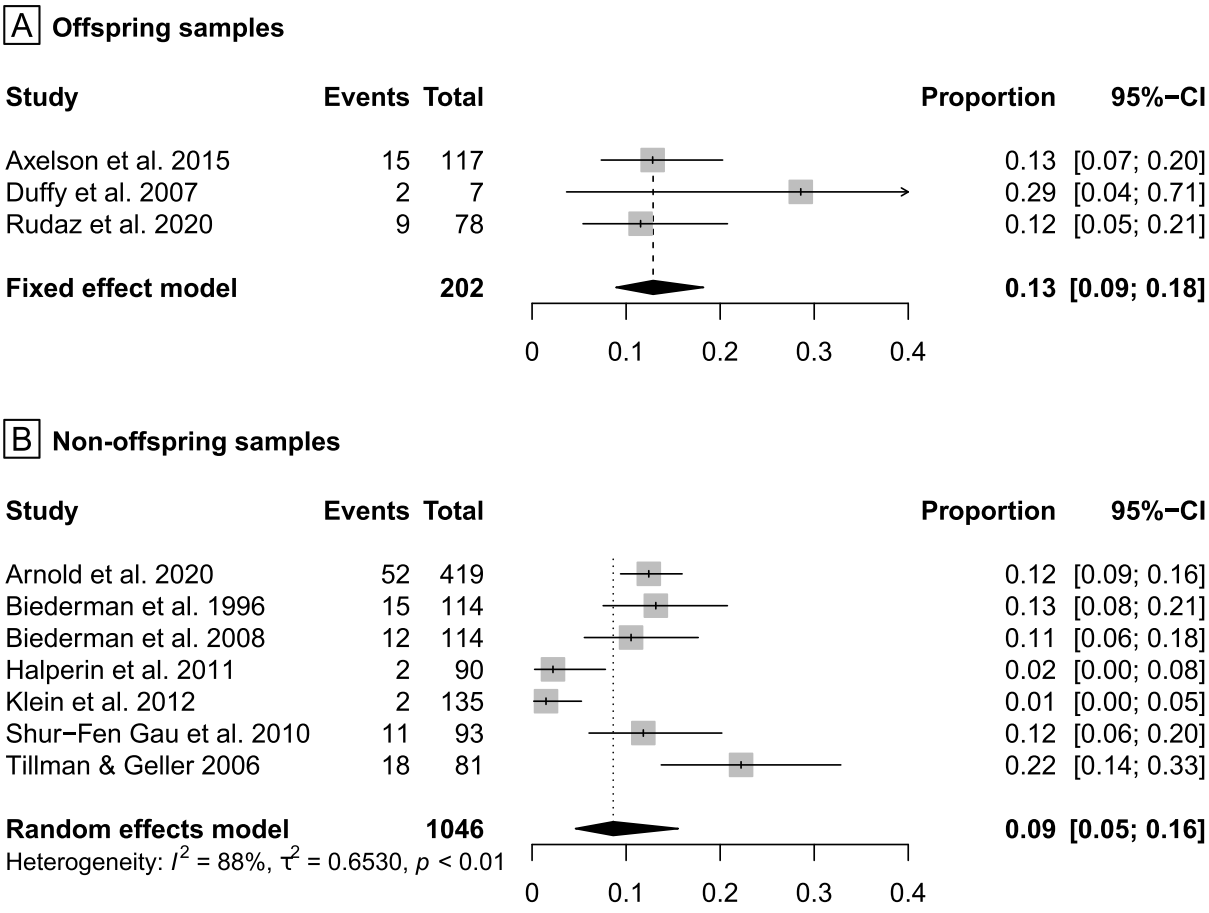

Fig. 3. Forest plots of subgroup meta-analyses according to sample type: studies including mood disorder offspring with ADHD (A; $n = 3$ studies) *versus* studies including non-offspring ADHD patients (B; $n = 7$ studies).

of the included studies which compared ADHD subjects *versus* HC. Control subjects in these studies were recruited from paediatric ambulatory services and medical centres for ordinary physical check-ups (Biederman et al. 1996, 2008; Klein et al. 2012), from schools (Duffy et al. 2007; Shur-Fen Gau et al. 2010) or through surveys (Tillman and Geller, 2006). The same exclusion criteria used for ADHD patients were applied to controls. Moreover, individuals were excluded from the control group whether they had a lifetime history of any psychiatric disorders (Duffy et al. 2007), ADHD and major mood disorders (Tillman and Geller, 2006) or ADHD only (Biederman et al. 1996, 2008) as assessed through formal psychiatric evaluations (i.e. standardized clinical interviews). Additionally, Klein and colleagues, 2012, recruited, as control subsects, children with unremarkable school behaviour as assessed by teachers and through regular inspections of school charts.

Forest and funnel plots of the RR meta-analyses are displayed in Fig. 4. The RR meta-analysis included proportions of BD occurrence in ADHD *versus* HC subjects from six studies that were homogeneous, with Cochran Q test leading to a non-significant p-value = 0.9014. The fixed effects model was considered to test significance. The RR meta-analysis showed a significantly greater risk of BD occurrence in ADHD patients *versus* HC (RR: 8.9677, 95% CI: [4.2621; 18.8685], p-value < 0.0001). Similarly, The OR meta-analysis, conducted through the fixed effects model (Cochran Q test likelihood-ratio p-value = 0.8638), showed a significantly greater risk of BD occurrence in ADHD patients *versus* HC

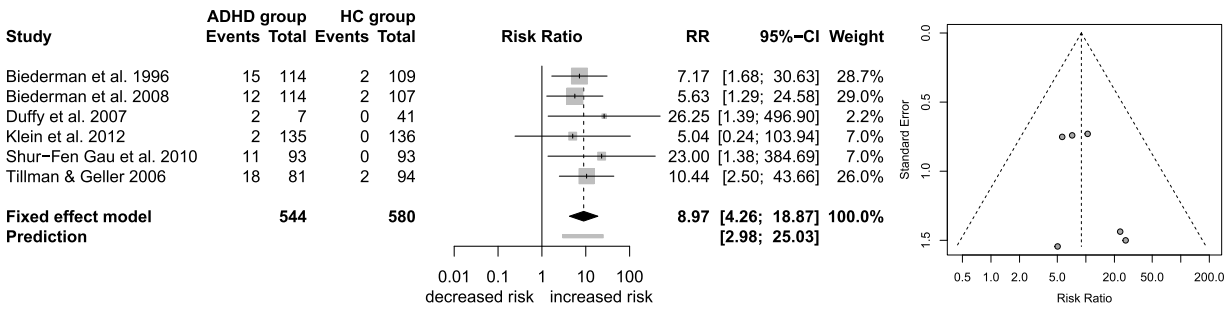

Fig. 4. Forest and funnel plots of the Risk Ratio meta-analysis.

(OR: 10.2974, 95% CI: [4.7387; 22.3765], p-value < 0.0001; Supplementary Fig. 2). The funnel plots revealed a fairly homogeneous distribution of studies across sample variance and estimate direction.

4. Discussion

The longitudinal relationship between ADHD and BD is a matter of controversies, since several prospective studies of hyperactive children outcomes showed conflicting findings (Arnold et al., 2020; Biederman, 1996; Fischer et al., 2002; Mannuzza et al., 1998; Tillman and Geller, 2006; Weiss et al., 1985). Our meta-analysis aimed to summarize the results of prospective studies of children or adolescents diagnosed with ADHD according to DSM-III-R or subsequent editions to estimate the proportion of patients who develop BD. In addition, we tried to determine whether ADHD itself poses a higher risk for BD than that observed in healthy subjects. Indeed, based on cross-sectional comorbidity studies, we hypothesized that about one or two ADHD patients in ten would be later diagnosed with BD. Ten studies were selected to this purpose, including a total of 1248 patients diagnosed with ADHD, mostly children or adolescents aged 6 to 18 years old, followed up for 4 to 33 years, with a weighted average follow-up duration of approximately 9.5 years. Only a minority (2 of 10) of these studies were specifically designed to observe the occurrence of BD in ADHD patients (Arnold et al., 2020; Tillman and Geller, 2006), while most studies reported other or general psychopathological outcomes of ADHD children over time (Biederman, 1996; Joseph Biederman et al., 2008; Halperin et al., 2011; Klein et al., 2012; Shur-Fen Gau et al., 2010) or prospectively investigated the precursors of mood disorders in high-risk individuals (Axelson et al., 2015; Duffy et al., 2007; Rudaz et al., 2020).

According to our meta-analytic synthesis of results, about 10% of ADHD patients received a BD diagnosis during their follow-up, regardless of mean age at follow-up entry and gender. Based on the limited duration of follow-up, this rate could have been underestimated. Indeed, while BD has been generally reported to first occur, on average, between the early-to-mid 20s to the early 30s, with possibly higher age at onset in BD type II (Baldessarini et al., 2010), a great proportion of the studies included in our meta-analysis (6 of 10) ended follow-up before the age of 25 years old, thus possibly preventing researchers to observe a further increase in BD rates in subsequent years.

4.1. The role of follow-up duration

Significantly, the rate of BD decreased in studies with longer mean follow-up duration. This result was largely driven by one study with the longest follow-up duration (33 years), that contributed to the highest degree of heterogeneity across studies (Klein et al., 2012). Several arguments may be put forward to account for such heterogeneity and the methodological peculiarities of the study. First, patients were recruited before DSM-III-R criteria were available. We conservatively decided not to exclude the study, despite our exclusion criteria, since the authors declared the original clinical status of included children to be "consistent with DSM-IV ADHD". Second, while all the other studies included in our meta-analysis enrolled clinically referred patients or high-risk offspring, Klein and colleagues recruited a community sample identified through teachers' referrals (Klein et al., 2012). In addition, patients with conduct problems were excluded from the sample, while relatively high rates are usually reported, ranging between 33% and 80% in the only three other studies reporting this information (Arnold et al., 2020; Biederman et al., 2008; Halperin et al., 2011), or reaching at least 27% as reported by a large epidemiological study on the general population (Larson et al., 2011). Given these arguments, the subjects recruited by Klein and co-workers are likely to represent milder forms of ADHD, decreasing the generalizability of their results to the clinical population. Finally, Klein et al., 2012, did not clearly delineate the diagnostic process, contrarily to the all the other reviewed studies, all of which reported that licensed child psychiatrists/psychologists or senior psychiatrists achieved or confirmed BD diagnoses.

When this outlier study was removed, based on the jack-knife sensitivity analysis and the methodological limitations mentioned above, a slight increase in BD rate was observed, as about 12% of patients with ADHD were found to be affected with BD at the end of follow-up. The negative relationship between follow-up duration and BD occurrence also disappeared, but we failed to confirm a significant positive association. This lack of increase in BD rates in longer follow-up studies is consistent with the age-dependent decrease in BD prevalence in epidemiological samples, and could be attributed to ascertainment biases due to early mortality, institutionalization, incarceration, and homelessness of BD patients, but also to recall bias in longer follow-ups or less frequent clinical assessments, in BD cases with a relatively benign course of illness or, more speculatively, in "developmentally limited forms" of BD (Cicero et al., 2009).

A possible, not alternative, explanation is that, in patients with ADHD, BD occurrence tend to decrease in longer follow-ups, suggesting that BD following ADHD is a specific, paediatric-onset, neurodevelopmentally-based, form of BD, different from adult-onset or older-age (neurodegenerative)-onset BD, despite phenotypical similarities. Early neurodevelopmental disorders, such as co-occurring ADHD and emotional dysregulation, may be considered a precursor in the pathway to neurodevelopmental, early-onset, bipolarity. Indeed, in about 24-50% of youth and 34-70% of adults, ADHD presents with emotional dysregulation, an impaired regulation of emotional states, excessive and inappropriate emotional expressions, high excitability and lability, temper outbursts, low tolerance to frustration, and slow return to baseline, which partially overlap with BD phenomenology (Faraone et al., 2019; Shaw et al., 2014).

Since an earlier age at BD onset of about 5 years has been repeatedly observed in comorbid patients (Masi et al., 2006b; Perroud et al., 2014; Perugi et al., 2013; Pinna et al., 2019; Tamam et al., 2008), with up to 60% of ADHD youths developing BD before 18 years old (Tamam et al., 2008), an early peak of onset in late adolescence seems plausible in this population, with decreasing probability in subsequent years. This might account for the null association between study duration and BD rates at the end of follow-up. Notably, only one of the studies included in our synthesis specified the age of BD onset in ADHD patients (Tillman and Geller, 2006). In that study, that conservatively focused on strictly defined BD type I, BD occurred on average at 11.4 years in ADHD patients, with all BD patients developing the disorder before the age of 17 years (Tillman and Geller, 2006). Further studies are thus needed to establish the timing of emergence of different forms of BD in ADHD patients.

4.2. Consistency between prospective and cross-sectional reports

The rate of 10 to 12% of ADHD patients developing BD is in line with the cross-sectional rates of 10-30% comorbidity with BD reported in adult ADHD patients (Bernardi et al., 2012; Chen et al., 2018; Kessler et al., 2006; Park et al., 2011), considering the persistence of ADHD into adulthood. This is even more the case if we assume a negative association between BD comorbidity and ADHD remission. Indeed, children and adolescents with ADHD still show significant symptoms and related impairment in adult years in approximately 40-60% of cases (Barkley et al., 2002; Faraone et al., 2006a; Sibley et al., 2016) and the persistence of ADHD has been strongly associated with BD-related comorbidities such as major depression and conduct disorder (Caye et al., 2016). Furthermore, emotional dysregulation is associated with a higher persistence of ADHD symptoms in adulthood (Biederman et al., 2010; Yoshimasu et al., 2018). Bipolar comorbidity has also been reported to interfere with the improvement of ADHD symptoms over time (Arnold et al., 2014). Hence, speculatively, if most of the 10-12% of ADHD patients who develop BD still satisfy ADHD criteria in adulthood, while more than half of the other ADHD patients remit, the expected rate of BD comorbidity in adults with ADHD would lie within the observed rates of

10-30%. Another possible explanation of discrepancies between prospective and cross-sectional accounts could stem from a sampling bias: while children with ADHD are mostly referred to paediatric psychiatric services by parents or teachers due to academic difficulties or co-occurring behavioural problems, adult ADHD patients are more likely to present to adult psychiatric services for mood and anxiety disorders. Patients recruited in adult studies, thus, represent a more frequently affectively ill subgroup of the whole, more heterogenous, population of children with ADHD. As early follow-up studies evidenced (Fischer et al., 2002; Mannuzza et al., 1998; Weiss et al., 1985), a substantial group of ADHD youths will eventually develop antisocial behaviours and will be less likely to be found in samples from adult psychiatric patients.

4.3. Consistency between prospective and register-based reports

According to the result of our second main analysis, children and adolescents with a diagnosis of ADHD were at significantly higher prospective risk of BD relative to children and adolescents without ADHD over follow-up intervals ranging between 4 and 33 years. A nine-fold increase of risk was found in ADHD patients compared with HC, which confirmed the findings obtained by the analyses of nation-wide register data (Chen et al., 2013; Meier et al., 2018). According to these latter studies, an adjusted hazard ratio of about 5 was observed for Taiwanese ADHD patients without disruptive behaviour disorders to be later diagnosed with BD, with higher ratios for comorbid patients (Chen et al., 2013), and an adjusted BD incidence rate ratio equal to 10 was found in Danish patients previously diagnosed with ADHD (Meier et al., 2018). Those register-based epidemiological studies certainly benefit from prospective data on large representative samples which enables to reduce attrition and selection biases and permit to adjust for confounding variables. However, the use of register-based diagnoses, which are pre-collected by others than researchers, may be subject to inaccuracy of assessment and lead to misclassification and nation-specific cultural and administrative influences on clinical practice (Thygesen and Ersbøll, 2014). Nevertheless, our meta-analysis of longitudinal studies, mostly conducted in North American countries, suggested a similarly high prospective risk of BD in ADHD patients. Importantly, no heterogeneity was found between the studies included in the analysis, with all of them but one (5 of 6) reporting a significant association between ADHD and subsequent BD. Finally, our finding is in line with that reported by Erskine et al., 2016, who identified a 7.1-fold increase in odds of BD occurrence in ADHD, despite the limited search strategy adopted by the authors with respect to BD. Importantly, while the studies included in the previous meta-analysis were mostly conducted by the Massachusetts General Hospital research team on the same patients, we excluded studies performed on overlapping samples.

4.4. BD as a specific outcome of ADHD

Based on our results, BD could be considered a major possible developmental outcome – or complication – of childhood and adolescent ADHD. Nonetheless, other long-term outcomes have received much more attention so far. ADHD has been found to often precede and predispose to substance abuse and dependence, antisocial behaviours, and major depression. However, according to the results of prospective investigations, the association between these latter outcomes and ADHD seems less strong than that observed for BD. Indeed, two different meta-analyses of prospective studies do not show more than three-fold increases in any substance abuse or dependence in ADHD children (Groenman et al., 2017; Lee et al., 2011). As for antisocial/disruptive disorders, a gradient of risk has been observed based on a recent meta-analysis, with decreasing odds ratios, in order, for oppositional defiant disorder (~8.8), conduct disorder (~5.1), and antisocial personality disorder (~3.1) (Erskine et al., 2016). Similarly, two- to three-fold increases in the risk of arrest, conviction and incarceration were associated with ADHD in another meta-analysis (Mohr-Jensen and Steinhausen, 2016). Finally, low to medium effect sizes have been reported, with odds ratios lower than 2, with respect to the association between ADHD and later depression (Erskine et al., 2016; Meinzer et al., 2014).

On one hand, a specifically increased risk of BD can be confirmed in ADHD patients compared to HC, which is higher than what expected based on the general predisposing effect on other kinds of psychopathology. On the other hand, ADHD could be regarded, though somewhat less specifically, as an important precursor of BD. Indeed, ADHD is one of the most frequent non-bipolar conditions diagnosed in high-risk BD offspring samples, with the highest risk ratio in a meta-analysis of comparisons with HC offspring (Lau et al., 2018). Significantly a higher rate of BD type I among relatives of ADHD probands have been observed (Faraone et al., 2012), and genetic overlap between ADHD and BD, especially when characterized by early onset, has been supported by significant single nucleotide polymorphism–based genetic correlation in a recent genome-wide analysis (van Hulzen et al., 2017). Additionally, more than one fourth of the genetic risk factors for adolescent hypomanic symptoms were found to be associated with ADHD symptoms in childhood and adolescence (Hosang et al., 2019).

4.5. Limitations

Our study displayed a number of limitations. First, a relatively limited amount of studies has been retrieved in the systematic search and included in the meta-analysis. However, according to Cochrane guidelines (Higgins et al., 2019), our meta-analysis was reasonably conducted, since the included studies could be meaningfully pooled. Such exiguity was, at least partially, related to our decision to restrain our search to prospective follow-up studies only, thus *a priori* excluding retrospective ones; on the other side of the coin, this represents a strength point of our review in terms of homogeneity of included studies and causal inferences. A major limitation was that most of these studies were not specifically aimed at assessing BD in followed-up ADHD patients, and thus likely under-reported the effective prevalence of the disorder. For this reason, timing of BD occurrence was almost never reported, though being a crucial information for clinical purposes. Similarly, other relevant clinical data of included patients were inconsistently reported across studies, preventing us from performing subgroup or meta-regression analyses, such as, for instance, pharmacological interventions, ADHD and BD subtypes, severity and psychiatric comorbidities at onset, which are known to influence psychopathological risk and developmental trajectories. One relevant exception to this issue is the study by Arnold et al. (2020), who, however, recruited high-risk patients based on subthreshold manic symptoms, which clearly contrasts with all the other included studies.

4.6. Future directions

A considerable proportion of ADHD children and adolescents is expected to develop a difficult-to-treat variant of BD, which merits further attention. As previously stated, comorbid patients will show more frequently a chronic BD course, with a higher number of mood episodes, a greater level of comorbidity, and poorer response to treatments (Bernardi et al., 2010; Jhanda et al., 2018; Nierenberg et al., 2005; Perugi et al., 2013; Pinna et al., 2019). An earlier recognition of this developmental variant of BD could allow to set proper treatments, but also, and importantly, to avoid the detrimental effects of inadequate treatments on the course of the disease and to prevent further complications, such as drug or substance abuse.

In light of clinical and epidemiological studies, a higher risk of developing BD is expected in ADHD patients, particularly in those with a family history for BD, concurrent anxiety, disruptive and sleep disorders and/or minor mood symptoms (Biederman et al., 2008; Chen et al., 2013; Duffy et al., 2019; Meier et al., 2018). Further studies are needed

to characterize the course and determine the timing of BD development in ADHD patients. Based on the described pattern of prodromal features, emotional dysregulation, both in its internalizing and externalizing facets, could be suggested as a promising psychopathological trans-nosographic heritable dimension which could underlie and facilitate the progression from ADHD to BD. Indeed, a greater risk of BD has been shown in ADHD patients scoring higher in the Child Behaviour Checklist-Dysregulation Profile, an indirect measure of emotional dysregulation (Biederman et al., 2009), that shows familial co-aggregation with BD (Biederman et al., 2018). Novel measures for the specific assessment of emotional dysregulation, including items related to affective instability and emotional impulsivity, have been developed or applied to adult ADHD and BD populations (Brancati et al., 2019; Marchant et al., 2013; Richard-Lepouriel et al., 2016). It remains, however, to be elucidated whether these measures might help clinicians to identify, among children or adolescent with ADHD, those at greater risk of BD.

4.7. Conclusions

While long-term follow-up studies of ADHD patients that specifically evaluate the occurrence of BD are lacking, our results indicate that about 10-12% of ADHD patients is expected to be later diagnosed with BD, mostly during development. It remains to be further elucidated which ones of the ADHD patients are more likely to develop BD. While putative predictors, such as emotional dysregulation, have been proposed, the prospective evidence to validate those risk factors is scarce. Importantly, the identification of a specific developmental timeframe for this transition and the validation of robust predictors of bipolarity in ADHD patients could allow an earlier diagnosis and treatment of BD, making it possible to prevent further complication of illness. Finally, the definition of specific developmental pathways to bipolarity could enable the characterization of different forms of BD, with distinctive courses and patterns of treatment response.

Contributors

Conceptualization and study design: GEB, GP, AM, GM and GS; systematic search, data analysis and manuscript drafting: GEB and GS; critical revision and supervision: GP, AM and GM.

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Declaration of Competing Interest

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Supplementary materials

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The efficacy of mindfulness-based interventions in attention-deficit/hyperactivity disorder beyond core symptoms: A systematic review, meta-analysis, and meta-regression.

Francesco Oliva [a,*], Francesca Malandrone [a], Giulia di Girolamo [b], Santina Mirabella [b], Nicoletta Colombi [c], Sara Carletto [b], Luca Ostacoli [a]

[a] Department of Clinical and Biological Sciences, University of Turin, Italy
[b] Department of Neuroscience "Rita Levi Montalcini", University of Turin, Italy
[c] Biblioteca Federata di Medicina "Ferdinando Rossi", University of Turin, Italy

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ABSTRACT

Background: Mindfulness-Based Interventions (MBIs) have been increasingly proposed as treatment in patients with Attention-Deficit/Hyperactivity Disorder (ADHD), showing promising results on different proposed outcomes, in both children and adults.
Objectives: To systematically review and meta-analyse studies concerning the effects of MBIs on either ADHD and associated features, associated clinical conditions, neurocognitive impairments, mindfulness skills, global functioning and quality of life.
Methods: Searches were conducted on five databases, including controlled and observational studies on both adults and children populations. The review process was compliant to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Meta-analyses and meta-regression models were conducted.
Results: Thirty-one full-texts were included. In both adults and children, MBIs showed to be more effective than waiting lists in improving ADHD symptoms and some other outcomes. In adults, a medium pooled effect size was shown by meta-analysis for ADHD symptoms but in some cases a publication bias was detected. Subgroup analysis and meta-regression confirmed the gap detected by our systematic review between the medium/large effect size of inactive-controlled studies and the low/negligible one of active-controlled studies. In children, no active-controlled studies have been conducted. Mindfulness Awareness Practice (MAP) and Mindfulness Based Cognitive Therapy (MBCT) were the most used protocols in adult studies, whereas a combination of MBCT and Mindfulness Based Stress Reduction (MBSR) was more preferred for children and adolescent patients.
Conclusions: Even if further studies with a better methodology are needed, we can suggest the MBIs may be useful as complementation and not as replacement of other active interventions.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder (Faraone et al., 2005; Faraone and Doyle, 2001; Levy et al., 1997; Rietveld et al., 2004; Sprich et al., 2000). The onset of ADHD takes place during childhood (American Psychiatric Association, 2013) with a prevalence of 5.3 (95% CI=5.0–5.6, Polanczyk et al., 2007) and it persists into adulthood in two-thirds of the cases (Faraone et al., 2006) affecting 2.5% of the adult population (Simon et al., 2009). The clinical presentation of ADHD may vary between patients, as inattention or hyperactivity/impulsivity could prevail or both of them could be equally represented (Faraone et al., 2015; Franke et al., 2018; Kooij et al., 2019).

ADHD treatment is multimodal, consisting of pharmacological and non-pharmacological approaches always associated with punctual psychoeducation (Kooij et al., 2019). The first-line medications are stimulants, i.e., methylphenidate (MPH) and amphetamines (Dalrymple et al., 2019). Non-pharmacological approaches (i.e., cognitive-behavioral

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* Corresponding author.
E-mail address: francesco.oliva@unito.it (F. Oliva).

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therapy - CBT, and coaching) complement medications addressing not only ADHD symptoms but also DSM-5 associated features (e.g., emotional dysregulation), neuropsychological dysfunction (Willcutt et al., 2005), delayed sleep onset (Kooij and Bijlenga, 2013; Wynchank et al., 2018), and anxiety/depression (Fayyad et al., 2017; Katzman et al., 2017).

Growing interest has been given to Mindfulness-Based Interventions (MBIs) since they have been increasingly used in combination with conventional treatments in mental health (McClintock et al., 2016). MBIs could play a role as augmentation strategies in ADHD since they have shown they can improve attention, awareness, sense of self and executive functions, and reduce impulsivity, emotional dysregulation, and stress levels (Baijal and Gupta, 2008; Hylander et al., 2017; Kozasa et al., 2012; Krisanaprakornkit et al., 2010; Lutz et al., 2008; Rapport et al., 2002; Schonert-Reichl et al., 2015; Tang et al., 2014, Tang et al., 2007; Tsai and Chou, 2016), ameliorating also some comorbid psychiatric conditions such as anxiety, depression, and substance abuse (Bueno et al., 2015; Cole et al., 2016; de Lisle et al., 2012; Gu et al., 2016; Hesslinger et al., 2002; Hofmann et al., 2010; Philipsen et al., 2007; van de Weijer-Bergsma et al., 2012; Vøllestad et al., 2012; Witkiewitz et al., 2013; Zylowska et al., 2008), even in patients with bipolar disorder (Chu et al., 2018; Lovas and Schuman-Olivier, 2018; Xuan et al., 2020).

Some systematic reviews of studies on MBIs and ADHD have already been conducted with promising, albeit still not definitive, conclusions (Cairncross and Miller, 2016; Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019; Tercelli and Ferreira, 2019; Xue et al., 2019). Overall, existing reviews have mainly focused on the effectiveness of mindfulness (or related interventions, such as meditation and yoga) in improving ADHD symptoms. The evidence of MBIs efficacy among adult patients (Lee et al., 2017) seems to be stronger than that detected in children (Chimiklis et al., 2018). Age and type of control condition seemed to affect the overall effect size on ADHD symptoms according to a prior meta-regression analysis (Xue et al., 2019). Moreover, the majority of these reviews claimed for the necessity of further investigations, pointing out the low quality and heterogeneity (Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019).

The aim of the present review was to evaluate the efficacy of MBIs in improving not only ADHD symptoms but also diagnostic associated features (i.e., emotional dysregulation, neuropsychological function impairment, circadian rhythm disorder with delayed sleep onset), health status and quality of life, and other associated conditions (e.g., anxiety and depression), focusing on the contribution of different control conditions to the overall effect.

2. Methods

2.1. Protocol registration

The review protocol was registered in the PROSPERO repository (CRD42019130639).

2.2. Search strategy for identification of studies

A literature search was performed on PubMed, Embase, CINAHL, PsycINFO, the Cochrane Central Register of Controlled Trials from the earliest dates available to June 25th, 2020 using keywords and text words for ADHD and MBIs. Moreover, we performed a search with the keywords 'ADHD', 'mindfulness' and 'attention deficit hyperactivity disorder' in Google Scholar in order to screen books and book chapters, scholarly articles, and other important grey literature related to the topic. From selected studies, cross-references were checked manually. The search strings are described in Supplementary material (S1.1).

2.3. Eligibility criteria

We included studies concerning patients with a diagnosis of ADHD. There was neither restriction by concurrent organic disease nor limit in terms of participants' gender or age (i.e., children, adolescents, and adults).

We included studies that evaluated MBIs alone or in addition to another treatment in a pre-post design, in comparison with no intervention, Waiting List (WL), Treatment As Usual (TAU) or other types of intervention (e.g. antidepressant medication, CBT, psychodynamic therapy). We included studies that provided quantitative data, as measured by standardized psychometric scales, before and after the intervention/s.

Any type of health-related outcome was included. The reasons for exclusion were: 1) qualitative studies, 2) systematic reviews, 3) case reports. No year or language restrictions were applied.

2.4. Data collection

Two authors (FO and FM) independently conducted standardized assessments to determine study eligibility, according to the inclusion criteria. First, they screened the abstracts and then retrieved and analyzed the full-texts for all the records deemed relevant. Any disagreement was solved involving a third author (LO).

Data from the selected studies were inserted in a standard template by two independent researchers (FO and FM). Article authors were reached via email for any missing information.

2.5. Quality assessment

The internal validity of the Randomized Controlled Trials (RCTs) and the quality of non-RCT studies were assessed by the Version 2 of the Cochrane risk-of-bias tool for RCTs (Sterne et al., 2019) and the MINORS Scale (Slim et al., 2003; Zeng et al., 2015), respectively. Both quality assessment tools were used according to instructions provided by authors.

The risk of bias was assessed by two independent coders (FO and FM) and any disagreements were discussed and resolved with a third reviewer (LO).

2.6. Statistical analysis

All meta-analysis procedures were performed using meta (Balduzzi et al., 2019), metafor (Viechtbauer, 2010), and dmetar (Harrer et al., 2019b) packages of R (R Core Team,2020).

We followed the same procedure for each eligible outcome (i.e., at least three controlled studies should have counted the outcome among those considered).

A random-effect-model based on inverse variance method with Hartung-Knapp-Sidik-Jonkman adjustment (Hartung, 1999) was performed to pooling effect sizes from post-intervention mean, standard deviation, and sample size of two compared groups (meta package). Hedges' g with 95% confidence interval (95%CI) and prediction interval with 95% confidence interval (95%CI) were calculated. Sidik-Jonkman method was used to estimate $\tau 2$ (Sidik and Jonkman, 2007). Heterogeneity was also assessed by Cochran's Q-statistic and Higgin's & Thompson's I^2 estimation (Higgins et al., 2003). No, low, moderate, and high heterogeneity were defined by 25%, between 25% and 50%, between 50 and 75%, and >75% I^2 values, respectively. Forest plots were used to present the model results.

Outliers were detected by checking for lack of overlap between studies and pooled confidence intervals using the dmetar package. Then, a conventional leaved-one-out (Viechtbauer and Cheung, 2010) with Baujat's graphical methods and, when possible, a more sophisticated Graphic Display of Heterogeneity (GOSH) plots with diagnostic methods (Harrer et al., 2019a; Olkin et al., 2012) were used for the influence

analysis. Finally, an adjusted model and the respective forest plot were performed excluding outliers and influential studies for a sensitivity analysis.

A contour-enhanced funnel plot and the Egger's test were used to detect publication biases (Egger et al., 1997; Peters et al., 2008). The contour-enhanced funnel plots included three shaded contours marking areas, one for each different significance level of effect size (dark blue, $0.025<p<0.05$; blue, $0.01<p<0.025$; light blue, $p<0.01$) into which the effects size of each study falls. The Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000) was adopted to calculate the bias-corrected effect size (meta package).

A subgroup analysis using a mixed-effects model (i.e., random-effects model without Hartung-Knapp-Sidik-Jonkman adjustment within subgroups, and fixed-effects model between subgroups) was conducted to evaluate the impact of the type of control condition on pooled effect size. A meta-regression model with control condition was performed and then it was compared through ANOVA test with a multiple meta-regression model using all possible dummy variables that can define subgroups (metafor package). ANOVA test included Akaike's Information Criterion with small sample adjustment (AICc) and Likelihood Ratio Test (LRT) calculations.

3. 3. Results

3.1. Study selection and study characteristics

The PRISMA flowchart describing the selection process, including reasons for exclusion, is presented in Fig. 1. The search retrieved 31 articles: 16 conducted on adults, 14 on children, and one study on a mixed sample of adolescents and adults.

3.2. Adults

All the details about included studies involving adult patients are summarized in Supplementary material S3.1.

Overall, the studies involved a sample of 1336 patients, 1040 (77.84%) of whom completed the study. The age ranged from 18 to 68 years.

The most employed MBIs protocols were MBCT, MAP and DBT.

3.3. Controlled studies on adults with ADHD

3.3.1. ADHD symptoms

All twelve controlled studies investigated the effects of MBIs on ADHD symptoms. Two of them (Cole et al., 2016; Groß et al., 2017) did not provide the required data for the computation of effect sizes and therefore were not included in the meta-analysis. Since not all the

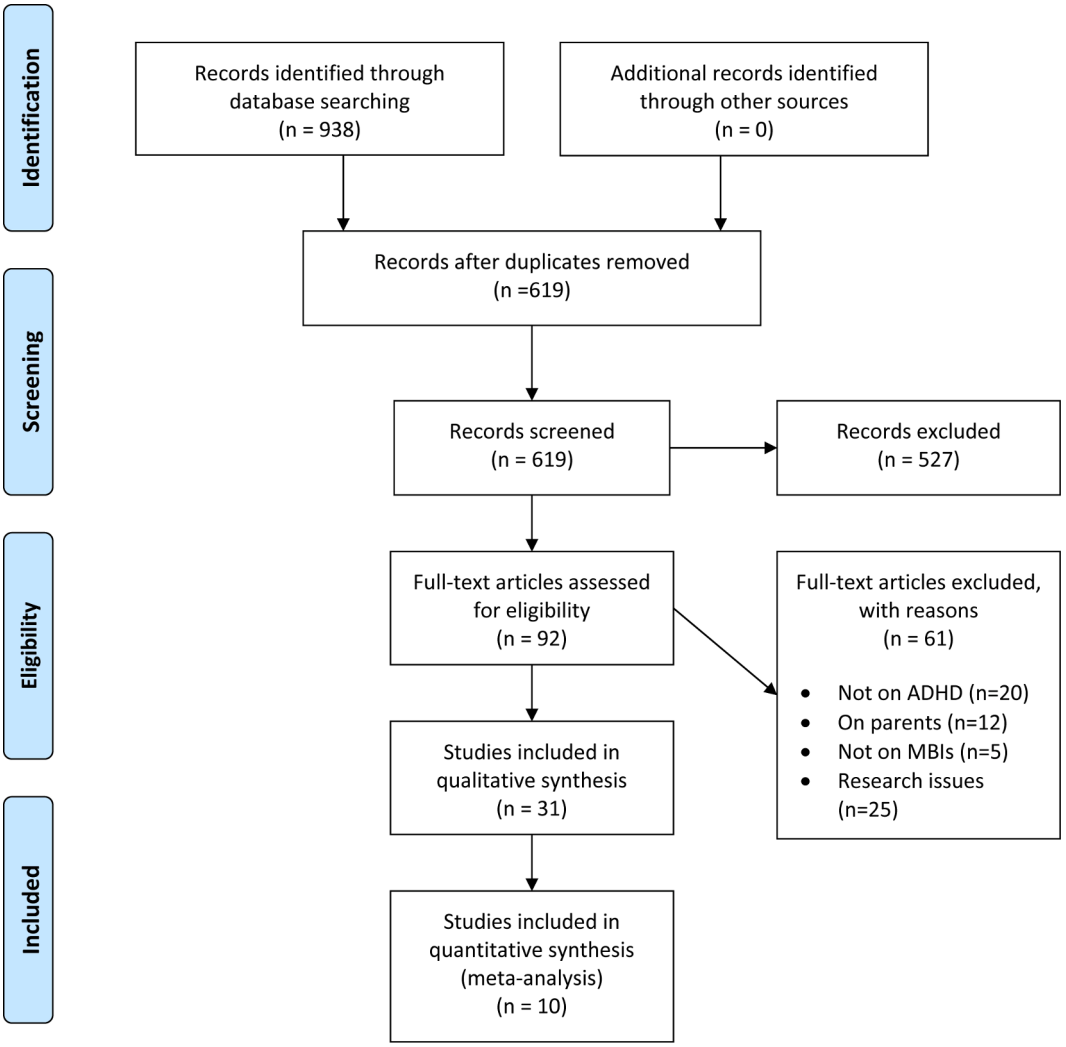

Fig. 1. PRISMA 2009 flow diagram.

eligible studies have reported results on both inattention and hyperactivity symptoms as well as ADHD total symptoms, we built three different models to include the maximum possible number of studies. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.1-S2.36).

The pooled effect size of MBIs on inattention (g=-0.69, 95%CI=-1.13/-0.25, p=0.006) was higher than either that on hyperactivity/impulsivity symptoms (g=-0.46, 95%CI=-0.80/-0.11, p=0.015) and that on ADHD total symptoms (g=-0.52, 95%CI=-0.96/-0.09, p=0.025)

Moderate and significant level of heterogeneity was detected for all three effect sizes (total symptoms, I^2=67.7%, Q=18.59, p=0.005; inattention, I^2=72.6%, Q=32.87, p<0.001; hyperactivity/impulsivity, I^2=57.1%, Q=18.67, p=0.017). No outliers were found in all three meta-analysis models, whereas some influential studies were identified. Sensitivity analysis excluding influential studies successfully reduced heterogeneity of each outcome (total symptoms, I^2=57.5%, Q=11.76, p=0.038; inattention, I^2=69.5, Q=26.24, p=0.001; hyperactivity/impulsivity, I^2=0.0%, Q=3.59, p=0.609) without any change in term of effect size of MBIs on inattention symptoms (g=-0.60, 95%CI=-0.99/-0.20, p=0.008) and with a great reduction of the effect size on ADHD total symptoms (g=-0.42, 95%CI=-0.82/-0.01, p=0.046) and hyperactivity/impulsivity symptoms (g=-0.38, 95%CI=0.61/0.15, p=0.008). A certain skewness for small-sized impacting studies could be noticed at funnel plots beyond not significant Egger's tests (total, Egger's test=-1.78, 95%CI=-9.23/-5.67, p=0.657; inattention, Egger's test=-4.02, 95%CI=-7.94/-0.10, p=0.074; hyperactivity/impulsivity symptoms, Egger's test=-2.90, 95%CI=-6.82/-1.02, p=0.183), suggesting possible publication biases. The effect size obtained by controlling for selective publication according to the trim-and-fill procedure was unchanged for total (g=-0.52, 95%CI=-0.96/-0.09, p=0.025), medium for inattention symptoms (g=0.50, 95%CI=-0.96/-0.04, p=0.035), and under significance level for hyperactivity/impulsivity (g=-0.30, 95%CI=-0.70/0.09, p=0.114).

Subgroup analysis underlined the impact of control conditions on between-studies heterogeneity for all three ADHD symptoms outcomes. Heterogeneity in both active and inactive control subgroups was null for total (Fig. 2) and attention symptoms (Fig. 3), and really low for hyperactivity/impulsivity (Fig. 4). Moreover, significant differences were found between studies with active and those with inactive control conditions in terms of effect size on total (χ2(1)=11.84, p<0.001), inattention (χ2(1)=15.99, p<0.001), and hyperactivity/impulsivity symptoms (χ2 (1)=7.79, p=0.005).

Multiple meta-regression model including both control conditions (active and inactive) and rater (patient, clinician, observer) did not outperform that with control condition alone in explaining ADHD symptoms heterogeneity of total ADHD symptoms (AICc control+rater=122.19, AICc control=11.57, LRT=1.38, p=0.846), inattentive (AICc control+rater=38.96, AICc control=11.06, LRT=2.10, p=0.552) and hyperactivity/impulsivity (AICc control+rater=53.19, AICc control=12.15, LRT=2.17, p=0.539). Indeed, the model with control condition only explained 100% of the heterogeneity and showed a significant moderation effect for total symptoms (F(1,5)=17.79, p=0.008), inattention (F(1,8)=28.54, p<0.001) and hyperactivity/impulsivity (F(1,7)=9.62, p=0.017). Among all the investigated predictors, inactive control only had a significant predictive value for both inattention (b=-0.898, t=-5.34, p<0.001) and hyperactivity/impulsivity (b=-0.578, t=-3.10, p=0.017) as well as total ADHD symptoms (b=-0.722, t=-4.22, p=0.008).

3.4. Neuropsychological functions

Overall eight studies (Bachmann et al., 2018; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Mitchell et al., 2017; Schoenberg et al., 2014) investigated neuropsychological functions. A meta-analysis on the effect of MBIs on neuropsychological functions was not conducted because of the extreme between-study difference in assessment tools and outcomes (See supplementary materials S3.1). However, four controlled studies (Fleming et al., 2015; Hepark et al., 2019; Janssen et al., 2018; Mitchell et al., 2017) have properly assessed pre-post intervention variations of executive functions with consistent tools and thus were meta-analytically investigated. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.37-S2.45). Pooled effect size was medium (g=-0.65, 95% CI=-1.24/-0.06, p=0.038) with low and non-significant heterogeneity (I^2=55.4%, Q=6.73, p=0.081). No outliers were detected and one

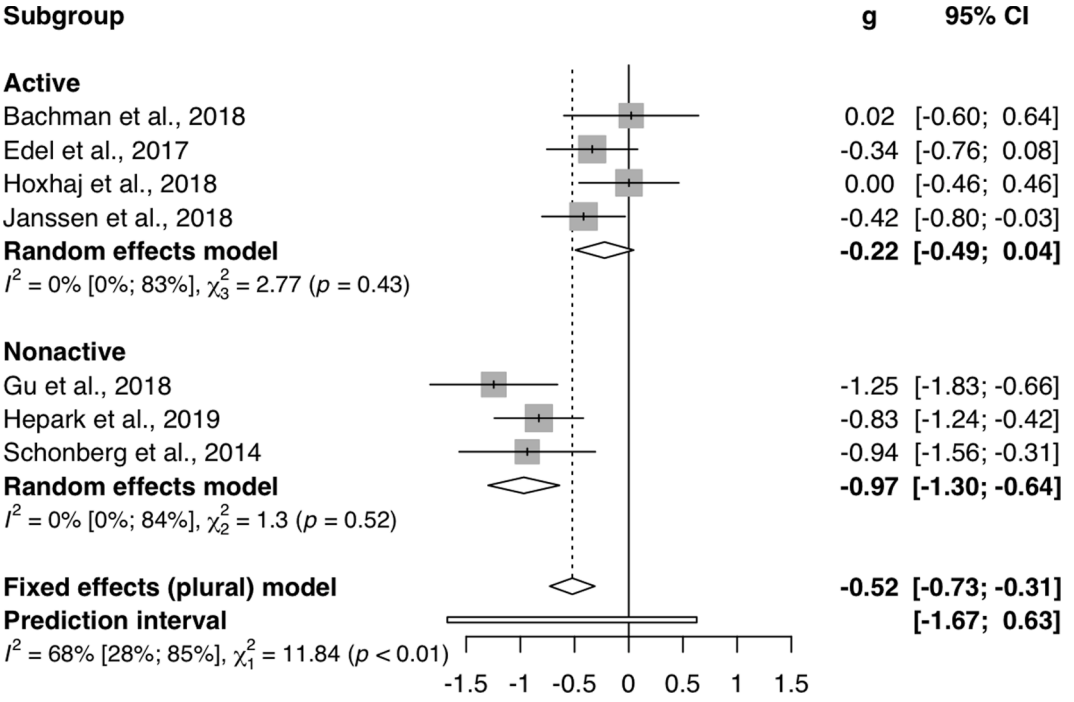

Fig. 2. Subgroup analysis for total ADHD symptoms (by control condition).

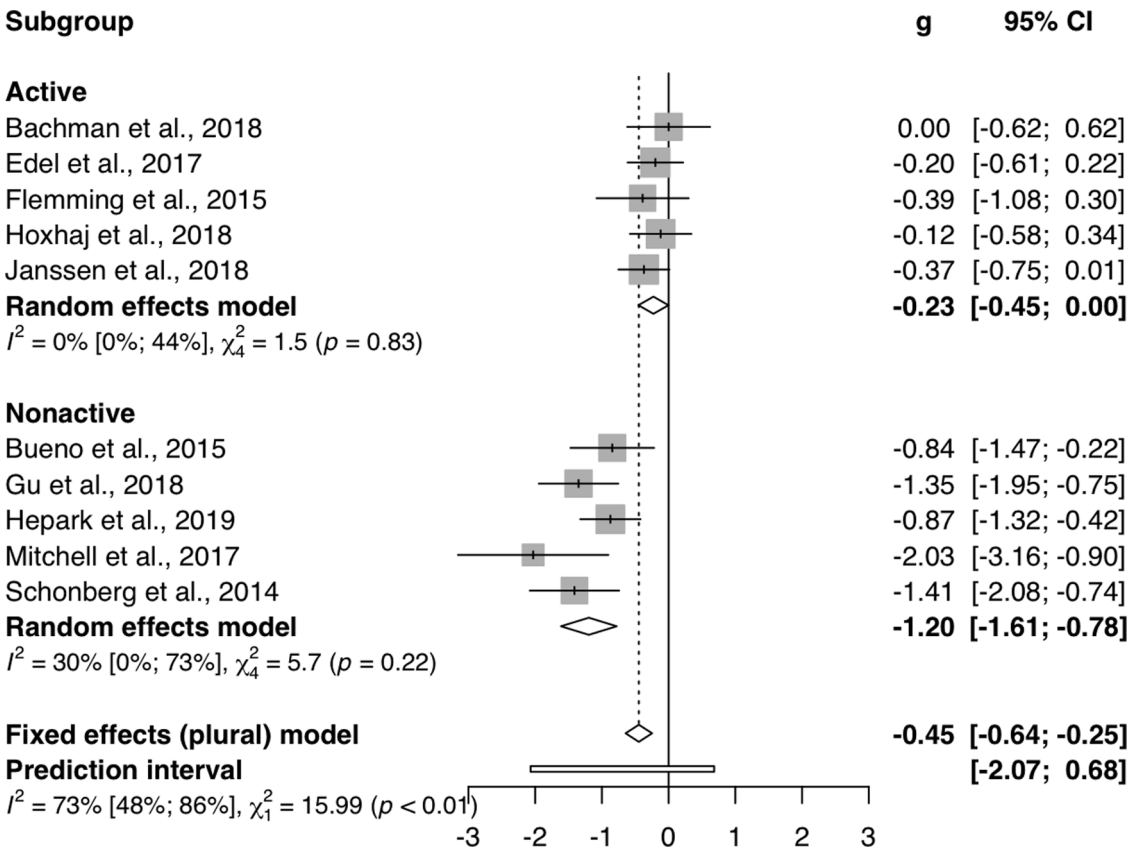

Fig. 3. Subgroup analysis for attention symptoms (by control condition).

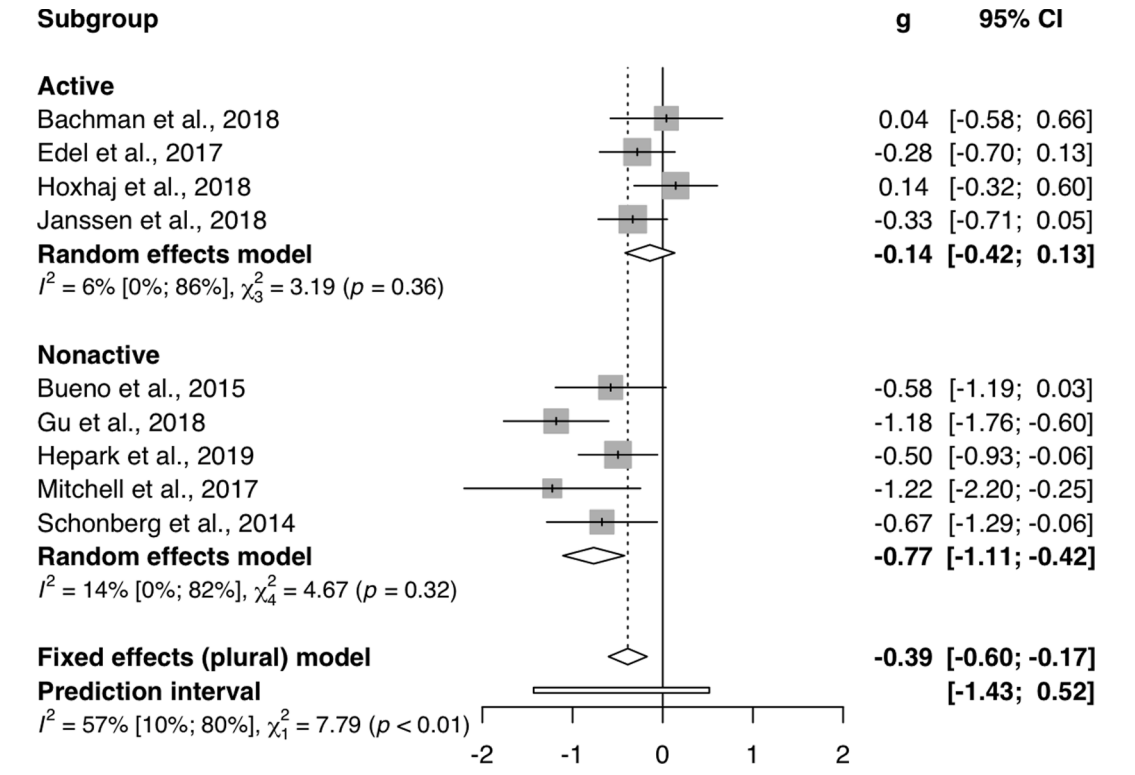

Fig. 4. Subgroup analysis for hyperactivity/impulsivity symptoms (by control condition).

influential study was identified and excluded in the sensitivity analysis, which showed a null heterogeneity (I^2=0.0%, Q=0.36, p=0.836) and an increased effect size (g=-0.89, 95%CI=-1.20/-0.57, p=0.007). However, a publication bias was detected and the model corrected according to trim-and-fill analysis presented a small effect size (g=-0.38, 95% CI=-0.97/0.22, p=0.164) and considerable heterogeneity (I^2=75.6%, Q=20.51, p=0.001).

Subgroup analysis showed a higher effect size for studies comparing MBI with inactive control conditions (χ2(1)=6.18, p=0.013; Fig. 5). The two groups presented a negligible heterogeneity (Fig. 5).

The meta-regression model with control conditions (active, inactive) fully explained the heterogeneity of effect size, but did not find any significant moderator effect (R^2=100.0%, F(1,4)= 7.90, p=0.107). No other models could be built with the available variables.

3.5. Associated conditions

Anxiety and depression were the only two associated conditions, which were investigated by at least three controlled studies.

The meta-analysis on five studies (Bueno et al., 2015; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018) investigating the efficacy of MBIs on depression showed a small effect size (g=-0.35, 95%CI=-0.64/-0.06, p=0.028) without between-studies heterogeneity (I^2=0.0%, Q=3.06, p=0.548). No outliers were detected and one possible influential study was found. Sensitivity analysis without the influential study showed a smaller effect size (g=-0.26, 95% CI=-0.43/-0.09, p=0.028) while maintaining null heterogeneity (I^2=0.0%, Q=0.55, p=0.90).

As regards anxiety, four studies (Bueno et al., 2015; Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019) were pooled showing a medium effect size (g=-0.61, 95%CI=-0.87/-0.35, p=0.005) without heterogeneity (I^2=0.0%, Q=1.08, p=0.782). No outliers were detected and one possible influential study was identified and excluded in sensitive analysis. The resulting model confirmed a moderate effect size (g=-0.53, 95%CI=-0.61/-0.46, p=0.001) without heterogeneity (I^2=0.0%, Q=0.02; p=0.988). No publication biases were found for both anxiety and depression meta-analyses. All respective forest plots, influential and sensitivity analyses, and funnel plots were presented in the Supplementary material S2 (S2.46-S2.63).

No subgroup analyses and meta-regressions were conducted considering the lack of between-study heterogeneity.

Anger and hopelessness (Cole et al., 2016), health status (Janssen et al., 2018), emotional dysregulation (Mitchell et al., 2017), and perceived stress (Schoenberg et al., 2014) were investigated in one study each. All authors reported a better outcome for MBIs than for control conditions.

3.6. Mindfulness related outcome

Two controlled studies (Cole et al., 2016; Edel et al., 2017) and six RCTs (Fleming et al., 2015; Gu et al., 2018; Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Schoenberg et al., 2014) investigated mindfulness related outcomes. A meta-analysis was conducted on seven controlled studies (see Supplementary material S2.64-S2.72 for details) as the study by Cole et al. (Cole et al., 2016) did not provide the necessary data. A medium effect size (g=0.58, 95%CI=0.25/.91, p=0.03) with a certain heterogeneity (I^2=56.5%, Q=13.78, p=0.032) was estimated. No outliers were found and one possible influential study was identified. Sensitive analysis without the influential study showed a similar effect size (g=0.66, 95%CI=0.37/0.95, p=0.002) with a not significant heterogeneity (I^2=313.9%, Q=7.34, p=0.196). A publication bias was detected and the model adjusted according to trim-and-fill procedure showed a low effect size (g=0.51, 95%CI=0.18/0.84, p=0.008) with significant heterogeneity (I^2=60.1%, Q=17.56, p=0.014).

Subgroup analysis focusing on control conditions showed a significantly high effect size for studies comparing MBI with inactive control condition (χ2(1)=4.91, p<0.026; Fig. 6). This subgroup analysis really impacted on between-studies heterogeneity as both groups presented low and not significant heterogeneity (Fig. 6).

The meta-regression model with control conditions (active, inactive) fully explained the heterogeneity of effect sizes, without showing a significant moderator effect (R^2=100.0%, F(1,5)= 4.88, p=0.078). The full model including also assessment tool and intervention as factors did not outperform that with control condition alone in explaining effect size heterogeneity (AICc control+assessment+intervention=119.29 AICc control=13.73, LRT= 6.45, p=0.168) and in revealing significant predictors.

3.7. General functioning and quality of life

Two controlled studies (Bueno et al., 2015; Cole et al., 2016) and

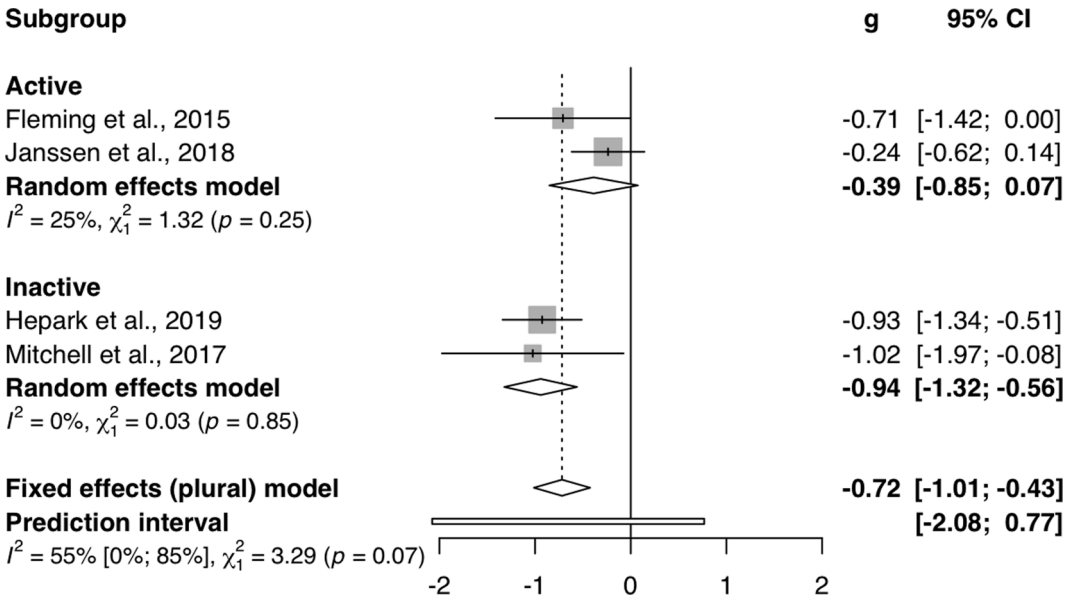

Fig. 5. Subgroup analysis for executive functions (by control condition).

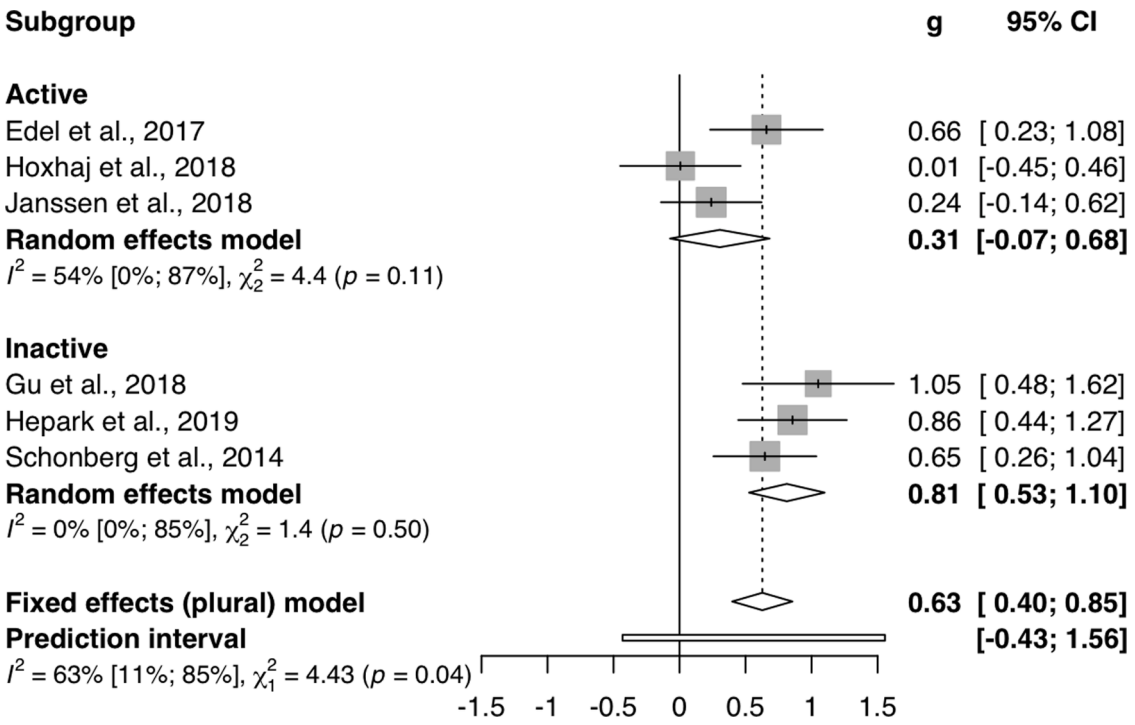

Fig. 6. Subgroup analysis for mindfulness skills (by control condition).

four RCTs (Hepark et al., 2019; Hoxhaj et al., 2018; Janssen et al., 2018; Schoenberg et al., 2014) also included these two outcomes.

A meta-analysis was conducted despite the low number of studies showing data on changes of quality of life and global functioning after MBI (see Supplementary material S2.73-S2.85 for details). The pooled effect size of the three studies considering quality of life was large (g=0.86, 95%CI=-0.59/2.31, p=0.125) and with considerable heterogeneity (I^2=75%, Q=8.06, p=0.018). No outliner was detected and one influential study was excluded. Sensitive analysis showed a large and significant effect size (g=1.24, 95%CI=0.46/2.01, p=0.031) without heterogeneity (I^2=0.0%, Q=0.06, p=0.809). A publication bias was detected and the trim-and-fill adjusted model had a small but not significant effect size (g=0.26, 95%CI=-0.94/1.46, p=0.579) with a considerable heterogeneity (I^2=86.7%, Q=30.02, p<0.001).

The pooled effect size of the three studies considering global functioning was low and not significant (g=-0.28, 95%CI=-0.82/0.26, p=0.156) and no heterogeneity was found (I^2=0.0%, Q=1.70, p=0.428). No outliner was identified and one influential study was excluded from the sensitive analysis model, which showed a large but not significant effect size (g=-0.40, 95%CI=-2.26/1.47, p=0.225) without heterogeneity (I^2=0.0%, Q=0.65, p=0.421). A publication bias was detected and the trim-and-fill adjusted model had a negligible effect size (g=-0.12, 95%CI=-0.52/0.28, p=0.449) with a certain heterogeneity (I^2=31.3%, Q=5.83, p=0.213).

No subgroup analysis and meta-regression were conducted considering the number of studies and the lack of between-study heterogeneity.

Lastly, only one study considered self-efficacy (Edel et al., 2017) finding no significant differences between MBI and control conditions in improving this outcome.

3.8. Observational studies on adults with ADHD

3.8.1. ADHD symptoms

All five studies found improvement in ADHD symptoms, reporting a significant reduction in both attention deficit and hyperactivity/impulsivity after MBIs (Hepark et al., 2014; Janssen et al., 2018; Philipsen et al., 2007; Tarrasch et al., 2016; Zylowska et al., 2008). One study specified the effect size to be large for both the symptoms domains (Hepark et al., 2014).

3.8.2. Neuropsychological functions

Two studies considered neuropsychological functioning (Janssen et al., 2017; Zylowksa et al., 2008) finding a significant enhancement of executive functions.

3.8.3. Associated conditions

Three studies (Philipsen et al., 2007; Tarrasch et al., 2016; Zylowska et al., 2008) reported a significant improvement in depressive symptoms, whereas anxiety responded to MBIs only in one out of three studies (Zylowska et al., 2008).

Two studies investigated health status (Janssen et al., 2017; Philipsen et al., 2007), finding significant improvements.

Other associated conditions were investigated in single studies (supplementary materials S3.1)

3.8.4. Mindfulness related outcomes

Two studies (Janssen et al., 2017; Tarrasch et al., 2016) observed a significant improvement in mindfulness related outcomes after MBI.

3.8.5. General functioning and quality of life

Quality of life (Hepark et al., 2014), general functioning (Janssen et al., 2017), and satisfaction with life (Tarrasch et al., 2016) were investigated in single studies (supplementary materials S3.1).

3.9. Risk of bias and quality of the studies on adults with ADHD

Nine RCTs were assessed with RoB2 (Supplementary material S1.2). As can be seen in Supplementary material S1.3, several methodological weaknesses were found. No study reached an overall low risk of bias.

Similarly, all eight observational and controlled studies showed a high risk of bias (Supplementary material S1.4).

3.10. Children and adolescents

Fifteen studies were included on children and adolescents with ADHD (see Supplementary material S3.2 for details). The whole population was composed by 412 children and adolescents, 384 (93.2%) of whom completed the study. The age ranged from seven to 16 years.

The most adopted protocol was a combination of MBSR and MBCT.

3.11. Controlled studies on children and adolescents with ADHD

3.11.1. ADHD symptoms

ADHD symptoms were measured in seven (Huguet et al., 2019; Muratori et al., 2020; Sidhu 2015; Rynczak, 2013; van der Oord et al., 2012; Vanzin et al., 2020a, Vanzin et al., 2020b) out of the eight controlled studies included. Two studies (Rynczak, 2013; Muratori et al., 2020) also considered impulsivity as a separate outcome, whereas Sibalis et al. (Sibalis et al., 2019), Sidhu (Sidhu 2015), and Vanzin et al. (Vanzin et al., 2020b) measured attention alone. In particular, the latter investigated focused and sustained attention, attention inhibition and flexibility. MBI outperformed any control condition, the only two exceptions being Vanzin et al. (Vanzin et al., 2020a; Vanzin et al., 2020b) who did not find any difference between ACT and placebo drugs.

3.11.2. Associated conditions

Only one controlled study considered emotion dysregulation as its outcome and found MBI significantly outperformed control condition in improving emotional dysregulation (Huguet et al., 2019).

3.11.3. Mindfulness related outcomes

Mindfulness level among children was measured in two studies (Muratori et al., 2020; van der Oord et al., 2012).

3.12. Observational studies on children and adolescents with ADHD

3.12.1. ADHD symptoms

Overall, these were the most investigated outcomes. Inattention was considered in seven studies (Haydicky et al., 2015; Huguet et al., 2017; van de Weijer-Bergsma et al., 2012; Vanzin et al., 2020b; Worth, 2014; Zhang et al., 2017; Zylowska et al., 2008) whilst hyperactivity/impulsivity was investigated only in four of them (Haydicky et al., 2015; Huguet et al., 2017; Worth, 2014; Zylowska et al., 2008). ADHD symptoms were always reduced after MBIs, only in one study the control condition outperformed MBI in ameliorating hyperactivity/impulsivity (Haydicky et al., 2015).

3.12.2. Neuropsychological functions

Executive functions were investigated in four studies (Huguet et al., 2017; van de Weijer-Bergsma et al., 2012; Worth, 2014; Zhang et al., 2017). Only Worth (Worth, 2014) did not find MBI outperforming the control condition.

Behavioral problems were considered in three studies (Carboni et al., 2013; van de Weijer-Bergsma et al., 2012; Zhang et al., 2017), however, only one of them found this outcome to significantly respond to MBI (Carboni et al., 2013).

3.12.3. Associated conditions

Three studies evaluated anxiety response to MBI (Haydicky et al., 2015; Huguet et al., 2017; Zylowska et al., 2008). Post-treatment anxiety levels were lower only in one study (Zylowska et al., 2008) as Huguet et al. (Huguet et al., 2017) noticed a statistically significant reduction of parent-reported but not of self-reported anxiety symptoms and Haydicky et al. (Haydicky et al., 2015) did not find any change from baseline.

The same three studies also evaluated depressive symptoms and again only Zylowska et al. (Zylowska et al., 2008) did find a significant pre-post intervention reduction.

Fatigue was considered in a single study (van de Weijer-Bergsma et al., 2012), which did not find any improvement after MBI (van de Weijer-Bergsma et al., 2012).

3.12.4. Mindfulness related outcomes

Mindful skills (Worth, 2014), acceptance level (Haydicky et al., 2015), and mindfulness awareness (van de Weijer-Bergsma et al., 2012) were considered in one study each, with conflicting results.

3.13. Risk of bias and quality of the studies on children and adolescents with ADHD

Three RCTs were assessed with RoB2 (Supplementary material S1.2). The study showed a high risk of bias. Conversely, two studies showed some concerns only (Huguet et al., 2019; Muratori et al., 2020). All eleven observational and controlled studies showed a high risk of bias (Supplementary material S1.4).

4. Discussion

Consistently with previous systematic reviews and meta-analysis (Cairncross and Miller, 2016; Chimiklis et al., 2018; Evans et al., 2018; Lee et al., 2017; Poissant et al., 2019; Tercelli and Ferreira, 2019; Xue et al., 2019) ADHD symptoms are confirmed to be the most studied outcomes. As regards adults, the highest efficacy of MBIs was detected on attention symptoms and total ADHD symptoms (medium effect size). The small effect on hyperactivity-impulsivity disappeared when publication bias adjustment was applied as well as sensitivity analysis greatly reduced the effect size on hyperactivity-impulsivity and even that on total ADHD. Overall, MBIs confirmed their efficacy on ADHD symptoms regardless of the different adjustments, though its effect seems to be higher on attention symptoms.

Subgroup analysis and meta-regression were consistent in supporting a significantly higher efficacy of MBIs vs. inactive controls than vs. active controls, which seemed to fully explain the pooled effect size heterogeneity. According to our findings in the majority of active-controlled studies, MBIs failed to outperform psychoeducation and skills training groups. The confidence interval of pooled effect size of studies with active controls included the null value in total ADHD symptoms and hyperactivity/impulsivity subgroup analysis, but not in that of attention symptoms. This small advantage of MBIs on psychoeducation should be confirmed by future and better designed RCTs, however, MBIs option should be taken into account in patients with predominantly inattentive presentation or if residual attention symptoms persist after psychoeducation or skills training. Among the inactive-controlled RCTs, three studies stood out for their large effect size on attention and total symptoms (Gu et al., 2018; Mitchell et al., 2017; Schoenberg et al., 2014), which was greater than that reached by the most efficacious stimulant treatments (see Cortese et al., 2018 for a comprehensive meta-analysis). Quality and size mainly explain this results, but differences between control groups (i.e., WL for aforementioned MBIs' studies and placebo drugs for stimulants RCTs) should be also taken into account, since some studies have reported a considerable pre-post effect of placebo drug at least in children (Sandler et al., 2010; Sandler and Bodfish, 2008). It could be suggested that any intervention seems to have a significantly higher effect than WL in improving ADHD symptoms.

Beyond ADHD symptoms, mindfulness skills, neuropsychological performance, and depression were the most studied outcomes in the adult ADHD population.

Concerning mindfulness skills, a medium effect size was estimated by meta-analysis that persisted after sensitivity analysis and publication bias adjustment, but it was affected by heterogeneity due to control conditions: MBIs showed a large effect size when compared to inactive control, whereas had no effect when compared to active control. Future studies should investigate this aspect, also evaluating the actual amount of mindfulness daily practice.

Only half of active-controlled studies found MBIs more effective in

improving executive functions. Meta-analysis partially solved this issue as both of those active-controlled studies had a confidence interval of effect size that included the null value. Overall sample size was medium without heterogeneity but both sensitivity analysis and publication bias adjustment really affected this estimation. Subgroup analysis found a large effect size for inactive-controlled studies, which contributed significantly to the overall effect size. Conversely, active-controlled studies did not show any effect. Meta-regression did not confirm a moderator effect of control condition on heterogeneity. Further studies are needed to confirm MBIs efficacy in ameliorating this outcome, regardless of the control condition. Moreover, a possible latency of the response could be involved as in a longitudinal study MBI showed a positive effect on executive functions only at follow-up but not at post-treatment. Only one study considered working memory, revealing that MBI and psychoeducation are similarly effective.

The poor performance of MBIs on depression levels suggested by our systematic review was confirmed by meta-analysis conducted on controlled studies that found a small and homogeneous effect size, regardless of sensitivity analysis and without publication bias. Conversely, anxiety levels seemed to remarkably improve according to meta-analysis conducted on controlled studies, which showed a medium effect size without heterogeneity and publication bias, which persisted after sensitivity analysis. Further active-controlled studies should include this outcome to provide data on the efficacy size of MBIs on anxiety in ADHD patients.

According to our findings, MBIs seemed not to confirm in ADHD patients the efficacy found in other clinical populations in reducing depressive and anxiety symptoms (Hofmann and Gómez, 2017).

Global functioning and quality of life are both improved by MBIs in all observational studies and once again MBIs were more effective than inactive but not than active controls. A meta-analytic subgroup analysis to confirm systematic review findings was not allowed due to the paucity of studies for either quality of life and global functioning. The meta-analysis showed a large effect size on quality of life with a lot of heterogeneity due to low effect reported by one active-controlled study, that was greatly reduced after publication bias adjustment, confirming the need for further controlled studies investigating this outcome. As regards global functioning, no effect of MBI was detected by meta-analysis even after publication bias adjustment.

Particularly noteworthy is that few authors have studied emotional dysregulation (Mitchell et al., 2017; Philipsen et al., 2007), anger outbursts (Cole et al., 2016), and delayed sleep onset (Tarrasch et al., 2016).

No study has considered self-esteem as an outcome, which is instead a common condition in ADHD, and can also lead to misdiagnosis (i.e., dysthymia, depression), significantly affecting patients' functioning and quality of life (Kooij et al., 2019).

As regards children and adolescents, the number of studies and the overall sample was really smaller than those including adults and no active-controlled studies have been conducted yet. As with adults, ADHD symptoms confirmed to be the most studied outcome. All the controlled and about half of observational studies found significant improvements. Notably, MBIs showed to be more effective on inattention than on hyperactivity/impulsivity. A meta-analytic investigation on children studies could not be performed because of the low number of studies.

With regard to other outcomes, really few observational studies considered depression, anxiety (in one study reported as internalizing symptoms), mindfulness related outcomes, and executive functions, whereas no controlled studies have investigated neuropsychological functions, general functioning and quality of life.

The most relevant finding regarding children and adolescents is that only one RCT considered emotional dysregulation, whereas none have evaluated the effect of MBIs on the other ADHD diagnostic-associated features, i.e., working memory and sleep quality.

The included studies had several limitations. The risk of bias assessment revealed that 75% of the RCTs have at least some concerns and that all controlled or observational studies have a high risk of bias. Only few studies performed a follow-up and the sample size was small in almost all of the included studies. Ad-hoc mindfulness protocols have often been used instead of already validated protocols to fit the studied populations (e.g., protocols adapted to children, to the school context or, more generally, to ADHD) without providing sufficient details on the adopted interventions and that reduces the methods reproducibility.

No studies compared mindfulness different protocols with each other or focused on the efficacy of mindfulness single components (self-judgment, self-compassion, participatory attention and observation, non-judgmental labeling, acceptance, etc.). Moreover, the number and the duration of sessions varied considerably across the studies. Few studies reported data on acceptability rate and adherence. Altogether, these limitations have important consequences on the possibility to draw a solid conclusion regarding the effectiveness of MBIs in ADHD and on the estimation of a true effect size during meta-analytic evaluation.

The selected studies also had some strengths. In most of the articles the outcome evaluation criteria were well explained and the assessment tools were validated. Furthermore, each study investigated a wide variety of outcomes, offering an overview of the potential that MBIs could have in treating patients with ADHD.

4.1. Limitations and strengths of this review

To our knowledge, this is the first systematic review that included any type of study design, MBI protocol, outcome, and age of the population. According to previous reviews findings about age, data were collected separately for adults and children, and subgroup analysis and meta-regression were performed to evaluate the impact of the type of control population on effect size. Moreover, unlike prior meta-analyses (Xue et al., 2019), influential studies were detected using different levels of methods (leave-one-out, Baujat's graphical method, and GOSH method).

4.2. Implications for clinical practice and research

This systematic review offers new perspectives for future research. The low general methodological quality highlights the need to conduct more active-controlled studies, on larger sample sizes with measurement at follow-up. Future studies should choose validated mindfulness protocols in order to reduce the heterogeneity and increase replicability and comparability.

Concerning outcomes, the systematic review highlights the importance of a deeper investigation on the most common ADHD associated features (i.e., emotional dysregulation, executive functions and working memory, delayed sleep onset). Future studies should also include among their outcomes the commonly present low self-esteem, especially when anxiety and depression are investigated.

From a clinical standpoint, according to the poor available evidence, we cannot conclude that MBIs are superior to other active interventions in ameliorating all the considered outcomes, suggesting a role as complementation and not as replacement of the psychoeducation in the management of patients with ADHD, consistently with some current guidelines' recommendations (Kooij et al., 2019).

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CRediT authorship contribution statement

Francesco Oliva: Conceptualization, Formal analysis, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Francesca Malandrone:** Writing - review & editing, Investigation, Methodology, Visualization, Writing - original draft, Writing -

original draft, Writing - review & editing. **Giulia di Girolamo:** Data curation, Writing - review & editing. **Santina Mirabella:** Data curation, Writing - original draft. **Nicoletta Colombi:** Methodology, Resources, Validation. **Sara Carletto:** Investigation, Supervision, Writing - review & editing. **Luca Ostacoli:** Conceptualization, Project administration, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.05.068.

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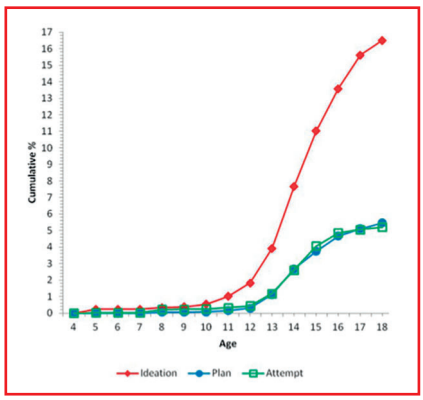

NEUROPSICHIATRIA INFANTILE

SARA CARUCCI[1], GIUSEPPE ABBRACCIAVENTO[2]

[1]*Clinica di Neuropsichiatria dell'Infanzia e dell'Adolescenza, ARNAS "G. Brotzu", Cagliari*
[2]*UOC di Neuropsichiatria Infantile, IRCCS Materno-Infantile "Burlo Garofolo", Trieste*

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ADHD

Non è soltanto un disturbo della prima infanzia né tipicamente maschile, è un disturbo complesso ed eterogeneo con traiettorie variabili che persistono sino all'età adulta. Gli individui affetti differiscono su multipli livelli quali: rischio genetico, esposizione ambientale, comorbidità, struttura e funzionalità cerebrale, aspetti cognitivi e motivazionali. Il pediatra può individuare i primi campanelli di allarme e incoraggiare la *compliance* agli interventi proposti oltreché valutare l'eventuale insorgenza di comorbidità che possono sopraggiungere nel percorso evolutivo. Riconoscere tutti questi aspetti è fondamentale per potenziare le opportunità cliniche e lavorare nell'ottica di una Medicina di precisione.

• Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet 2020;395(10222):450-462. doi: 10.1016/S0140-6736(19)33004-1.
• Narducci C. Traiettorie evolutive: una lezione dall'ADHD. Medico e Bambino 2021;40(5):321-4 doi: 10.53126/MEB40321.

AUTISMO, SCREENING

Lo screening dei disturbi dello spettro autistico (DSA) e la diagnosi precoce sono oggi temi di crescente interesse per pediatri ed esperti dei disturbi del neurosviluppo. Sebbene non siano stati ancora individuati predittori precoci degli *outcome* evolutivi per DSA (sviluppo del linguaggio e sviluppo cognitivo), recenti studi hanno individuato specifici segni clinici, valutabili con strumenti di screening tra i 12 e i 18 mesi nell'ambulatorio del pediatra, in grado di suggerire fragilità del neurosviluppo e orientare verso un più rapido invio allo specialista. Ad esempio: attenzione condivisa alterata, assenza di semplici gesti comunicativi, presenza di movimenti stereotipati con dita vicino agli occhi.

• Devescovi R, Monasta L, Bin M, et al. A Two-Stage Screening Approach with I-TC and Q-CHAT to Identify Toddlers at Risk for Autism Spectrum Disorder within the Italian Public Health System. Brain Sci 2020;10(3):184. doi: 10.3390/brainsci10030184.

BISOGNI E RISORSE

A livello legislativo viene definito come articolare i Servizi di Neuropsichiatria a livello nazionale: Unità Operative Territoriali ogni 100.000 abitanti e Unità Operative Ospedaliere (in presidi di II e III livello). A distanza di 21 anni dalla formulazione di tali raccomandazioni, si continua a registrare una estrema disomogeneità dei Servizi a livello nazionale, con ampi territori sprovvisti di neuropsichiatri o intere regioni prive di Unità Ospedaliere dedicate. A fronte di un costante aumento dell'utenza, senza un accorato sostegno a questa branca specialistica i pazienti sempre più spesso dovranno rinunciare al diritto alla cura.

• Decreto ministeriale 24 aprile 2000. Adozione del progetto obiettivo materno-infantile relativo al "Piano sanitario nazionale per il triennio 1998-2000".

BIPOLARE

Il disturbo bipolare a insorgenza precoce (< 18 anni) ha una prevalenza variabile tra l'1,1% e il 2,5%. È associato a un decorso di malattia più severo con peggior funzionamento globale, più elevato rischio di suicidio e aumentata comorbidità, in particolare ADHD e ansia. La stabilità diagnostica in 10 anni varia tra il 73% e il 100%; la remissione da un episodio indice è stimata tra l'81,5% e il 100%, le recidive hanno un tasso tra il 35% e il 67%, mentre la prevalenza cumulativa di tentativi di suicidi in 5 anni dall'insorgenza del disturbo è stimata intorno al 20%. Più precoce è l'età di esordio, peggiore è il decorso clinico. Se l'identificazione e il trattamento precoce possano migliorare la prognosi nel lungo termine è ancora da chiarire.

• Cirone C, Secci I, Favole I, et al. What Do We Know about the Long-Term Course of Early Onset Bipolar Disorder? A Review of the Current Evidence. Brain Sci 2021;11(3):341. doi: 10.3390/brainsci11030341.

DISTURBO DELLA CONDOTTA ALIMENTARE, PREVENZIONE

Programmi di prevenzione basati sulla dissonanza cognitiva risultano maggiormente efficaci rispetto ad azioni di sensibilizzazione sulla patologia e sull'igiene alimentare. La dissonanza cognitiva è un approccio che utilizza principi di persuasione per promuovere l'accettazione del proprio corpo e modulare idee di magrezza già interiorizzate. Sebbene altri programmi di prevenzione nell'ambito familiare risultino ancora poco studiati, si ipotizzano benefici con interventi diretti sui genitori, affrontando tematiche che riguardano l'idea e l'immagine di magrezza, l'accettazione del corpo e del peso e il contrasto all'inadeguatezza.

• Le LK, Barendregt JJ, Hay P, Mihalopoulos C. Prevention of eating disorders: A systematic review and meta-analysis. Clin Psychol Rev 2017;53:46-58. doi: 10.1016/j.cpr.2017.02.001.

Disturbo di condotta

Nonostante il suo alto costo a livello individuale e sociale, attualmente nessun farmaco ha l'indicazione per il trattamento di questo disturbo, a eccezione del *Risperidone* nei soggetti con disabilità intellettiva. Le linee guida suggeriscono gli interventi psicoeducativi come prima linea di trattamento a causa della mancanza di evidenze rispetto ai trattamenti farmacologici. La presenza di tratti calloso-anemozionali e specifici *pattern* di funzionamento neuropsicologico dovrebbero essere maggiormente investigati per lo sviluppo di terapie mirate adeguate.

• Balia C, Carucci S, Coghill D, Zuddas A. The pharmacological treatment of aggression in children and adolescents with conduct disorder. Do callous-unemotional traits modulate the efficacy of medication? Neurosci Biobehav Rev 2018;91:218-38. doi: 10.1016/j.neubiorev.2017.01.024.

Depressione

Rappresenta una delle patologie psichiatriche più debilitanti con alto rischio di recidive, uso di sostanze e rischio suicidario e una prevalenza intorno al 2% nei bambini e dal 4% all'8% negli adolescenti. Il rischio di depressione nei soggetti con malattie croniche è sino a 2-3 volte superiore rispetto alla popolazione pediatrica generale. È importante non sovrastimare la presenza di sintomi depressivi in soggetti che presentano una fisiologica alterazione emotiva reattiva alla malattia, tuttavia sintomi vegetativi associati a senso di colpa, impotenza, perdita di speranza, irritabilità e labilità affettiva meritano di essere approfonditi al fine di escludere un disturbo depressivo maggiore.

• Malas N, Plioplys S, Pao M. Depression in Medically Ill Children and Adolescents. Child Adolesc Psychiatr Clin N Am 2019;28(3):421-45. doi: 10.1016/j.chc.2019.02.005.

Disturbo da sintomi somatici

Il comportamento di adolescenti con disturbi da sintomi somatici (SSD) nel periodo del *lockdown*, caratterizzato dalla sospensione della scuola, ci ha permesso di ampliare le conoscenze su tale quadro diagnostico. In un recente studio sono stati confrontati alcuni indicatori di distress psicologico (dolori somatici, ansia sociale, depressione, tensione e irrequietezza) tra un gruppo di adolescenti con pregressa diagnosi di SSD e un gruppo di controllo senza storia neuropsichiatrica. I dati mostrano che i giovani con diagnosi di SSD registravano valori significativamente inferiori di stress percepito rispetto ai coetanei del gruppo di controllo. Ciò suggerisce che le difficoltà di adattamento nell'ambito scolastico potrebbero rappresentare uno dei principali meccanismi all'origine del disturbo. Potrebbe quindi risultare vantaggioso un maggiore coinvolgimento della scuola nei processi di prevezione e di cura per questo tipo di condizione.

• De Nardi L, Abbracciavento G, Cozzi G, et al. Adolescents with somatic symptom disorder experienced less anxiety and depression than healthy peers during the first COVID-19 lockdown. Acta Paediatr 2021 Apr 16. doi: 10.1111/apa.15877.

Dialectical Behavior Therapy

Dialectical Behavior Therapy (DBT) è un trattamento non farmacologico con evidenze di efficacia, validato per l'autolesionismo non suicidario e per disturbi della condotta alimentare con abbuffate. Consiste in una combinazione di psicoterapia individuale, gruppo di *skills training*, consultazione telefonica e *team meeting* di consultazione. Si sviluppa in quattro fasi. Nella fase 1 (addestramento delle abilità dialettico comportamentali) l'obbiettivo è diminuire i comportamenti disadattivi e disfunzionali migliorando l'aderenza al trattamento; nella fase 2 (disperazione tranquilla) l'agito è controllato, ma la sofferenza emotiva è ancora presente e l'obiettivo è di accettare una gamma completa di emozioni; la fase 3 ha l'obiettivo di risolvere i problemi ordinari di vita; nella fase 4 aumenta il senso di completezza.

• Linehan MM, Wilks CR. The Course and Evolution of Dialectical Behavior Therapy. Am J Psychother 2015;69(2):97-110. doi: 10.1176/appi.psychotherapy.2015.69.2.97.

Encefalite autoimmune

L'encefalite autoimmune non è rara. Anzi, è probabile che sia, a qualsiasi età, la forma più frequente di encefalite, costituendo il gruppo più numeroso di quel cinquanta percento dei casi che ancora oggi rimane senza una diagnosi eziologica. La forma che interessa il bambino e l'adolescente è quasi sempre quella dovuta alla presenza di autoanticorpi contro il recettore del N-metilD-aspartato (NMDA-R) il cui dosaggio nel liquor e nel sangue sarò utile per la diagnosi. L'importanza di conoscere questo argomento risiede principalmente nel fatto che si tratta di encefaliti suscettibili di terapia (corticosteroidi, immunoglobuline ad alte dosi, anticorpi monoclonali contro i linfociti B - rituximab) e la cui prognosi dipende dalla tempestività della diagnosi e del trattamento. La clinica è caratterizzata dalla presenza concomitante di segni neurologici quali: disturbi del movimento e convulsioni, associati a disturbi del comportamento e della personalità, insonnia, agitazione, allucinazioni, disturbi del linguaggio (fino al mutismo) e, a volte, segni di disregolazione autonomica (frequenza cardiaca, pressione arteriosa, distermia). La RM non aiuterà nella diagnosi se non per il fatto che è quasi sempre negativa. Cosa importante da ricordare è che, nella bambina/adolescente, la metà dei casi si accompagna alla presenza di un teratoma ovarico: tumore che esprime il NMDA-R e che va cercato con attenzione e asportato immediatamente per ottenere la guarigione.

• Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med 2018;378(9):840-51. doi: 10.1056/NEJMra1708712.

Epidemiologia e psico-educazione

La prevalenza mondiale dei disturbi mentali in età evolutiva è stimata intorno al 13,4%: ansia 6,5%, disturbi dirompenti 5,7%, ADHD 3,4% e disturbi depressivi 2,6% con un grosso impatto economico e sociale. Tali dati evidenziano l'importanza di un'opportuna prevenzione e promozione della salute mentale. I domini principali di una buona salute mentale includono l'approccio e la conoscenza dei disturbi, autostima, abilità cognitive, performance scolastiche, abilità sociali e relazionali, salute fisica e sessuale, qualità di vita.
Tra i vari tipi di intervento la psico-educazione risulta quello maggiormente efficace nel promuovere la conoscenza della salute mentale e migliorare le abilità cognitive.

• Salazar de Pablo G, De Micheli A, Nieman DH, et al. Universal and selective interventions to promote good mental health in young people: Systematic review and meta-analysis. Eur Neuropsychopharmacol 2020;41:28-39. doi: 10.1016/j.euroneuro.2020.10.007.

EPILESSIA E MEDICINA DI PRECISIONE

Le tecniche avanzate di Neurofisiologia e di *Neuroimaging* consentono oggi di localizzare con maggiore precisione displasie corticali focali (FCD), sempre più frequentemente diagnosticate e quindi bersaglio chirurgico di epilessie focali pediatriche resistenti ai farmaci. Un sottogruppo di questi pazienti presenta mutazioni che coinvolgono un gruppo di geni tra cui quelli associati alla sclerosi tuberosa TSC1 e TSC2. In questi pazienti il trattamento aggiuntivo con inibitori farmacologici di mTOR risulta efficace nel controllo delle crisi e il suo impiego in combinazione con la chirurgia potrebbe rappresentare un esempio di trattamento personalizzato dell'epilessia.

• Guerrini R, Barba C. Focal cortical dysplasia: an update on diagnosis and treatment. Expert Rev Neurother 2021:1-12. doi: 10.1080/14737175.2021.1915135.

EPILESSIA, TRANSIZIONE

Rappresenta il passaggio di presa in carico dall'età evolutiva all'età adulta e risulta una fase di significativa vulnerabilità psicologica. In letteratura viene posta grande attenzione ai passaggi evolutivi nell'ambito dell'epilessia dove il processo di transizione deve tener conto che il quadro clinico neurologico tende a variare nell'età adulta.
Alcune sindromi epilettiche evolvono richiedendo trattamenti differenti rispetto a quelli avviati in età evolutiva e in alcune specifiche condizioni nel corso del tempo possono comparire comorbidità psichiatriche modificando i bisogni di salute. È quindi necessario porre molta cura in questa fase di passaggio, ponendo maggiore attenzione alle possibili evoluzioni cliniche e alla comparsa di nuovi bisogni di salute.

• Nabbout R, Andrade DM, Bahi-Buisson N, et al. Outcome of childhood-onset epilepsy from adolescence to adulthood: Transition issues. Epilepsy Behav 2017;69:161-9. doi: 10.1016/j.yebeh.2016.11.010.

NEUROPSICHIATRIA INFANTILE

La Neuropsichiatria infantile svolge attività di prevenzione, diagnosi, cura e riabilitazione di patologie neurologiche, psichiatriche e di disordini neuropsicologici della popolazione in età 0-17 anni, e di tutti i disordini dello sviluppo del bambino e dell'adolescente nelle sue varie linee di espressione psicomotoria, cognitiva, linguistica, affettiva e relazionale.
L'ampio ventaglio di competenze del neuropsichiatra infantile si declina oggi in modo differente nelle diverse realtà locali del Paese per via delle peculiari cornici culturali, di contesto e di formazione nelle quali si è sviluppata la disciplina.

• Calamoneri F. Storia della Neuropsichiatria infantile in Italia e nel mondo. In: Persico A (a cura di). Manuale di Neuropsichiatria Infantile e dell'Adolescenza. Società Editrice Universo 2018:1-17.

OPPOSITIVO PROVOCATORIO (DOP)

Tale disturbo nell'infanzia è predittivo di psicopatologia futura in adolescenza e nell'età adulta. I *pattern* sintomatologici dimensionali introdotti nel DSM-5 forniscono specifiche informazioni cliniche in questo senso: la dimensione "collerico/irritabile" evolve più spesso verso disturbi di ansia o dell'umore, la dimensione "provocatoria e sfidante" è maggiormente correlata all'ADHD, mentre quella "vendicativa" ai tratti calloso-anemozionali. La severità del disturbo già nei primi anni di vita deve guidare l'impostazione di un adeguato trattamento.

• Roetman PJ, Siebelink BM, Vermeiren RRJM, Colins OF. Classes of Oppositional Defiant Disorder Behavior in Clinic-referred Children and Adolescents: Concurrent Features and Outcomes: Classification Des Comportements Dans le Trouble Oppositionnel Avec Provocation Chez Des Enfants et des Adolescents Aiguillés à Une Clinique: Caractéristiques Co-occurrentes et Résultats. Can J Psychiatry 2020: 706743720974840. doi: 10.1177/0706743720974840.

PLUSDOTAZIONE COGNITIVA

La plusdotazione cognitiva è una condizione non patologica per la quale non esiste una definizione univoca, si stima che tale condizione potrebbe caratterizzare circa il 2% della popolazione nell'età dell'infanzia e dell'adolescenza. Esistono vari tipi di plusdotazione cognitiva, ma solo alcuni necessitano di sostegno. Il profilo *drop-out* manifesta rabbia verso gli altri, ostilità nei confronti della scuola, talvolta comportamenti problematici con difficoltà a integrarsi nel gruppo dei pari. Il profilo "con doppia eccezionalità" presenta quadri diagnostici definiti come disturbi specifici dell'apprendimento o ADHD. Nel profilo "sotterraneo" le competenze cognitive non sono evidenti nell'ambito scolastico o nelle *performance* del soggetto. Talvolta ci sono sentimenti di vergogna con sentimenti di inadeguatezza e sintomi ansiosi associati.

• Abbracciavento G. Il bambino troppo intelligente: gioie o dolori? Medico e Bambino 2020;39:377-83.

PSICOFARMACOLOGIA

I farmaci psicotropi trovano ampio uso in Psichiatria dell'infanzia e dell'adolescenza *(Figura 1)*, ma spesso sono utilizzati *off-label* e, a fronte di una comparabile efficacia, hanno profili di sicurezza differenti. Da una recente meta-revisione sistematica emerge che i farmaci con miglior profilo di sicurezza sono escitalopram e fluoxetina tra gli antidepressivi, *Lurasidone* tra i D-2 bloccanti, metilfenidato per l'ADHD, e il litio tra gli stabilizzanti dell'umore. Tali dati dovrebbero guidare le scelte cliniche, la ricerca e le linee guida di trattamento.

• Piovani D, Clavenna A, Cartabia M, et al. Psychotropic medicine prescriptions in Italian youths: a multiregional study. Eur Child Adolesc Psychiatry 2016;25:235-45. doi:10.1007/s00787-015-0726-0.
• Solmi M, Fornaro M, Ostinelli EG, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry 2020;19(2):214-32. doi: 10.1002/wps.20765.

RISPERIDONE

In Italia è indicato in età evolutiva esclusivamente per il trattamento dei disturbi del comportamento con irritabilità e aggressività dai 5 anni in soggetti con disabilità intellettiva. Il Risperidone viene comunque utilizzato off-label nei Disturbi dell'Umore, nel Disturbo di Condotta, nei Disturbi del neurosviluppo, nel Tourette e come potenziamento delle terapie antidepressive. Gli effetti indesiderati più comuni includono: incremento ponderale, sonnolenza, alterazioni metaboliche e sintomi extra-piramidali quali distonia acuta, discinesie, tremori e acatisia. Tra gli effetti indesiderati più severi bisogna tenere a mente la Sindrome Maligna da Neurolettici. Nel corso del trattamento è bene monitorare periodicamente (almeno ogni sei mesi): prolattina, funzionalità epatica e tiroidea, profilo glicemico e lipidico, peso/BMI, circonferenza addominale, pressione arteriosa, glicemia e QTc.

• McNeil SE, Gibbons JR, Cogburn M. Risperidone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2021.

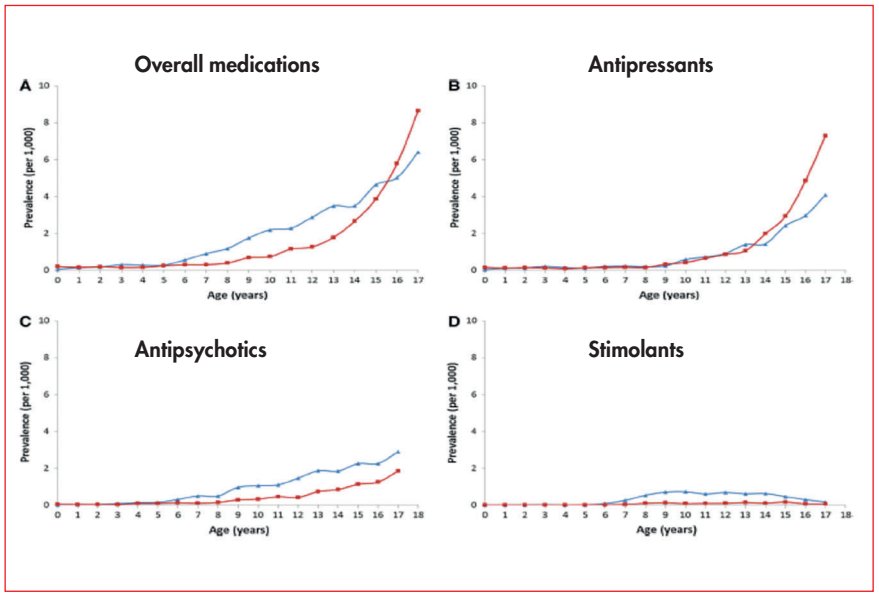

Figura 1. *Prevalenza delle prescrizioni di farmaci psicotropi per età e genere (blu = maschi; rosso = femmine). La prevalenza dell'utilizzo dei farmaci psicotropi segue un trend di crescita esponenziale sulla base dell'età. Gli antidepressivi sono risultati i farmaci maggiormente prescritti sia nella popolazione totale che nelle femmine, mentre gli antipsicotici risultano maggiormente prescritti nei soggetti di genere maschile. I maschi risultano più esposti ad antipsicotici e stimolanti soprattutto in età scolare (da: Piovani D, et al. Eur Child Adolesc Psychiatry 2016;25(3):235-45, modificata).*

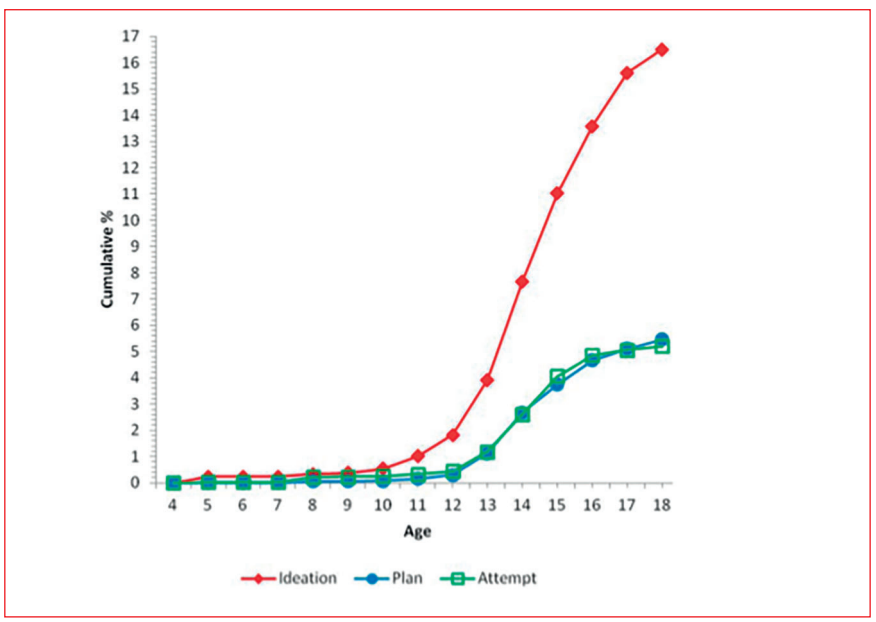

Figura 2. *Curva di età di insorgenza dei comportamenti suicidari: ideazione, pianificazione, tentativo suicidario. L'ideazione suicidaria è molto bassa (< 1%) prima dei 10 anni, aumenta lievemente fino ai 12 anni per poi crescere esponenzialmente tra i 12 e i 17 anni. La pianificazione e i tentativi suicidari risultano invece meno frequenti prima dei 12 anni, aumentano in maniera lineare sino ai 15 anni e poi più lentamente sino ai 17 anni di età (da: Nock MK, et al. JAMA Psychiatry 2013;70(3):300-10, modificata).*

Schizofrenia

Sia la forma a esordio precoce (< 18 anni) che quella a esordio molto precoce (< 13 anni) si caratterizzano per una severa compromissione nel funzionamento emotivo, cognitivo e sociale, elevato rischio suicidario e aggressività eterodiretta con possibile disabilità nel lungo termine. Le comorbidità (in particolare ADHD e disturbo post-traumatico da stress), un peggior funzionamento premorboso e il trattamento tardivo sono associati a una peggiore prognosi. Saper riconoscere i sintomi positivi e negativi, favorire l'invio al Servizio specialistico e avviare il trattamento precoce è cruciale nella fase acuta di malattia per una miglior prognosi. L'essenzialità di una diagnosi precoce induce a sviluppare nuovi modelli di prevenzione che considerino segni precoci aspecifici associati ad altri fattori di rischio; un esempio è la familiarità di primo grado per episodi psicotici o altre condizioni psicopatologiche gravi (depressione maggiore, disturbo bipolare). Per avviare campagne di prevenzione sarebbe necessario superare difficoltà comunicative tra Servizi e professionisti che seguono componenti dello stesso nucleo familiare (medico di base, pediatra, psichiatra, neuropsichiatra, assistente sociale). È inoltre necessario implementare i Servizi di salute mentale con risorse e visioni per programmi di promozione di salute mentale e di prevenzione, risorse che oggi risultano evidentemente carenti e che vengono assorbite nella risposta a domande complesse in condizione di emergenza e urgenza.

• Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. J Child Adolesc Psychopharmacol 2016; 26(5):410-27. doi: 10.1089/cap.2015.0097.
• Maziade M. At Risk for Serious Mental Illness - Screening Children of Patients with Mood Disorders or Schizophrenia. N Engl J Med 2017;37(10):910-2.

Suicidio

È la seconda causa di morte nei giovani dopo gli incidenti. La *Figura 2* riporta la curva di insorgenza dei comportamenti suicidari in riferimento all'età.
I fattori di rischio maggiormente associati all'ideazione e ai tentativi suicidari includono il sesso maschile, la comorbidità con uso di sostanze e disturbi dell'umore, l'impulsività, la disabilità intellettiva, la rigidità cognitiva, prece-

denti tentativi di suicidio, essere vittima di bullismo e appartenere a una minoranza etnica o sessuale. Studi recenti suggeriscono che la disregolazione emotiva sia il miglior predittore di rischio. Recentemente è stato approvato in Italia per gli adulti l'utilizzo di esketamina *spray* nasale in associazione agli antidepressivi nella depressione resistente con rischio suicidario. Attualmente in corso gli studi negli adolescenti con risultati promettenti.

• Benton TD, Muhrer E, Jones JD, Lewis J. Dysregulation and Suicide in Children and Adolescents. Child Adolesc Psychiatr Clin N Am 2021;30(2):389-99. doi: 10.1016/j.chc.2020.10.008.

TRAIETTORIA EVOLUTIVA, NEUROSVILUPPO E NEUROSCIENZE

La traiettoria di sviluppo intende il percorso evolutivo, orientato da fattori genetici, neurobiologici, ambientali e culturali, nel quale si susseguono, nel corso della vita, una serie di cambiamenti psico-comportamentali. Si distinguono uno sviluppo tipico, sovrapponibile a quanto atteso per età cronologica, e uno atipico, in cui una compromissione evolutiva di varia natura altera il percorso. La prospettiva del neurosviluppo che consente di rintracciare la storia naturale dei disturbi e la loro evoluzione è ormai confermata dalle neuroscienze. Sempre più studi hanno evidenziato come le reti neurali si modificano nel tempo in base alle traiettorie di sviluppo secondo un processo di reciproco condizionamento.

• Kujawa A, Klein DN, Pegg S, Weinberg A. Developmental trajectories to reduced activation of positive valence systems: A review of biological and environmental contributions. Dev Cogn Neurosci 2020;43:100791. doi: 10.1016/j.dcn.2020.100791.

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
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)
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